Title	Synthesis of Nitropyridines and Nitroanilines Using Three Component Ring Transformation
Author(s)	LE, Thi Song
Citation	高知工科大学, 博士論文.
Date of issue	2015-09
URL	http://hdl.handle.net/10173/1326
Rights	
Text version	ETD

KOCHI UNIVETSITY OF TECHNOLOGY

School of Environmental Science and Engineering

A thesis submitted in partial fulfilment for the degree of

Doctor of Engineering

LE THI SONG

SYNTHESIS OF NITROPYRIDINES AND NITROANILINES USING THREE COMPONENT RING TRANSFORMATION

Supervisor: **Professor Nagatoshi NISHIWAKI**

Co-supervisor **Professor Ryuichi SUGIMOTO**

Professor Kazuya KOBIRO

Kochi, Japan, 2015

Author’s Declaration

I hereby declare that the work in this thesis was carried out in accordance with the Regulations of Kochi University of Technology, Kochi, Japan. The work is original except where indicated by special reference in the text and no part of the dissertation has been submitted for any other degree. Any views expressed in the dissertation are those of the author and do not necessarily represent those of Kochi University of Technology. The thesis has not been presented to any other university for examination either in the Japan or overseas.

Acknowledgements

It is with immense gratitude that I acknowledge the support and help to all those who have been beside me during my research period and the preparation of this thesis.

Particular thanks are due to my academic supervisor, Professor **Nagatoshi Nishiwaki**, professor of Kochi University of Technology, for the insightful advice, continuous encouragement and patient personal counselling he has given to, and for the appreciate guidance and commendation he has spent with me.

I wish to express my gratitude and my sincere thanks to my co-supervisor Professor Sugimoto, Professor Kobiro; professor of Kochi University of Technology and Professor Saigo; professor of Kochi University for their valuable suggestions, comments and hearty encouragements.

Warm thanks are also sent to my lab mates, Dr. Haruyasu Asahara, Mr. Sho Hirai and other lab members for their cooperation and academic support.

Thanks are due to IRC staff members of Kochi University of Technology, for their support and academicals assistance. I would like to thank to Kochi University of Technology Professors, whose inspiring teachings motivated me to complete my study.

Words cannot express my gratitude to my husband, my parents, my younger brother and younger sister for their encouragement and so many sacrifices to ensure me to complete the study.

Le Thi Song

Kochi University of Technology, Kochi, Japan, 2015

Table of Contents

List of publications

This thesis is based on the following publications, which will be referred in the text.

1. Synthesis of 2-Aryl-5-Nitropyridines by Three-Component Ring Transformation of 3,5-Dinitro-2-pyridone

Song Thi Le, Haruyasu Asahara, Kazuya Kobiro, Ryuichi Sugimoto, Kazuhiko Saigo, and Nagatoshi Nishiwaki

Asian Journal of Organic Chemistry **2014**, *3*, 297-302, impact factor 3.318, Q1

2. An Efficient Synthesis of Nitrated Cycloalka[b]pyridines

Song Thi Le, Haruyasu Asahara, and Nagatoshi Nishiwaki

Synthesis **2014**, 2175-2178, impact factor 2.689, Q2

3. Tailor-Made Synthesis of N,N,2,6-Tetrasubstituted 4-Nitroanilines by Three-Component Ring Transformation of Dinitropyridone

Song Thi Le, Haruyasu Asahara, and Nagatoshi Nishiwaki

European Journal of Organic Chemistry **2015**, 1203-1206, impact factor 3.065, Q1

4. Metal-free Synthesis of 2-Alkenyl/Alkynyl 5-Nitropyridines Using a Three-Component Ring Transformation

Song Thi Le, Haruyasu Asahara and Nagatoshi Nishiwaki

Chemistry Letters **2015**, *44*, impact factor 1.230, Q3

5. An Alternative Synthetic Approach to 3-Alkylated/Alkynyl 5-Nitropyridines

Song Thi Le, Haruyasu Asahara and Nagatoshi Nishiwaki

Journal of Organic Chemistry, **2015**, *80*, 8856-8856**,** impact factor 4.721, Q1

The contributions of the author of this thesis for these publications are:

I. All experiments (except HRMS and X-ray measurements) and major part of writing.

II. All experiments (except HRMS) and major part of writing.

III. All experiments (except HRMS) and major part of writing.

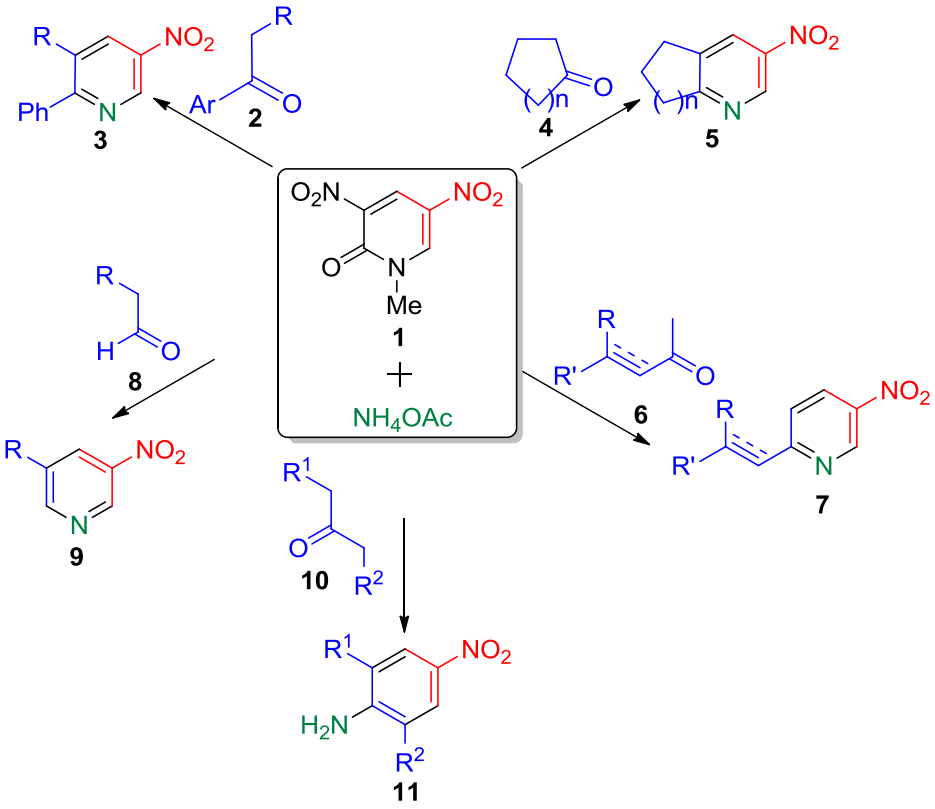
IV. All experiments (except HRMS) and major part of writing.

V. All experiments (except HRMS) and major part of writing

Abstract

Nitro compounds show great importance in chemistry, biology and material sciences. Among them, nitropyridines and nitroanilines are widely used as useful intermediates for synthesis of biologically active compounds, pharmaceutical and agrochemical importance. Although nitration is the easiest way for introducing nitro group to scaffold frameworks, harsh conditions are sometimes necessary, which means the control of the reaction is quite difficult and a reactive functional group cannot be tolerated. Furthermore, a strategy to install substituents directly into pyridine framework is not easily performed because of low reactivity of pyridines and its derivatives. Thus, the development of an efficient method for synthesis of these compounds still remains a challenge. Therefore, the goal of this Ph.D Thesis was the development of a new method for synthesis of various kinds of nitro compounds by using a three component ring transformation (TCRT) of dinitropyridone **1** with ketones in the presence of less nucleophilic ammonium acetate (NH_4OAc) as nitrogen source .

As results, various kinds of nitro compounds such as arylated nitropyridine **3**, nitrated cycloalka[*b*]pyridines **5**, 2-alkylated/arylated 5-nitropyridines **7**, 3-substituted 5-nitropyridines **9** and nitroanilines **11** were prepared by TCRT of dinitropyridone **1** with ketones such as aromatic ketones **2**, cyclic ketone **4**, α,β-unsaturated ketones **6**, aldehyde **8** and aliphatic ketone **10**, respectively, in the presence of ammonium acetate as nitrogen source (Scheme 1).



Scheme 1. TCRT of dinitropyridone affording various kinds of nitropyridines and nitroanilines

In summary, a facile and efficient method for construction libraries containing a large number of nitropyridine and nitropyridine derivatives, was successfully developed. This method requires only simple manipulations, single step reaction, and mild conditions. Furthermore, the modification of nitropyridine or nitroaniline frameworks can be easily obtained only chaining a commercially available substrates. These features improve the synthetic value of this method, and it will be alternative approach to nitro compounds.

Chapter 1. General Introduction

1. Nitro compounds

Nitro compounds constitute an important class among organic compounds and are widely used in industrial production of chemicals such as drugs, dyes, explosives and pesticides (Scheme 1). These compounds are organic molecules that consist of at least one nitro group attached to molecules. Indeed, a nitro group is one of the important functional group in chemical syntheses because of the following properties:[1]

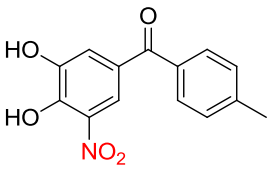
(1) A nitro group behaves as an electron-withdrawing group by both inductive and resonance effects. Thus, a nitro group considerably decreases electron density of the scaffold frameworks to facilitate reactions with nucleophiles.

(2) The electron-withdrawing nitro group activates various skeletons. Although most halobenzenes caused no reaction upon treatment with nucleophiles, nitrated ones easily undergo the nucleophilic substitution.

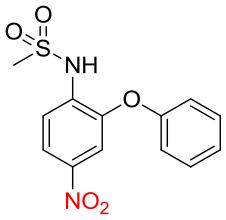
(3) A nitro group assists the adjacent carbon-carbon bond cleavage, and can be transferred to versatile functional groups. Thus, a large number of nitro compounds are also widely employed as the key intermediates leading to versatile compounds (Scheme 2).

Furthermore, when some organic compounds with multiple nitro groups react with nucleophiles, stable Meisenheimer complex can be formed. (ref.nitoaromatic compounds)

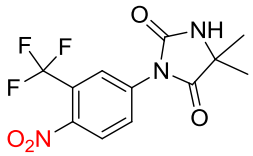
(a) Certain drugs containing a nitro group



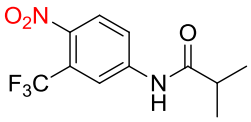
Tolcapone



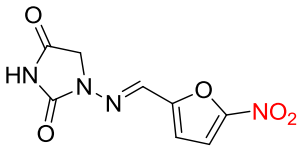
Nimesulide



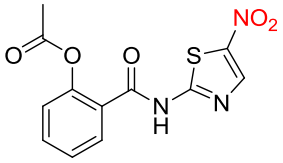
Nilutamide



Flutamide

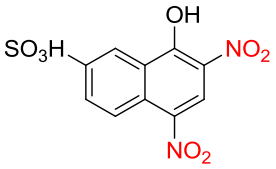


Nitrofurantoin

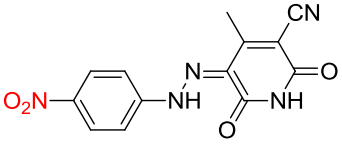


Nitazoxanide

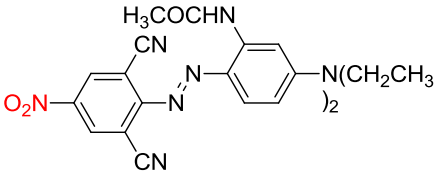
(b) Dyes containing a nitro group



Naphthol yellow

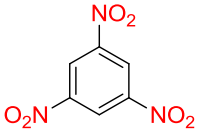


Azohydroxypyridone dyes

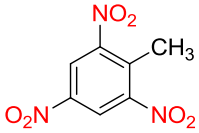


Disperse blue 165

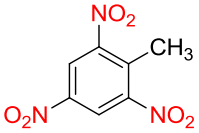
(c) Nitroaromatic explosives



TBN

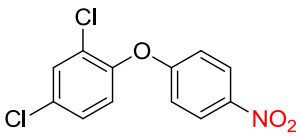


TNT

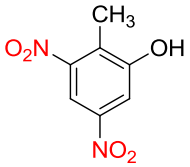


Nitramine

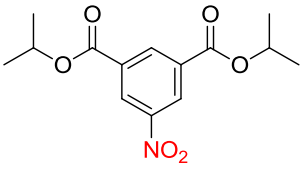
(d) Pesticides containing a nitro group



Nitrofen

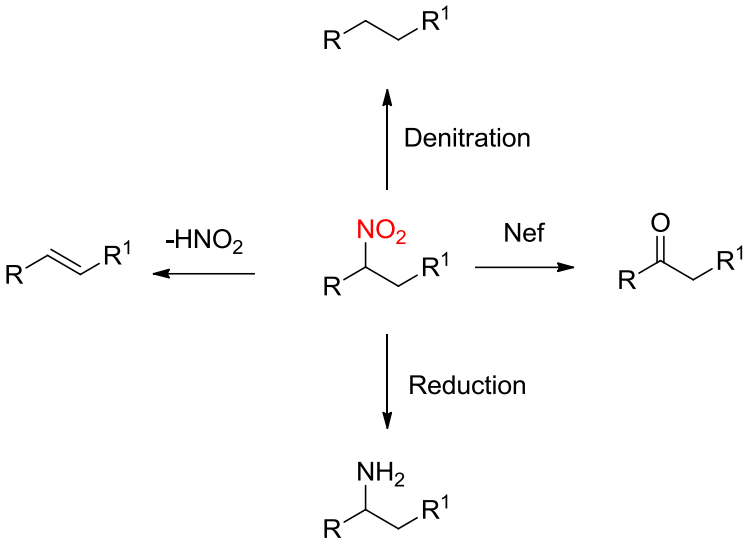


4,6-Dinitro-*o*-Cresol



Nitrothal-isopropyl

Scheme 1. Application of nitro compounds[2]

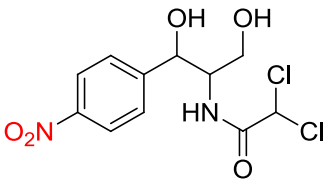


Scheme 2. Conversion of a nitro group into other functionalities

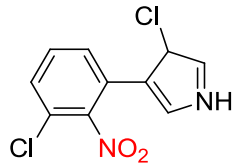
Nitro compounds are generally divided into two categories: naturally occurring nitro compounds and synthesized nitro compounds.

1.1 Naturally occurring nitro compounds

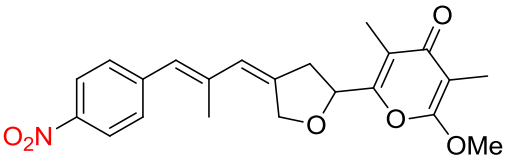
Nitro group are often found in a variety of natural products and show great importance in a wide range of biological activities. Thus, these compounds have attracted many researcher's interest, and their isolations, structural determination, total synthesis and modifications have been an important subject over the past decades. Generally, these compounds have been isolated from plants, fungi, bacteria and mammals. For example, the potent antibiotic chloramphenicol is produced from bacterium *Streptomyces venezuelae*;[3] the antifungal agent pyrrolnitrin is produced from *Pseudomonas fluorescens*; [3] the antitumoral pyrone metabolite aureothin from *Streptomyces thioluteus;*[3] the metabolite nitropropionic acid was found in both *palnts* and *fungi*[3] (Scheme 3). It is interesting to note that there are two main pathways are conceivable for the formation of nitro compounds in nature: nitration or oxygenation of amines. However, as the best of our knowledge, only around 200 naturally occurring nitro compounds have been identified till date.



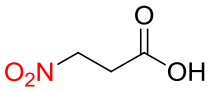
Antibiotic Chloramphenicol



Antifungal agent pyrrolnitri



Antitumoral pyrobe metabolite aureothin



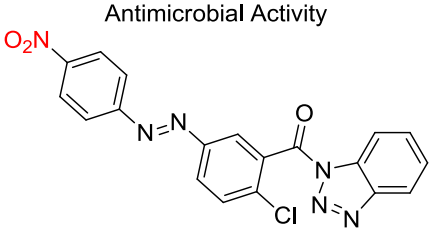
Metabolite nitropropionic acid

Scheme 3. Naturally occurring nitro compounds

1.2 Unnatural nitro compounds

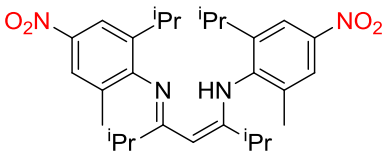
On the other hand, unnatural nitro compounds have also gained a lot of attention recently because of their excellent pharmacological and physiological activities. Among these compounds, nitropyridines and nitroanilines such as 2-arylated 5-nitropyridines, cycloalka[*b*]pyridines, 2-alkenyl/alkynyl 5-nitropyridines, 3-alkylated/arylated 5-nitropyridines and nitroanilines, are focused on the presence thesis.

Antimicrobial Activity

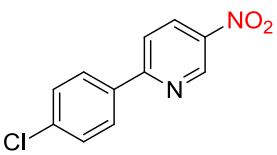


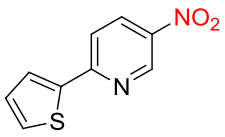
DGA1 inhibitors

b-Diketiminate Ligand



Regulators of Vasalin containing proteins





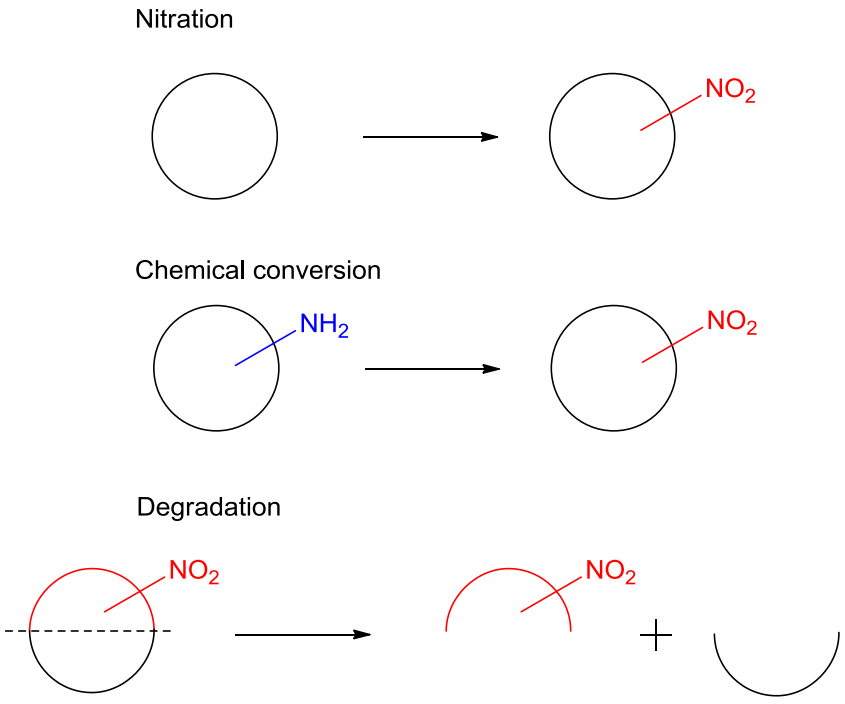
Scheme 4. Example of some naturally occurring and unnatural nitro compounds[4]

2. Synthetic methods of nitro compounds

Generally, preparative methods for nitro compounds are divided into three categories:[5] (1) the direct approach to nitro compounds, (2) built-in methods using a nitrated building block, and (3) ring transformation, which are supplementary method to each other.

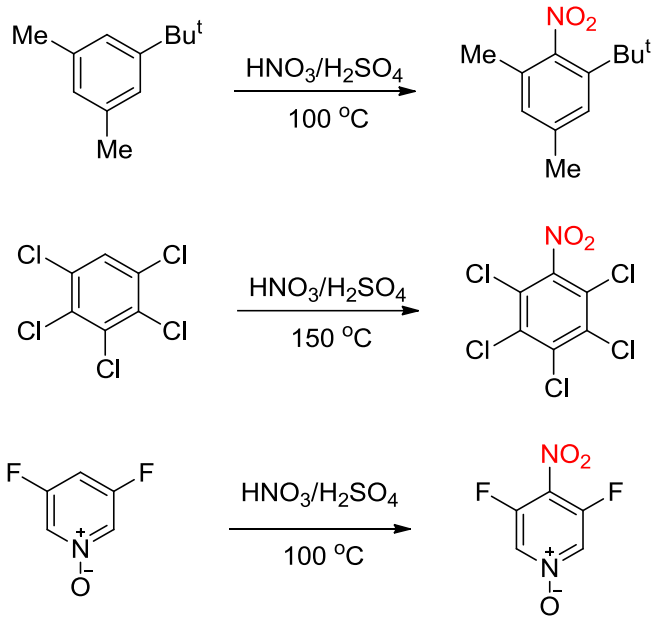
2.1 Direct approach to nitro compounds

In this synthetic pathway, three strategies are often employed: (1) nitration, which is directly introduce a nitro group to scaffold frameworks; (2) chemical conversion, which is chemical transformation of other functional groups into a nitro group when these functional groups can be easily introduced; and (3) degradation, which is often used when nitro compounds with an additional functional group are necessary.



2.1.1 Nitration

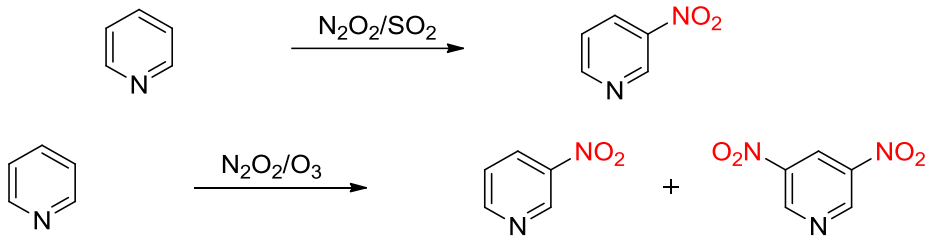
Because nitro compounds are widely employed for various purposes as mentioned before, considerable attention has been paid to the synthesis of these compounds for a long time. The nitration is the most common way to introduce a nitro group directly into the scaffold frameworks,[6] which has been performed using HNO_3 or a combination of HNO_3 and H_2SO_4 as nitrating agent. Several examples are shown in Scheme 5.[7] Although other nitrating agent also has been employed, however, these are not applicable to large scale nitration because harsh conditions are sometimes necessary and a reactive functional group cannot be tolerated. In addition, large amounts of waste acids are produced, which should be then treated after reaction.



Scheme 5. Some examples of nitration

It is known that the direct nitration of the heterocyclic compounds such as pyridine is quite difficult and often results in low yields of products because it is prevented by the low electron density and the basic nitrogen forming a salt with acid catalyst. Recently,

some strong nitrating agents have been developed that facilitates nitration of pyridine and its derivatives under mild conditions. Bakke's group firstly reported the nitration of pyridine using dinitrogen pentoxide in sulfur dioxide solution, which gave 3-nitropyridines in good yield.[8] However, this method is troublesome because it is necessary to prepare nitrating agent beforehand. Suzuki and co-workers also reported an excellent nitration method using nitrogen dioxide and ozone.[9] Unfortunately, this method gave a mixture of 3-nitropyridine and 3,5-dinitropyridine in low yield. In addition, excessive oxidation of the nitrated compounds also occurs because nitrating agents are strong oxidants. Although *ipso*-nitration methods have been developed to overcome these disadvantages,[10] it is not cost-effective and not environmental benign. Therefore, this method is not practically used.



Scheme 6. Direct nitration of pyridine using different nitrating agent

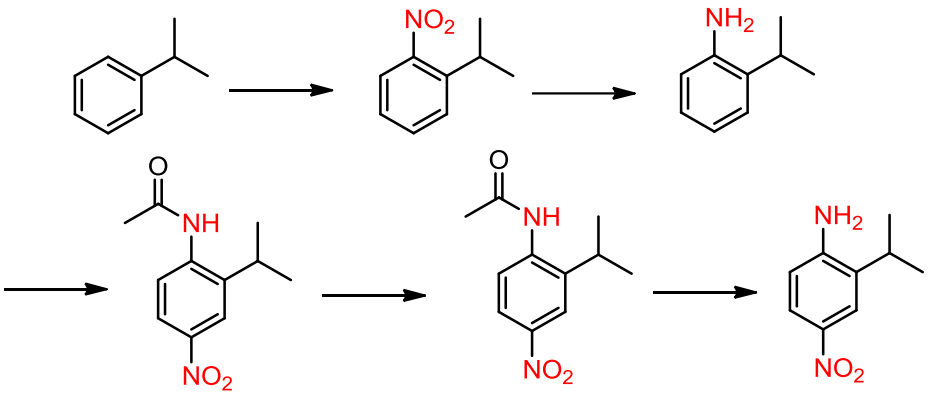
2.1.2 Chemical conversion

When a suitable functional groups presents in the molecule, the chemical transformation of functional groups into a nitro groups becomes alternative approach to nitro compounds. Oxidation of an amino group to a nitro group using O_3 can be used however, side reactions sometimes proceed competitively. Although these side reactions can be avoided by the use of solid media such as silica gel or catalytic systems, this method is not practically used because O_3 is not easily treatable reagent.

Another approach to nitro compounds by chemical conversion is also reported, in which carbonyl compounds can be converted to nitro compounds via oximes.[11] However, strong oxidants such as CF_3CO_3H should be used. In addition, the chemical conversion of alkyl azides are also used for preparation of nitroalkanes using triphenylphophine and

O_3 or HOF-MeCN complex. These methods are also troublesome because it is necessary to prepare catalyst beforehand.

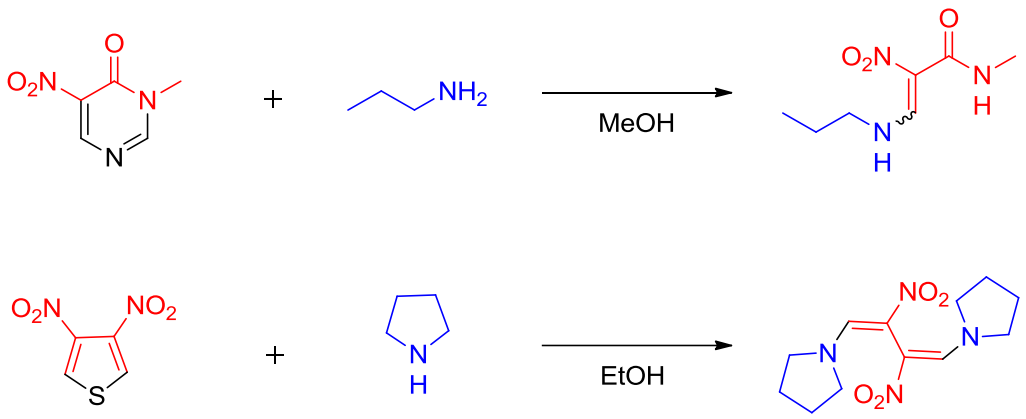
On the other hand, the preparation of nitropyridines or nitroanilines by chemical conversion are not a convenient way because these methods require many steps, in which protection and deportection of functional groups are necessary. Moreover, the starting material are not easily available because these compounds are often prepared by coupling reaction.



Scheme 7. Multi-Step for the synthesis of the nitroaniline derivatives

2.1.3 Degradation

Heterocyclic compounds easily cause the ring opening reaction to give degraded products because of their low aromaticity and polarized structure. Thus, degradation of nitrated heterocyclic compounds is often employed for construction of multipl functionalized nitro compounds. Some examples are illustrated in Scheme 5.[12] However, this method is not usable for preparation of nitropyridines or nitroanilines.

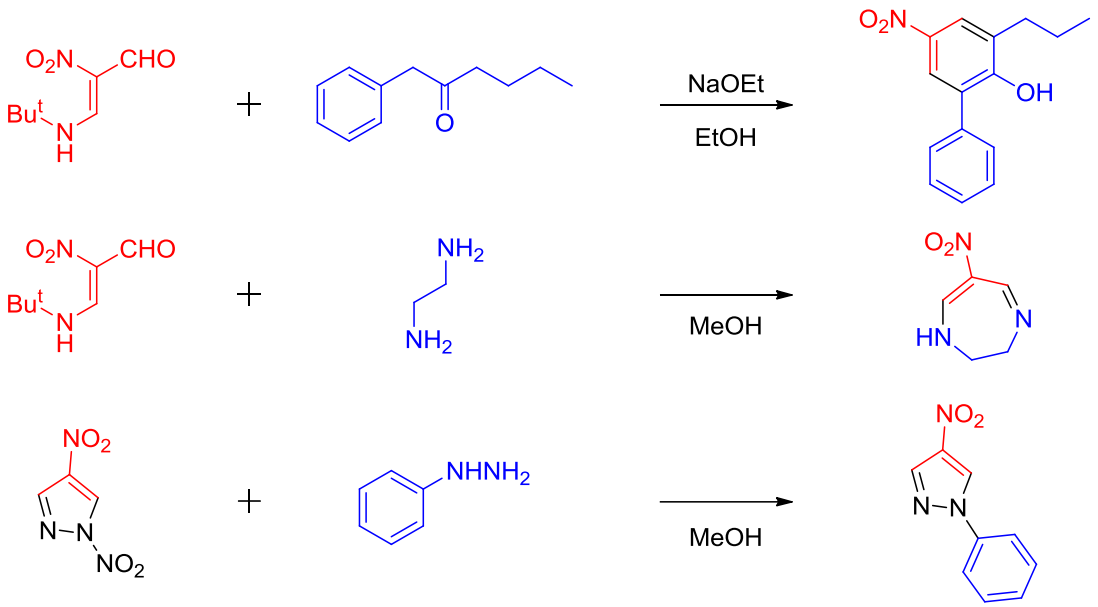


Scheme 8. Some examples of degradation

2.2 Built-in methods using a nitrated building block

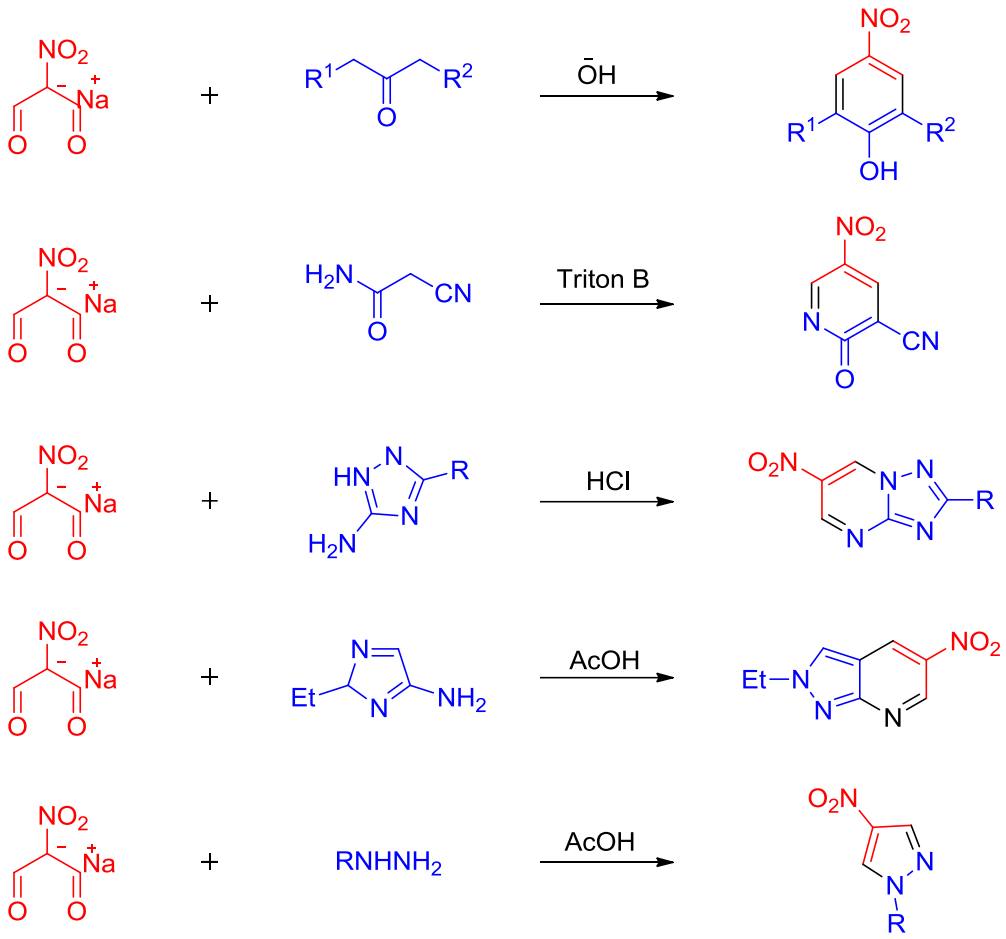
Although nitration is a direct method to introduce a nitro group into framework, however, there are some compounds cannot be prepared by nitration. As a supplementary method, built-in method is employed. This method is known as the incorporation of a nitro compound bearing an additional functional group as the building block.

Indeed, built-in method for construction of a large number of nitro compounds using nitroalkanes, nitroalkenes, and bromonitromethane as building block have been reported widely. Some examples are shown in Scheme 9.[13] Furthermore, such building blocks are also often appear as a synthon in the retrosynthesis of nitro compounds, among which nitromaloaldehyde (NMA-H) is an important substrate. However, this method suffers from several disadvantages since NMA-H is too unstable in aqueous solution to be isolated. Therefore, several synthetic equivalents of NMA-H have been developed such as formylnitroenamine for synthesis of nitrated phenols and pyrimidines; 1,4-dinitropyrazole for synthesis of nitropyrazoles.



Scheme 9. Several synthetic equivalent of NMA-H

As an excellent synthetic equivalent of NMA-H, sodium nitromaloaldehyde (NMA-Na) is extensively employed to afford 2,6-disubstituted 4-nitrophenols, 3-nitropyridines, nitropyrimidines and their condensed derivatives, pyrazolopyridine and other ring systems as illustrated in Scheme 10.[14] Despite the high synthetic value of NMA-Na, the preparation of NMA-Na is troublesome since it is impact-sensitive, thermally unstable and should be handled as a potentially explosive material.

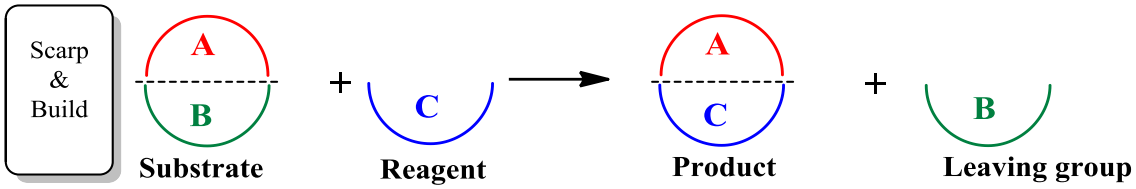


Scheme 10. Condensation of sodium nitromaloaldehyde as synthetic equivalent of NMA-H

2.3 Ring transformation

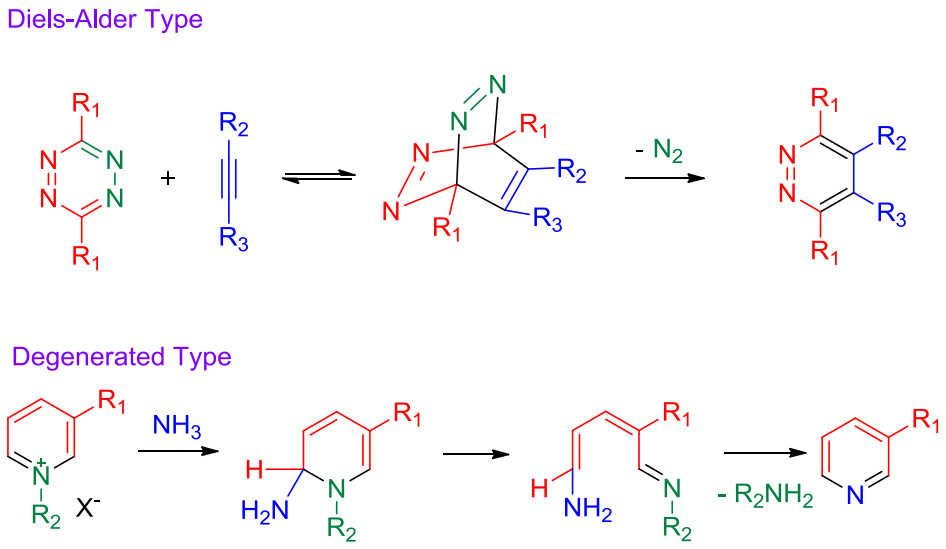
As mentioned so far, it is not easy to obtain nitrated heterocyclic compounds, expecially heteroaromatic compounds. Thus, a supplementary method for construction of nitrated heterocyclic compounds is of great important in both medicinal and synthetic chemists. Meanwhile, ring transformation is known as one of the powerful methods for synthesizing functionalized heterocyclic compounds that are not easily available by other methods.[15] Ring transformation is restructuring reaction including “scrap and build”. Namely, the partial structure A of the substrate (A+B) is transferred to the reagent C to

form a new ring systems (A+C) accompanied by elimination of the good leaving group B (Scheme 7).



Scheme 11. Concept of ring transformation

While Diels-Alder-type[16] and ANRORC-type[17] ring transformations have been energetically studied, a nucleophilic-type ring transformation is still remaining challenge. From this viewpoint, the goal of this PhD thesis was the study on nucleophilic type ring transformation which can be used to construct a great number of heterocyclic compounds.



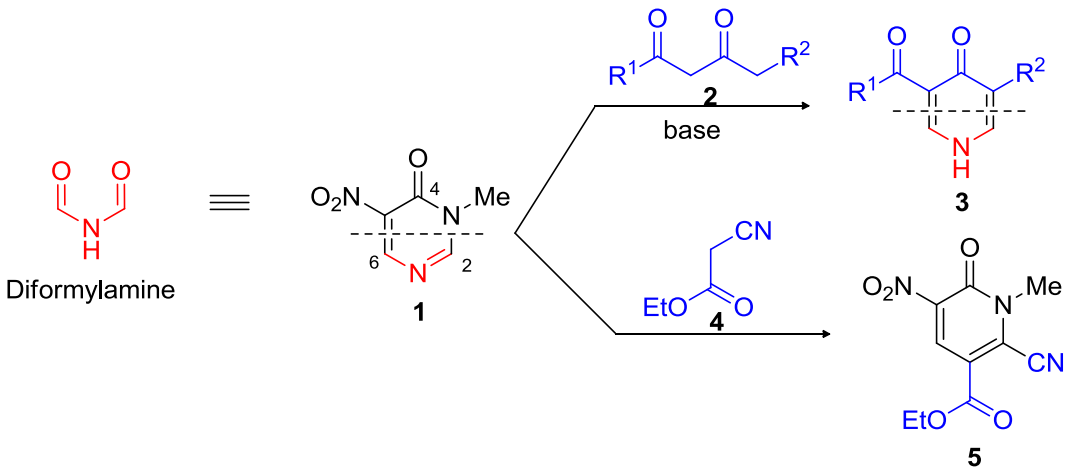
Scheme 12. Example of Diels-Alder type and Degenerated type ring transformation

2.3.1 Nucleophilic type ring transformation

The nucleophilic type ring transformation is known as the use of a combination of dinucleophilic reagent and dielectrophilic substrate. The substrates for this reaction

should be electron-deficiency and are required to have a good leaving group as a partial structure.[18] Indeed, nitropyridines are often employed as substrates for nucleophilic ring transformation; however, severe conditions such as strong base and high temperature are necessary to destroy aromaticity of the pyridine nuclei. Therefore, several substrates for nucleophilic ring transformation have been developed. Indeed, the nucleophilic ring transformation of 5-nitropyrimidine has been energetically studied by van der Plas and co-workers.[19]

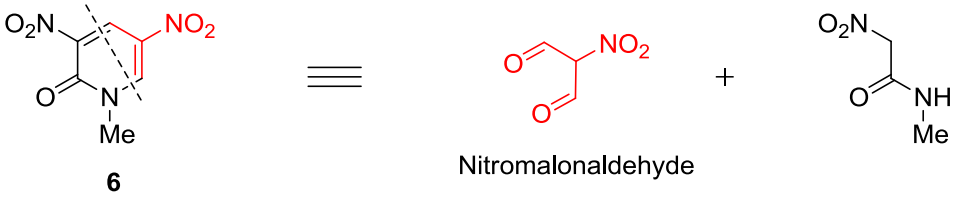
Nitropyrimmidinones **1** underwent the nucleophilic ring transformation easily under mild conditions because this compounds are highly electron-deficient with low aromaticity and containing good leaving group anionic nitroacetamide as the partial structure. In these reactions, 5-nitro-4-pyrimmidinones **1** behaves synthetic equivalent of unstable nitromaloaldehyde. Indeed, difunctionalized 4-pyridones and polyfunctionalized pyridines were prepared by the ring transformation of 5-nitro-4-pyrimidinone **1** with β-keto esters and active methylene compounds, respectively (Scheme 13).



Scheme 13. The nucleophilic ring transformation of 5-nitro-4-pyrimidinone

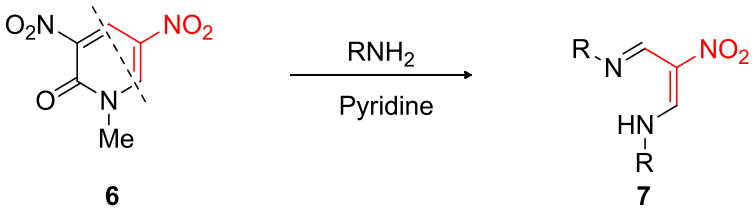
Dinitropyridone **6**, which serves as synthetic equivalent of unstable nitromaloaldehyde,[20] is reported as superior substrate for nucleophilic ring transformation. However, only few literatures dealing with ring transformation using dinitropyridone **6**

as substrate. Thus, the ring transformation of dinitropyridone **6** is emphasized in the present thesis.



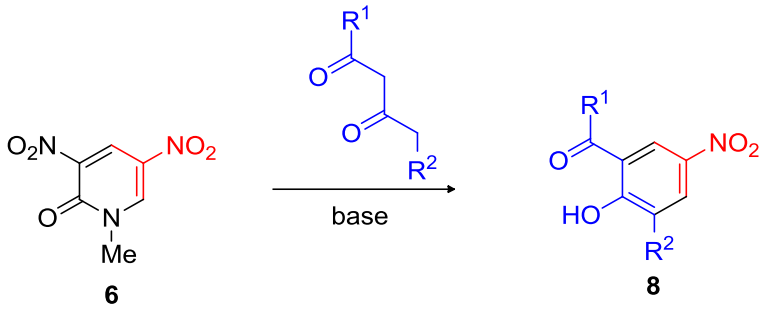
Scheme 14. Dinitropyridone behaves as synthetic equivalent of unstable nitromaloaldehyde

Before conducting ring transformation, the electron deficiency and electrophlicity of dinitropyridone **6** was allowed to react with amine. As a results, the aminolysis of dinitropyridone easily proceeds leading to formation of azadienamines **7** having a nitro group when this compound is treated with amines in a pyridine solution.[14]



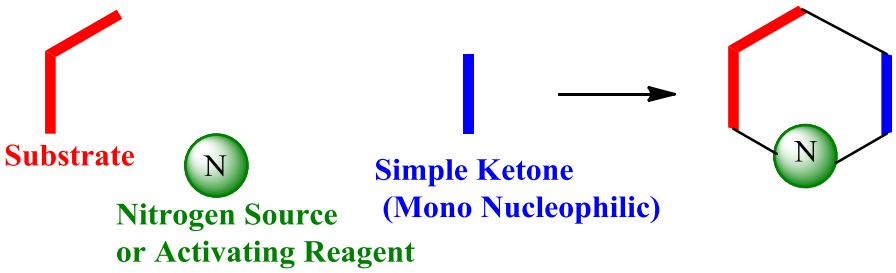
Scheme 15. The aminolysis of dinitropyridone

The ring transformation of dinitropyridone **6** with β-keto esters under basic conditions have been reported, by which difunctionalized 4-nitrophenols **8** are formed.[21]



Scheme 16. Ring transformation of dinitropyridone **6** with dicarbonyl compounds

Although 1,3-dicarbonyl compounds surely behave as the excellent dinucleophilic reagents, only several kinds of ring transformation products can be obtained due to limited availability of these reagents. In order to improve the synthetic utility of ring transformation, a simple ketones should be used as a substrate. In this case, another nucleophile is required, which severs as a nitrogen source or activator of substrate. This kind of ring transformation is called three component ring transformation (TCRT).

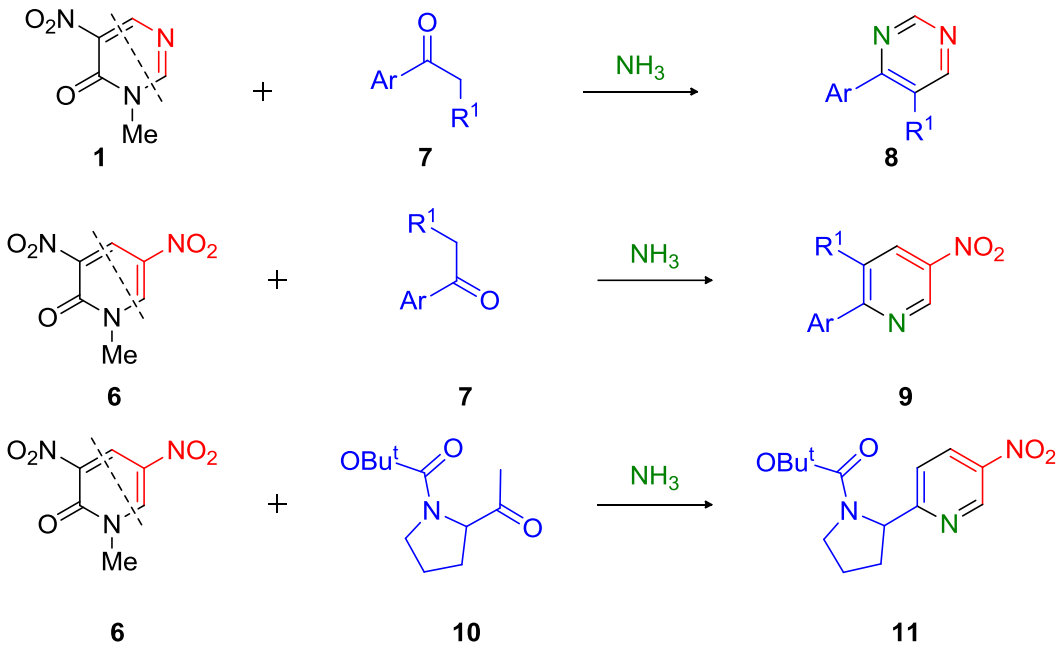


Scheme 17. A concept of three component ring transformation

2.3.2 Three component ring transformation (TCRT)

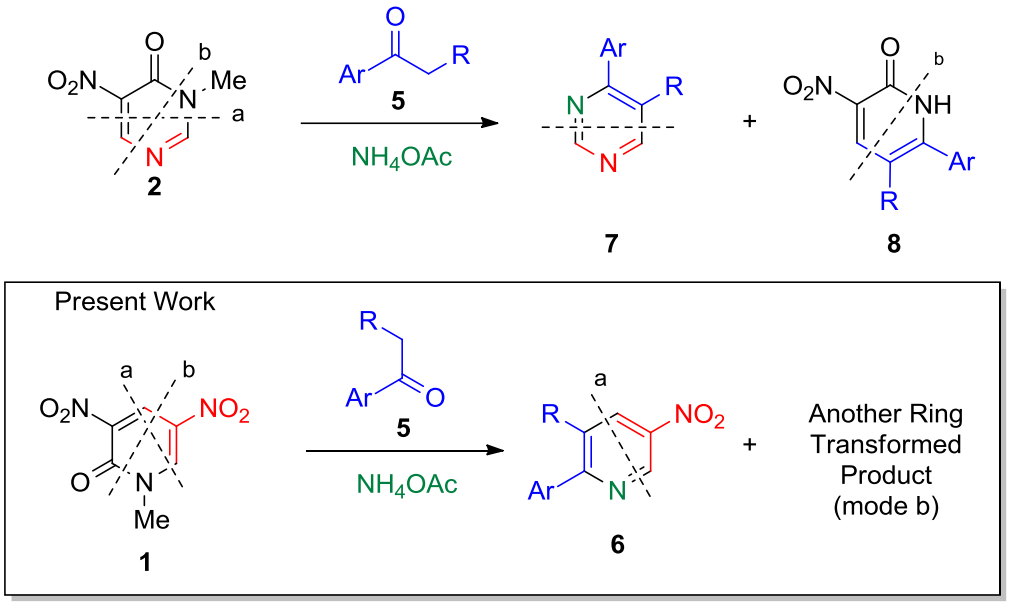
The TCRT is a combination of the substrate with simple ketones in the presence of nitrogen source or activator of substrate. Nitropyrimidinone **1** and dinitropyridone **6** enable to undergo TCRT upon treatment with ketones **7**, in the presence of NH_3 as a nitrogen source, which afford 2,3-disubstituted 5-nitropyridines **8** and 4,5-disubstituted pyrimidines **9**, respectively.[22-25] Unfortunately, this method requires preparation of

methanolic ammonia beforehand, and suffers from low yields of the products because of the competitive ammonolysis of substrate **1** and **6**.[26] In addition, Henry *et al*. reported the TCRT of dinitropyridone[27] with protected acetylpyridine in the presence of NH_3, which afforded nitropyridines in good yield. However, microwave irradiation is needed. If competitive ammonolysis is suppressed, the TCRT will be a powerful protocol for synthesis of arylated nitropyridines which are not easily prepared by other methods.



Scheme 18. The TCRT of the the nitropyrimidinone **1** and dinitropyridone **6**

Indeed, less nucleophilic ammonium acetate (NH_4OAc) is similarly considered as the nitrogen source and activates the ketones, which enables the substrates undergo the TCRT under mild conditions. When nitropyrimidinone **1** was allowed to react with ketone **5** in the presence of NH_4OAc, the yield of pyrimidine **7** was considerably increased (Scheme 19, mode a).[25] In addition, a new type ring transformation was found to proceed between the 4- and 6-positions of nitropyrimidinone **1**, leading to the 5,6-disubstituted 3-nitro-2-pyridones **12** (Scheme 19, mode b).[25a] Therefore, the goal of this Ph.D Thesis was the study on TCRT of dinitropyridone **6** with ketones in the presence of NH_4OAc as nitrogen source, which avoids the aminolysis of **6** (Scheme 19, path b).



Scheme 19. Two kinds of TCRTs by using NH_4OAc as a nitrogen source

3. Purpose of thesis

In this thesis, an alternative approach to nitropyridines and nitroanilines has been developed using TCRT of dinitropyridone with ketones in the presence of nitrogen source. As results, a great number of nitropyridines and nitroanilines were synthesized from good to excellent yields.

4. Reference

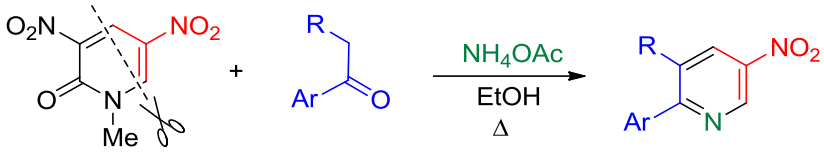
1. Ono, N.; *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, **2001**.
2. Winkler, R.; Hertweck, C. *Chem. Bio. Chem*, **2007**, *8*, 973 – 977.
3. Koh, J. S.; Kim, S.; Kim, J. P. *Color. Technol*. **2014**, *120*, 241-246.
4. (a) Jamkhandi. *Int. J. Pharm. Sci*, **2013**, *5*, 225; (b) Rajendran. *Organometallics*, **2014**, *33*, 217.
5. Nishiwaki. N. *Comprehensive Organic Synthesis*, 2nd edition, Oxford: Elsevier; **2014**, *6*, 100-130.
6. Olah, G. A.; Malhotra, R.; Narang, S. C. Nitration; VCH: New York, **1990**.

7. (a)Suzuki, H.; Mori, T. J. Chem. Soc. Perkin Trans. 1 **1991**, 1049–1050. (b)Suzuki, H.; Hisatome, K.; Nonoyama, N. Synthesis **1999**, 1291–1293.
8. Bakke, J. M.; Ranes, E.; Riha, J.; Svensen, H. *Acta Chemica Scandinavica*, **1999**, *53*, 141-144.
9. (a) Matsunaga, M. *Chimica Oggi* **1994**, 58–61; (b) Suzuki, H.; Noyori, R. *Chemtracts*. **1997**, *10*, 813–815; (c) Mori, T.; Suzuki, H. *Synlett* **1995**, 383–392.
10. Saito, S.; Koizumi, Y. *Tetrahedron Lett*. **2005**, *46*, 4715–4717.
11. Emmons, W. D.; Pagano, A. S. *J. Am. Chem. Soc*. **1955**, *77*, 4557–4559.
12. Nishiwaki, N.; Terai, R.; Mizukawa, Y.; Tohda, Y.; Ariga, M. *Arkivoc* **2000**, *1*, 103–111
13. (a) Nakaike, Y.; Hayashi, D.; Nishiwaki, N.; Tobe, Y.; Ariga, M. *Org. Biomol. Chem*. **2009**, *7*, 325–334; (b) Nishiwaki, N.; Ogihara, T.; Takami, T.; Tamura, M.; Ariga, M. *J. Org. Chem*. **2004**, *69*, 8382–8386; (c) J˛edrysiak, R.; Sawicki, M.; Wagner, P.; Suwiński, J. *ARKIVOC* **2007**, *vi*, 103–111.
14. Nishiwaki, N.; Hirao, S.; Sawayama, J.; Saigo, K. *Heterocycles*, **2012**, *84*, 115 – 134.
15. Nishiwaki, N.; Ariga, M. *Top Heterocycl Chem* **2007**, *8*, 43–72.
16. For example: (a) Kirkham, J. D.; Butlin, R. J.; Harrity, J. P. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 6402–6405; (b) Sabot, C.; Oueis, E.; Brune, X.; Renard, P.-Y. *Chem. Commun.* **2012**, *48*, 768– 770; (c) Anderson, E. D.; Boger, D. L. *Org. Lett*. **2011**, *13*, 2492–2494; (d) Delaunay, T.; Genix, P.; Es-Sayed, M.; Vors, J.-P.; Monterio, N.; Balme, G. *Org. Lett*. **2010**, *12*, 3328–3331; (e) Wu, C.; Fang, Y.; Larock, R. C.; Shi, F. *Org. Lett.* **2010**, *12*, 2234– 2237; (f) Miura, T.; Yamauchi, M.; Murakami, M. *Chem. Commun.* **2009**, 1470– 1472; (g) Yoshino, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2009**, *131*, 7494–7495; (h) Xie, H.; Zu, L.; Oueis, H. R.; Li, H.; Wang, J.; Wang, W. *Org. Lett*. **2008**, *10*, 1923–1926.
17. (a) Bonacorso, H. G.; Navarini, J.; Porte, L. M. F.; Pittaluga, E. P.; Junges, A. F.; Mayer, A. R.; Martins, M. A. P.; Zanatta, N. *J. Fluor. Chem.* **2013**, *151*, 38–44; (b) Koutentis, P. A.; Koyioni, M.; Michaelidou, S. S. *Org. Biomol. Chem.* **2013**, *11*, 621–629; (c) Rykowski, A.; Wolinska, E.; Branowska, D.; van der Plas, H. C. *ARKIVOC* **2004**, *iii*, 74–84; (c) Hajós, G.; Riedl, Z.; Kollenz, G. *Eur. J. Org. Chem.* **2001**, 3405–3414; (d) van der Plas, H. C. *J. Heterocycl. Chem*. **2000**, *37*, 427–438; (e) van der Plas, H. C. *Adv. Heterocycl. Chem.*, Vol. 74, Academic Press, London (**1999**).

18. (a) Nishiwaki, N.; Nakanishi, M.; Hida, T.; Miwa, Y.; Tamura, M.; Hori, K.; Tohda, Y.; Ariga, M.; *J. Org. Chem.* **2001**, *66*, 7535; (b) Ariga, M.; Nishiwaki, N.; Miwa, Y.; Tani, K.; Tohda, Y. *Heterocycles*, **1997**, *44*, 81
19. Van der Plas, H. C. *Advances in Heterocyclic Chemistry*. Academic Press: London, **1999**; Vol. 74.
20. a) N. Nishiwaki, *Kochi Univ. Tech. Res. Bull*. **2013**, *10*, 29-35; b) N. Nishiwaki, S. Hirao, J. Sawayama, K. Saigo, *Heterocycles* **2012**, *84*, 115–134.
21. Matsumura, E.; Ariga ,M.; Tohda, Y. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 2413
22. Nishiwaki, N.; Ariga, M. in *Top. Heterocycl. Chem.* 2**007**, *Bioactive Heterocycles II*, Ed. by Eguchi, S., 43–72, Springer, Berlin.
23. (a) Nishiwaki, N.; Hirao, S.; Sawayama, J.; Saigo, K. *Heterocycles* **2012**, *84*, 115–134; (a) Nishiwaki, N.; Tatsumichi, H.; Tamura, M.; Ariga, M. *Lett. Org. Chem.* **2006**, *3*, 629–633; (b) Tohda, Y.; Kawahara, T.; Eiraku, M.; Tani, K.; Nishiwaki, N.; Ariga, M. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2176– 2186; (c) Tohda, Y; Eiraku, M; Nagakawa, T; Usami, Y; Ariga, M; Kawashima, T; Tani, K; Wanatabe, H; Mori.Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2820–2827.
24. Recently, other groups also reported the three component ring transformation using the dinitropyridone **1**. (a) Henry, C; Haupt, A; Turner, S. C. *J. Org. Chem.* **2009**, *74*, 1932–1938; (b) Sagitullina, G. P; Garkushenko, A. K; Vinokurova, Y. O; Nyrkova, V.A; Atavin, E. G; Sagitullin, R. S. *Russ.Org. Chem.* **2009**, *45*, 1045–1049.
25. (a) Nishiwaki, N.; Sugimoto, R.; Saigo, K.; Kobiro, K. *Tetrahedron Lett.* **2013**, *54*, 956–959; (b) Nishiwaki, N.; Nishimoto, T.; Tamura, M.; Ariga, M. *Synlett* **2006**, 1437–1439; (c) Nishiwaki, N.; Yamashita, K.; Azuma, M.; Adachi, T.; Tamura, M.; Ariga, M. *Synthesis.* **2004**, 1996–2000; (d) Nishiwaki, N.; Matsushima, K.; Chatani, M.; Tamura, M.; Ariga, M. *Synlett* **2004**, 703– 707; (e) Nishiwaki, N.; Azuma, M.; Tamura, M.; Hori, K.; Tohda, Y.; Ariga, M. *Chem. Commun*. **2002**, 2170–2171.
26. Tohda, Y.; Ariga, M.; Kawashima, T.; Matsumura, E.; *Bull. Chem. Soc. Jpn.* **1987**, *60*, 201–204.
27. Henry, C.; Haupt, A.; Turner, S. C. J. Org. Chem. **2009**, *74*, 1932–1938.

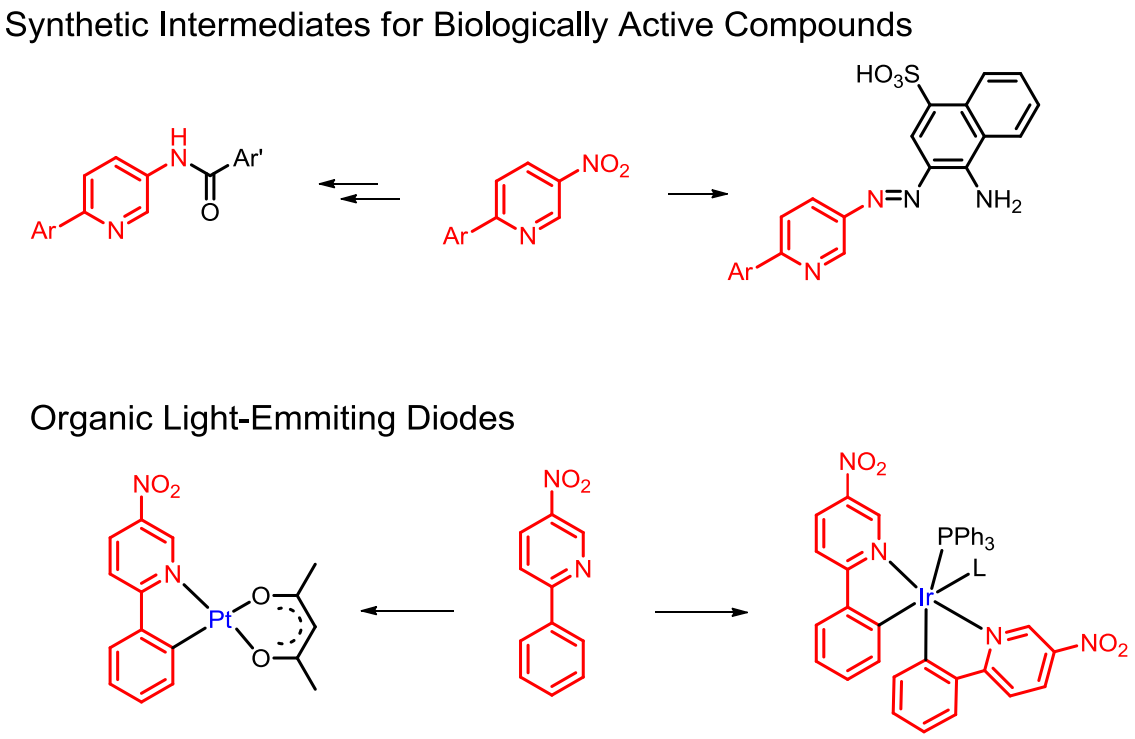
Chapter 2. Synthesis of 2-Aryl-5-Nitropyditines

In this chapter, the TCRTs of dinitropyridone with aromatic ketones and NH_4OAc were investigated, which afforded 2-arylated-5-nitropyridines from good to excellent yields. Furthermore, the application of various kinds of (het)aryl ketones as substrates for this reaction affording the corresponding (het)arylated pyridines was also studied.



1. Introduction

Arylated nitropyridines are widely used for various purposes. Hood and co-workers reported arylated nitropyridines as precursors for synthesis of Wnt inhibitiors.[1] These compounds can be also used as synthetic intermediate for synthesis of inhibitors of stearoyl-CoA desaturase as reported by Bischoff's group;[2] bacterial RNAP inhibitors as reported by Mcphillie and co-workers;[3] drugs for eye diseases and Paget disease as reported by Zafar's group,[4] and so on (Scheme 2). In the literature, the push-pull property of electrons of some nitropyridines substituted with an electron-donating aryl group were also reported.[5] These compounds have widespread applications in pharmaceuticals and functional materials synthesis (Scheme 1). Because of many applications, the synthesis of arylated nitropyridnes has gained increasing attention.

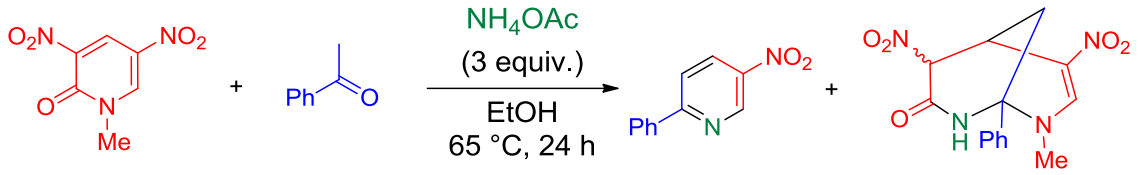


Scheme 1. Synthetic application of 2-arylated-5-nitropyridines

Despite the high utilities of biaryl frameworks as mentioned before, arylation of the pyridine framework is commonly performed by transition-metal catalyzed coupling reaction using phenylboronic acid (Suzuki reaction) or phenylmagnesium bromide (Kumada-Tamao reaction). However, these methods suffer from availability of functionalized halopyridines and coupling partners.[6-10] Especially, electron-deficient aryl groups are not easily introduced to the pyridine framework by these methods, even when severe reaction conditions such as high temperature, long time, and high catalyst loading are used. Moreover, it is difficult to prepare arylated nitropyridines by above-mentioned reactions. Hence, development of efficient, easily manipulated and environmentally benign methods for synthesis of arylated nitropyridines remains a significant challenge.

2. TCRT of dinitropyridone 1 with aromatic ketones in the presence of NH_4OAc affording 2-arylated 5-nitropyridines

2.1 The structural determination of bicyclic compounds



1 **2a** (1 equiv.) **3a** (19%) **4a** (61%)

At first, dinitropyridone **1** was allowed to react with acetophenone (**2a**) in the presence of 3 equiv. of NH_4OAc in ethanol for 24 h at 65 °C. In this reaction, bicyclic product **4a**[11] was isolated in 61% yield besides 19% of 2-phenyl-5-nitropyridine (**3a**).[6] In the ^1H NMR spectrum of **4a**, a pair of several signals were observed between 2 and 6 ppm, which indicates that **4a** is a mixture of two non-aromatic stereoisomers. On the basis of spectral and analytical data, the product **4a** was determined to be a 2,8-diazabicyclo[3.3.1]non-3-ene derivative,[12] which corresponds to the structure formed by insertion of **2a** and a nitrogen atom between the 1- and 2-positions of the dinitropyridone **1**. The bicyclic structure was finally confirmed by X-ray single crystal analysis using product **4b**, which was derived from 4-nitroacetophenone (**2b**). The isomeric structure was assigned by NOESY spectrum; while both protons H^9 and $H^{9'}$ of the *exo*-**4a** showed correlation with H^6, the correlation between $H^{9'}$ and H^6 was not observed in the case of the *endo*-**4a** (Figure 1). The DFT calculations using B3LYP 6-3l+G** showed the *exo*-**4a** was more stable than the *endo*-**4a** with 3.3 kcal/mol.

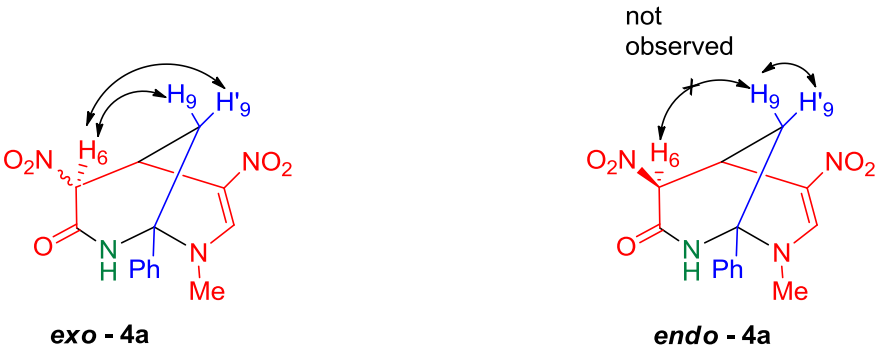


Figure 1. Correlations between H^6 and H^9, $H^{9'}$ of the isomers **4a** in the NOESY spectra

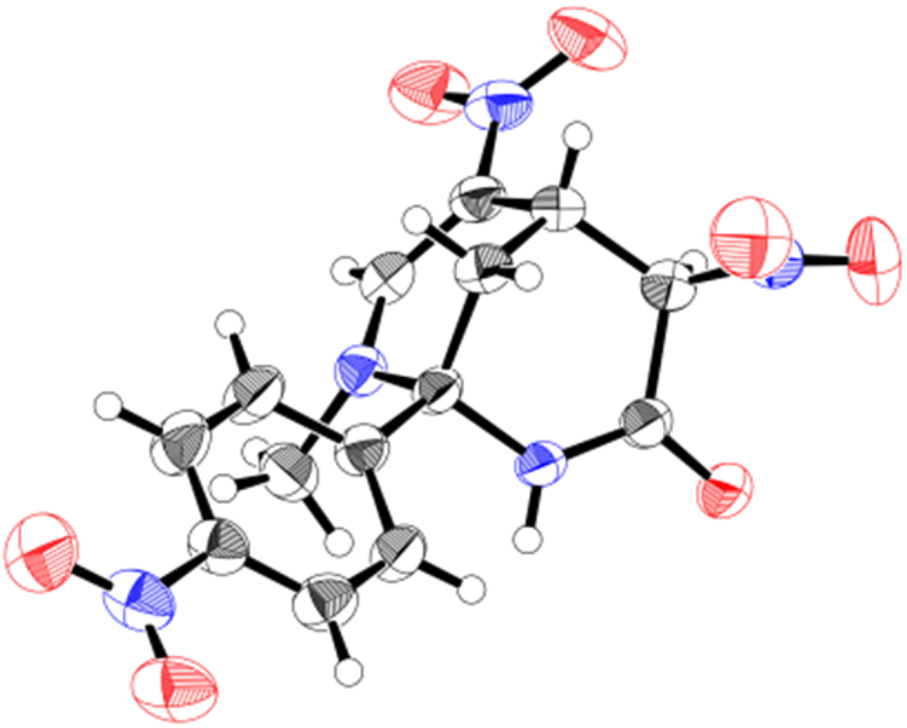
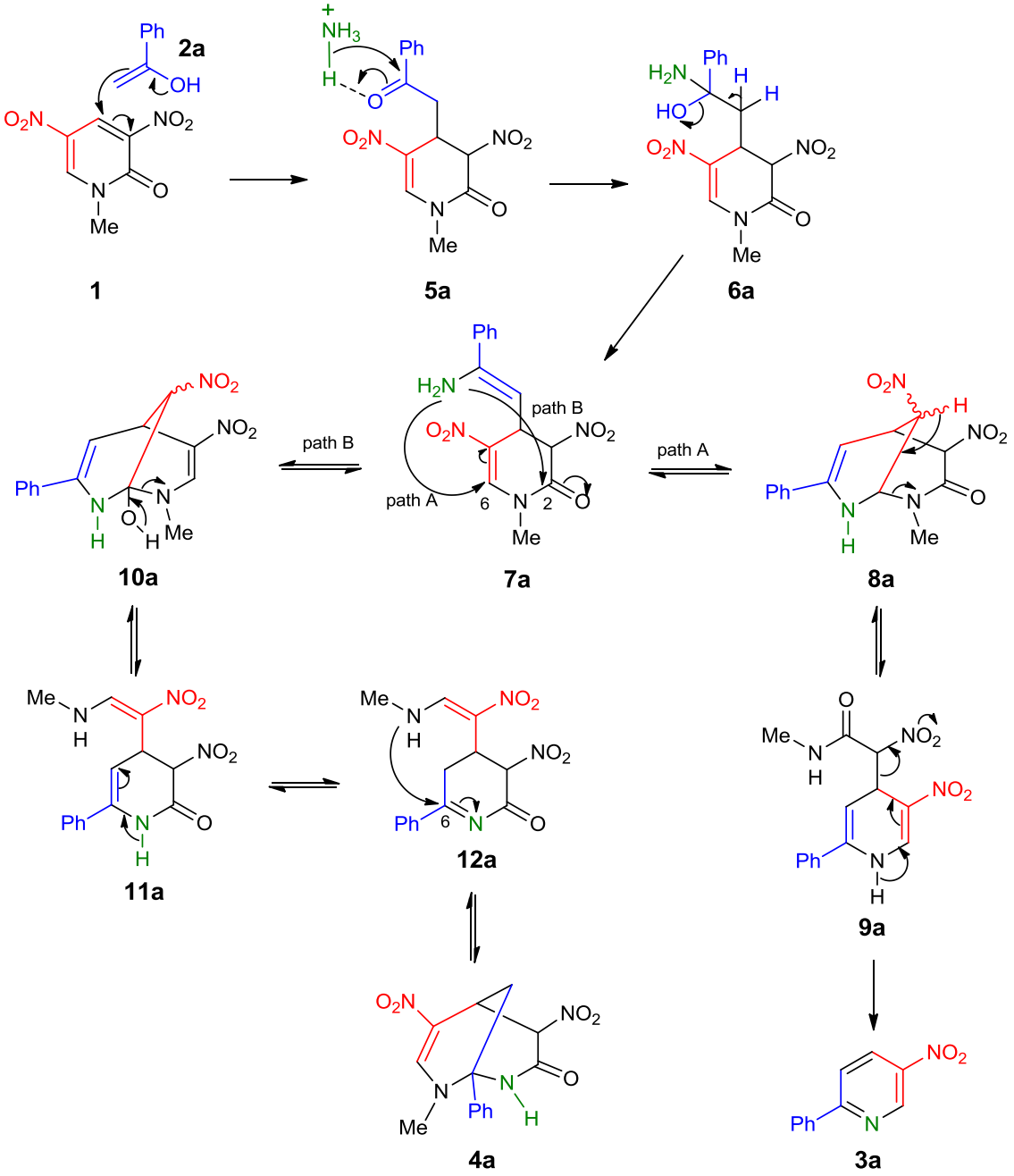


Figure 2. An ORTEP drawing of **4b** with 50% probability thermal ellipsoids

2.2 A plausible mechanism

A plausible mechanism for the formation of the products **3a** and **4a** is illustrated in Scheme 2. The reaction is initiated by the addition the ketone **2a** in an enol form at the 4-position of the dinitropyridone **1** giving the adduct, benzoylmethylpyridone **5a**, which is then converted to the enaminopyridone **7a** as a result of the reaction with an ammonium ion. As another route to **7a**, addition of enamine is also acceptable that is formed in situ from **2a** and NH_4OAc. The enamine **7a** serves as a common intermediate for both products **3a** and **4a**. When the amino group of **7a** attacks at the 6-position (mode a in Scheme 1, path A in Scheme 2), the nitropyridine **3a** is produced by the formation of the bicyclic intermediate **8a**, which undergoes the ring opening reaction and the aromatization accompanied by the elimination of nitroacatamide.[15]



Scheme 2. A plausible mechanism for the formation of products **3a** and **4a**

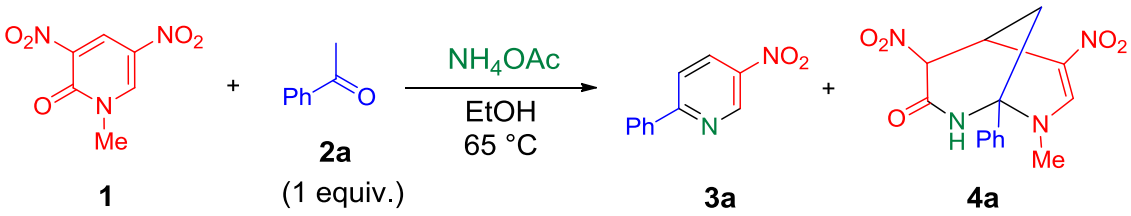
On the other hand, when the amino group of **7a** attacks the carbonyl group at the 2-position (mode b in Scheme 1, path B in Scheme 2),[13,14] the bicyclic intermediate **10a** is formed. Since its bridgehead carbons are connected with three hetero atoms, the ring

opening reaction easily proceeds leading to the intermediate **11a**. Then, the amino group attacks the 6-position of the tautomer **12a** to afford bicyclic product **4a**.

2.3 Study on the effect of amount of ammonium acetate and the reaction time

The selectivity between paths A and B was considerably affected by the amount of NH_4OAc. The nitropyridine **3a** was obtained in only 19% yield, when 3 equiv. of NH_4OAc was used (Table 1, entry 1). The yield of **3a** increased up to 79% accompanied by decreasing in the yield of bicyclic product **4a** with largely increasing the amount of NH_4OAc (entries 2-4).

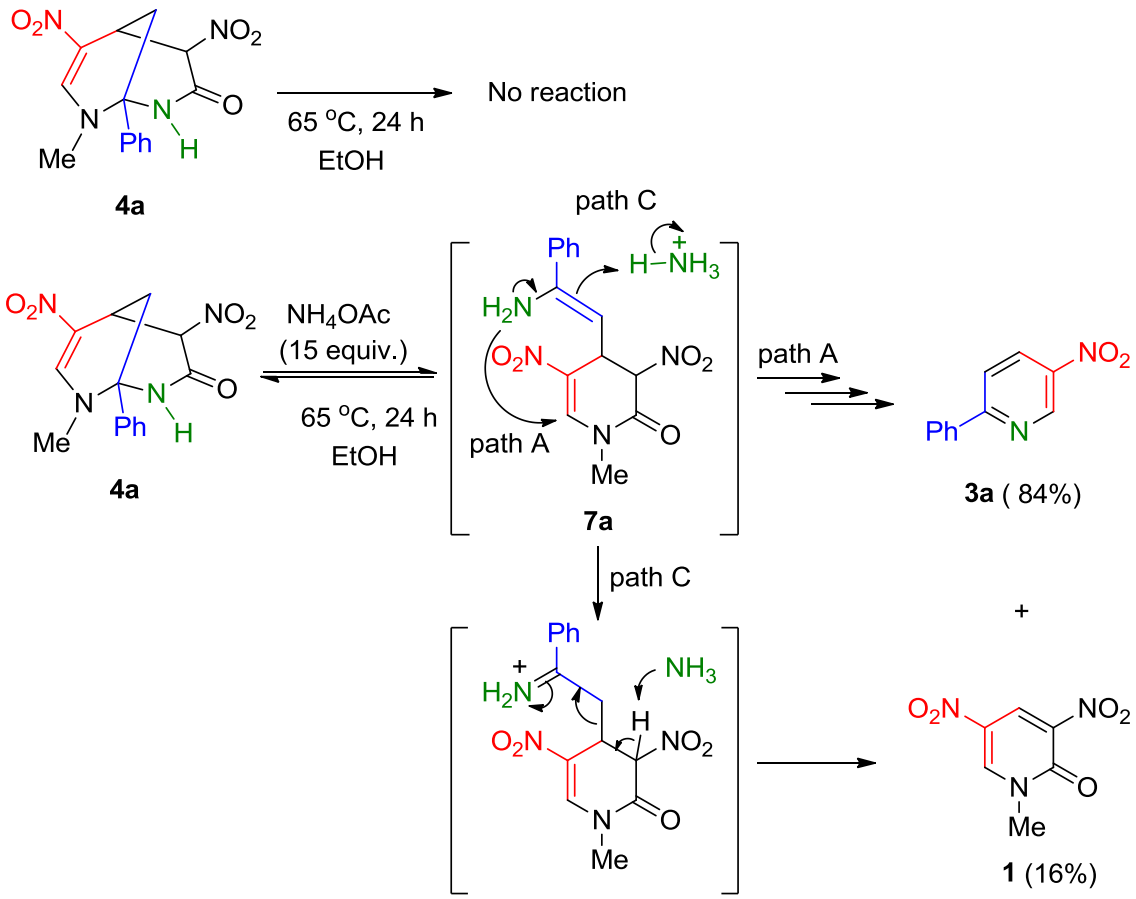
Table 1. Study on the amount of NH_4OAc affecting the ratio of the products



Entry	NH_4OAc (equiv.)	Time (h)	Yield (%)			Ratio of **3a/4a**	Ratio of *exo*/*endo*
			3a	**4a**	**3a+4a**		
1	3	24	19	61	80	24/76	56/44
2	5	24	43	46	89	48/52	59/41
3	10	24	64	25	89	72/28	70/30
4	15	24	79	0	79	100/0	-
5	15	16	75	8	83	90/10	25/75
6	15	8	61	14	75	81/19	46/54
7[a]	5	7	92	5	97	95/5	60/40
8[a]	15	5	90	0	90	100/0	-

[a] Microwave heating was applied.

When the reaction time was shortened, the ratio of **3a/4a** decreased although the total yields were almost similar (entries 4-6). This result indicated that the bicyclic product **4a** was converted to **3a** upon heating the reaction mixture for a longer time. In addition, microwave heating was found to be more effective than conventional heating, which considerably reduced the reaction time and increased the yield of **3a** (entries 7 and 8). As shown in Table 1, the conversion from **4a** to **3a** possibly proceeded under severe conditions. While the bicyclic product **3a** was intact in an ethanol solution at 65 °C, it was converted to the aromatized nitropyridine **3a** and dinitropyridone **1**, in 84% and 16%, respectively, in the presence of NH_4OAc (Scheme 3, paths A and C). This result indicates that there is an equilibrium between **4a** and **7a**.



Scheme 3. Conversion of the bicyclic compound **4a** to nitropyridine **3a** and dinitropyridone **1**

The Mülliken population of the enaminopyridone **7a** determined by DFT calculations revealed that the 2-position is electron-deficient to be attacked by the amino group easily (Figure 2). Thus, the bicyclic product **4a** is predominantly formed via path B in the earlier stage of the reaction; the bicyclic product **4a** is a kinetically controlled product. When the reaction mixture is heated for a longer time, the bicyclic product **4a** is converted to the dinitropyridone **1** via the intermediate **7a** under equilibrium, leading to the stable aromatic product **3a** via path A; the product **3a** is a thermodynamically controlled product. In the present TCRT, competitive thermal decomposition of NH_4OAc also proceeded, and ammonia gas went away from the reaction mixture. When all NH_4OAc were consumed by the TCRT or the decomposition, the TCRT could not proceed anymore because of lacking a nitrogen source. Hence, further increasing the amount of NH_4OAc prolongs real reaction time, which consequently increased the yield of the nitropyridine **3a**.

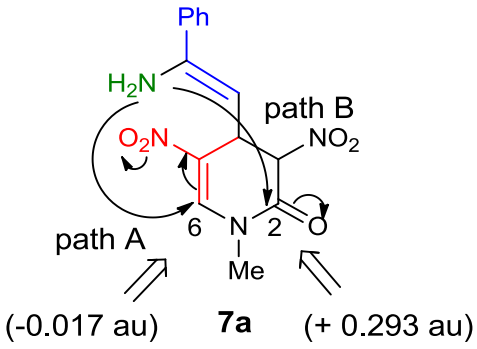


Figure 2. Mülliken population of the enaminopyridone **7a** determined by DFT calculations (DFT B3LYP/6-3l+G**)

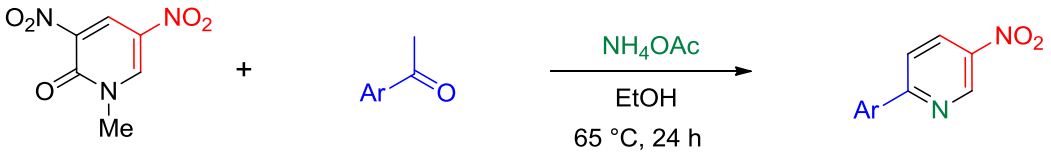
2.4 Study on the effect of electron property of the substituent

The yield of nitropyridines **3** was not only affected by the amount of NH_4OAc but also affected by electron property of the substituent. Therefore, other substituted acetophenones were employed to study the influence of the electronic property of the ketones **2** for the present TCRT (Table 2). The acetophenones **2c** and **2d** having a strong electron-donating methoxy group at the 4- and 2-position revealed high reactivity to afford the corresponding nitropyridines **3c** and **3d** in high yields without the detectable

bicyclic product **4c** and **4d** (entries 3 and 4). In the case of 3-methoxyacetophenone (**2e**), the yield of the nitropyridine **3e** decreased because the 3-methoxy group behaves as an electron-withdrawing group for the carbonyl group by an inductive effect, which prevents the approach to the electron-deficient dinitropyridone **1**. The efficiency of the reaction was improved by increasing the amount of NH_4OAc (entries 5 and 6). 4-Methylacetophenone and 4-chloroacetophenones (**2f** and **2g**) also underwent the TCRT to furnish the corresponding nitropyridines **3f** and **3g** in high yields, respectively (entries 7-9). In the case of the electron-poor 4-nitroacetophenone (**2b**), the nitropyridine **3b** was efficiently formed in 93% yield by using 15 equiv. of NH_4OAc (entries 10 and 11).

The present TCRT was applied to the heterocyclic ketones **2h-m** to afford bihetaryl compounds **3h-m**. While the reaction of the dinitropyridone **1** with 3-acetylpyridine (**2i**) afforded the pyridylpyridine **3i** exclusively, considerable amounts of the bicyclic products **4h** and **4j** were obtained, when the more electron-deficient ketones **2h** and **2j** were employed (entries 12-14). To the contrary, the electron-rich ketones **2k-m** showed high reactivity leading to **3k-m** in good yields, respectively (entries 15-17).

Table 2. Ring transformation with other aromatic ketones **2**



1 **2** (1 equiv.) **3**

Entry	Ar	R		NH_4OAc (equiv.)	Yield (%)		
					3	**4**	**3+4**
1	Ph	H	**a**	5	43	46	89
2	Ph	H	**a**	15	79	0	79
3[a][b]	4-$MeOC_6H_4$	H	**c**	5	95	0	95
4	2-$MeOC_6H_4$	H	**d**	5	94	0	94
5	3-$MeOC_6H_4$	H	**e**	5	74	0	74
6	3-$MeOC_6H_4$	H	**e**	10	97	0	97
7	4-MeC_6H_4	H	**f**	5	88	0	88
8	4-ClC_6H_4	H	**g**	5	84	0	84
9	4-ClC_6H_4	H	**g**	10	96	0	96
10	4-$NO_2C_6H_4$	H	**b**	5	42	15	57
11	4-$NO_2C_6H_4$	H	**b**	15	93	2	95
12	4-Pyridyl	H	**h**	15	66	33	99
13	3-Pyridyl	H	**i**	15	97	0	97
14	2-Pyridyl	H	**j**	15	80	12	92
15	2-Furyl	H	**k**	5	87	0	87
16	2-Thienyl	H	**l**	10	85	0	85
17	2-Pyrrolyl	H	**m**	10	87	0	87
18	Ph	Me	**n**	15	31	0	31
19[a][c]	Ph	Me	**n**	15	98	0	98
20	Ph	Pr	**o**	15	34	0	34
21[a][c]	Ph	Pr	**o**	15	97	0	97

[a] Microwave heating was applied. [b] For 6 h. [c] at 80 °C for 2 h.

3. Conclusions

In summary, the author has successfully developed a highly efficient and general methodology for synthesis of 2-aryl-5-nitropyridines **3** in good to excellent yields using three component ring transformation (TCRT) reaction of the dinitropyridone **1** with the aromatic ketones **2** in the presence of NH_4OAc. In this reaction, the bicyclic product **4** was isolated and the ratio of the nitropyridine **3** and the bicyclic product **4** was found to be affected by the amount of NH_4OAc. Furthermore, the bicyclic product **4** was converted to the nitropyridine **3** via the dinitropyridone **1** under equilibrium.

From environmental and economic points of view, the present TCRT has great advantages. This method requires only simple manipulations, mild conditions during both the reaction and work-up. Especially, solid NH_4OAc is an easily treatable nitrogen source than gaseous ammonia, and unreacted NH_4OAc is easily removed from the reaction mixture by thermal decomposition even when an excess amount of NH_4OAc is used. Furthermore, this method is transition metal free, which enables to omit a purification step for removal of the poisonous transition metal contamination.

This method also facilitates to modify the 2- and 3-positions of the nitropyridines **3** by only changing the ketones **2**, which affords nitropyridines having either an electron-rich or an electron-poor (het)aryl group on demand. Hence, the present ring transformation provides a new methodology for the synthesis of various kinds of (het)arylated nitropyridines, which are not easily prepared by alternative methods.

4. Experimental section and characterization of compounds

4.1 Experimental section

General

The melting points were determined on a Yanaco micro-melting-points apparatus, and were uncorrected. The dinitropyridone **1** was synthesized according to literature procedures.[15] All the reagents and solvents were commercially available and used as received. The ^{1}H NMR spectra were measured on a Bruker Ascend-400 at 400 MHz with TMS as an internal standard. The ^{13}C NMR spectra were measured on a Bruker Ascend-

400 at 100 MHz, and assignments of ^{13}C NMR spectra were performed by DEPT experiments. The IR spectra were recorded on a JASCO FT/IR-4200 spectrometer. The mass spectra and the high resolution mass spectra were measured on a JEOL JMS-DX303HF.

Crystal Structure Determination

X-ray diffraction data were collected on a Rigaku AFC7R diffractometer with graphite monochromatized Mo-Kα radiation. Unit cell parameters were determined by least-squares refinement of 22 automatically centered reflections. The data were corrected for Lorentz and polarization effects. Direct methods (SIR-2008) were used to determine the structure.[30] All calculations were performed using the CrystalStructure[31] crystallographic software package except for refinement, which was performed using SHELXL-97[32]. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed in their idealized positions and refined as rigid atoms with the relative isotropic displacement parameters. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no.CCDC-976536. Copies of the data can be obtained free of charge on application to CCDC, 12 UnionRoad, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).

General procedure of TCRT

To a solution of the nitropyridone **1** (50 mg, 0.25 mmol) in ethanol (5 mL), were added acetophenone (**2a**) (29 µL, 0.25 mmol) and NH_4OAc (96.3 mg, 1.25 mmol), and then the resultant mixture was heated at 65 °C for 24 h. After removal of the solvent, the residue was washed with benzene (3 × 10 mL) to remove unreacted ketone **2a**, which affords a mixture of the nitropyridine **3a** and the bicyclic product **4a**. The mixture was extracted with chloroform (3 × 10 mL) to give almost pure nitropyridine **3a** (21.5 mg, 0.12 mmol, 43%) from the organic layer, the bicyclic product **4a** was obtained as a residue (34.2 mg, 0.12 mmol, 46%). It is noted that all NH_4OAc were consumed or competitively

decomposed during reaction. The TCRT reaction of the dinitropyridone **1** with other ketones was performed in a similar way.

*Conversion of the bicyclic product **4a** to the nitropyridine **3a** and the dinitropyridone **1***

To a solution of the bicyclic product **4a** (30 mg, 0.09 mmol) in ethanol (5 mL), was added NH_4OAc (289 mg, 3.75 mmol), and the mixture was heated at 65 °C for 24 h. After removal of solvent, the residue was extracted with chloroform (10 mL × 3) to give a mixture of the nitropyridine **3a** (15 mg, 0.075 mmol, 84%) and the dinitropyridone **1** (2.8 mg, 0.014 mmol, 16%).

4.2 Characterization of compounds

*2,8-Diaza-2-methyl-4,6-dinitro-7-oxo-1-phenyl-bicyclo[3.3.1]nona-3-ene (**4a**)*

Yellow powder; mp 227–228 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.23-2.46 (m, $2H_{endo}$+$2H_{exo}$), 2.89 (s, $3H_{endo}$+$3H_{exo}$), 2.86 (s, $3H_{endo}$+$3H_{exo}$), 3.96-4.18 (m, $1H_{endo}$+$1H_{exo}$), 5.30 (s, $1H_{endo}$), 6.01 (d, J = 5.2 Hz, $1H_{exo}$), 7.43-7.51 (m, $5H_{endo}$+$5H_{exo}$), 8.47 (s, $1H_{endo}$), 8.55 (s, $1H_{exo}$), 9.91 (s, $1H_{endo}$+$1H_{exo}$); ^{13}C NMR (DMSO-d_6, 100 MHz) *exo*-isomer: δ 31.9 (CH), 35.0 (CH_2), 38.9 (CH_3), 72.2 (C), 87.2 (CH), 120.0 (C), 125.9 (CH), 128.9 (CH), 129.0 (CH), 147.6 (CH), 163.4 (C) (one signal was not observed due to overlapping); *endo*-isomer: δ 31.0 (CH), 32.5 (CH_2), 38.2 (CH_3), 71.8 (C), 84.4 (CH), 119.1 (C), 125.8 (CH), 128.8 (CH), 129.0 (CH), 146.6 (CH), 161.5 (C) (one signal was not observed due to overlapping); MS (EI) *m/z* 318 (M^+, 3), 216 (100), 199 (42), 115 (46), 104 (49), 77 (54); IR (KBr, cm^{-1}): 1357, 1558, 1608, 1702, 3459; HRMS (EI, magnetic field) Calcd for $C_{14}H_{14}N_4O_5$: 318.0964. Found: 318.0965.

*2,8-Diaza-2-methyl-4,6-dinitro-1-(4-nitrophenyl)-7-oxo-bicyclo[3.3.1]nona-3-ene (**4b**)*

Yellow powder (14 mg, 0.38 mmol, Yield 15%); mp 185–187 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.23-2.44 (m, $2H_{endo}$+$2H_{exo}$), 2.90 (s, $3H_{endo}$+$3H_{exo}$), 4.02-4.22

(m, 1H$_{endo}$+1H$_{exo}$), 5.35 (s, 1H$_{endo}$), 6.02 (d, *J* = 4.8 Hz, 1H$_{exo}$), 7.75 (d, *J* = 8.8 Hz, 1H$_{endo}$), 7.76 (d, *J* = 8.8 Hz, 1H$_{exo}$), 8.34 (d, *J*= 8.8 Hz, 1H$_{endo}$), 8.35 (d, *J*= 8.8 Hz, 1H$_{exo}$), 8.47 (s, 1H$_{endo}$), 8.56 (s, 1H$_{exo}$), 10.1-10.2 (br, 1H$_{endo}$+1H$_{exo}$); ^{13}C NMR (DMSO-d_6, 100 MHz) *exo*-isomer δ 31.8 (CH), 32.3 (CH$_2$), 34.7 (CH$_3$), 72.1 (C), 87.1 (CH), 120.0 (2C), 125.9 (CH), 128.9 (CH), 129.0 (CH), 147.6 (CH), 163.4 (C); *endo*-isomer δ 31.0 (CH), 32.5 (CH$_2$), 38.2 (CH$_3$), 71.8 (C), 84.2 (CH), 119.6 (2C), 124.0 (CH), 127.8 (CH), 146.5 (CH), 147.7 (C), 161.5 (C); MS (EI) *m/z* 261 (100), 199 (67), 164 (55), 149 (50), 102 (57); IR (KBr, cm^{-1}) 1349, 1558, 1616, 1693, 3444; HRMS (EI, magnetic field) Calcd for $C_{14}H_{13}N_5O_7$: 363.0815. Found: 363.0813.

*2,8-Diaza-2-methyl-4,6-dinitro-7-oxo-1-(4-pyridyl)bicyclo[3.3.1]nona-3-ene (**4h**)*

Yellow powder (26 mg, 0.083 mmol, Yield 33%); mp 232–233 ˚C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.23-2.44 (m, 2H$_{endo}$+2H$_{exo}$), 2.90 (s, 3H$_{endo}$+3H$_{exo}$), 4.02-4.24 (m, 1H$_{endo}$+1H$_{exo}$), 5.34 (s, 1H$_{endo}$), 6.01 (d, *J* = 5.2 Hz, 1H$_{exo}$), 7.46 (dd, *J* = 1.6, 6.4 Hz, 2H$_{endo}$), 7.51 (dd, *J* = 1.6, 6.4 Hz, 2H$_{exo}$), 8.48 (s, 1H$_{endo}$), 8.56 (s, 1H$_{exo}$), 8.71-8.74 (m, 2H$_{endo}$+2H$_{exo}$), 9.93-10.11 (br, 1H$_{endo}$+1H$_{exo}$); ^{13}C NMR (DMSO-d_6, 100 MHz) *exo*-isomer δ 31.7 (CH), 34.4 (CH$_2$), 37.9 (CH$_3$), 71.1 (C), 87.1 (CH), 120.4 (C), 121.0 (CH), 146.5 (C), 147.4 (CH), 150.5 (CH), 163.5 (C); *endo*-isomer: δ 30.9 (CH), 32.0 (CH$_2$), 37.2 (CH$_3$), 71.3 (C), 84.3 (CH), 119.5 (C), 120.9 (CH), 145.9 (C), 147.4 (CH), 150.4 (CH), 161.5 (C); IR (KBr, cm^{-1}) 1280, 1558, 1612, 1700, 3457; HRMS (EI, magnetic field) Calcd for $C_{13}H_{13}N_5O_5$: 319.0917. Found: 319.0915.

*2,8-Diaza-2-methyl-4,6-dinitro-7-oxo-1-(2-pyridyl)bicyclo[3.3.1]nona-3-ene (**4j**)*

Yellow powder (10 mg, 0.03 mmol, Yield 12%); mp 228–230 ˚C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.24-2.40 (m, 2H$_{endo}$+2H$_{exo}$), 2.85 (s, 3H$_{endo}$), 2.86(s, 3H$_{exo}$), 4.02-4.04 (m, 1H$_{endo}$+1H$_{exo}$), 4.22-4.25 (m, 1H$_{endo}$+1H$_{exo}$), 5.33 (s, 1H$_{endo}$), 6.01 (d, *J* = 5.2 Hz, 1H$_{exo}$), 7.51-7.53 (m, 1H$_{endo}$+1H$_{exo}$), 7.64-7.72 (m, 1H$_{endo}$+1H$_{exo}$), 7.98-8.04 (m, 1H$_{endo}$+1H$_{exo}$), 8.48 (s, 1H$_{endo}$), 8.56 (s, 1H$_{exo}$), 8.68-8.87 (m, H$_{endo}$+H$_{exo}$), 9.67-9.82 (br, 1H$_{endo}$+1H$_{exo}$); ^{13}C NMR (DMSO-d_6, 100 MHz) *exo*-isomer δ 30.9 (CH), 33.0 (CH$_2$), 38.4 (CH$_3$), 72.3 (C), 87.3 (CH), 120.3 (C), 121.4 (CH), 124.4 (CH), 138.1 (CH), 147.2 (CH),

149.1 (C), 149.4 (CH), 163.5 (C); *endo*-isomer δ 30.6 (CH), 31.7 (CH_2), 38.1 (CH_3), 72.0 (C), 84.4 (CH), 121.3 (C), 121.4 (CH), 124.4 (CH), 137.9 (CH), 146.3 (CH), 149.0 (C), 149.3 (CH), 161.5 (C); IR (KBr, cm^{-1}) 1307, 1580, 1612, 1675, 3465; HRMS (EI, magnetic field) Calcd for $C_{13}H_{13}N_5O_5$: 319.0917. Found: 319.0919.

*2-Phenyl-3-propyl-5-nitropyridine (**3o**)*

Yellow powder (58 mg, 0.24 mmol, Yield 97%); mp 90–92 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.2, 14.4 Hz, 3H), 1.65 (tq, J = 7.6, 15.6 Hz , 2H), 2.75 (t, J = 7.6, 15.6 Hz, 2H), 7.48-7.51 (m, 5H), 8.40 (d, J = 2.6 Hz, 1H), 9.32 (d, J = 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.75 (CH_3), 23.67 (CH_2), 34.33 (CH_2), 128.46 (CH), 128.70 (CH), 129.10 (CH), 131.93 (CH), 136.77 (CH), 138.88 (C), 141.90 (C), 143.11 (C), 164.44 (CH); IR (KBr, cm^{-1}) 1346, 1571; HRMS (EI, magnetic field) Calcd for $C_{14}H_{14}N_2O_2$: 242.1055. Found: 242.1052.

5. Reference

1. M. C. Kozlowski, B. J. Morgan, E. C. Linton, *Chem. Soc. Rev*. **2009**, *38*, 3193–3207.
2. T. Guo, A. E. P. Adang, R. E. Dolle, G. Dong, D. Fitzpatrick, P. Geng, K.-K. Ho, S. G. Kultgen, R. Liu, E. McDonald, B. F. McGuinness, K. W. Saionz, K. J. Valenzano, N. C. R. van Straten, D. Xie, M. L. Webb, *Bioorg. Med. Chem. Lett*. **2004,** *14*, 1713–1716.
3. R. G. Carter, B. O. Ashburn, M. R. Naffziger, J. P. Schwartz, *PCT Int. Appl*. (**2008**), WO 2008156656.
4. Y.-L. Zhao, Y. Li, S.-M. Li, Y.-G. Zhou, F.-Y. Sun, L.-X. Gao, F.-S. Han, *Adv. Synth. Cat.* **2011**, *353*, 1543–1550.
5. E. A. Jefferson, P. P. Seth, D. E. Robinson, D. K. Winter, A. Miyaji, L. M. Risen, S. A. Osgood, M. Bertrand, E. E. Swayze, *Bioorg. Med. Chem. Lett*. **2004,** *14*, 5257–5261.
6. a) C. Liu, N. Han, X. Song, J. Qiu, *Eur. J. Org. Chem.* **2010**, 5548–5551; b) G. Kerric, E. L. Grognec, F. Zammattio, M. Paris, J.-P. Quintard, *J. Organometal. Chem.* **2009**, *695*, 103–110.

7. a) A. El Kadib, K. McEleney, T. Seki, T. K. Wood, C. M. Crudden, *ChemCatChem* **2011**, *3*, 1281–1285; b) J. Z. Deng, D. V. Paone, A. T. Ginnetti, H. Kurihara, S. D. Dreher, S. A. Weissman, S. R. Stauffer, C. S. Burgey, *Org. Lett.* **2009**, *11*, 345–347; c) C.-Y. Wang, Y.-H. Liu, S.-M. Peng, J.-T. Chen, S.-T. Liu, *J. Organometal. Chem.* **2007**, *692*, 3976–3983.
8. S.-L. Mao, Y. Sun, G.-A. Yue, C. Zhao, Z.-J. Han, J. Yuan, X. Zhu, Q. Yang, S.-H. Liu, *Org. Biomol. Chem.* **2012**, *10*, 9410–9417.
9. a) A. Kakizuka, S. Hori, H. Ikeda, N. Yoshimura, N. Nakano, T. Shudo, T. Fuchigami, *PCT Int. Appl.* **2012**, WO 2012043891; b) A. Kakizuka, S. Hori, T. Shudo, T. Fuchigami, *PCT Int. Appl.* **2010**, WO 2012014994.
10. M. A. Pena, J. P. Sestelo, L. A. Sarandeses, *J. Org. Chem.* **2007**, *72*, 1271–1275.
11. J. Hood, S. K. Kc, *PCT Int. Appl.* **2013**, WO 2013040215.
12. A. Bischoff, H. Subramanya, K. Sundaresan, S. Sammeta, V. Raju, K. Anil, *US Pat.* **2010**, US 20100160323.
13. M. J. McPhillie, R. Trowbridge, K. R. Mariner, A. J. O'Neill, A. P. Johnson, I. Chopra, C. W. G. Fishwick, *Med. Chem. Lett.* **2011**, *2*, 729–734.
14. S. Zafar, Z. H. Khan, M. S. Khan. *Can. J. Pure Appl. Sci.* **2012**, *6*, 1827–1835.
15. a) N. Nishiwaki, M. Ariga, in *Topics in Heterocycl. Chem.*, Vol. 8, *Bioactive Heterocycles II*, Ed. by S. Eguchi, pp. 43–72, Springer, Berlin (**2007**), and references are cited in; b) Y. Tohda, T. Kawahara, M. Eiraku, K. Tani, N. Nishiwaki, M. Ariga, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2176– 2186.
16. Recently, other groups also reported the three component ring transformation using the dinitropyridone **1**. a) C. Henry, A. Haupt, S. C. Turner, *J. Org. Chem.* **2009**, *74*, 1932–1938; b) G. P. Sagitullina, A. K. Garkushenko, Y. O. Vinokurova, V. A. Nyrkova, E. G. Atavin, R. S. Sagitullin, *Russ.Org. Chem.* **2009**, *45*, 1045–1049.
17. a) N. Nishiwaki, *Kochi Univ. Tech. Res. Bull*. **2013**, *10*, 29-35; b) N. Nishiwaki, S. Hirao, J. Sawayama, K. Saigo, *Heterocycles* **2012**, *84*, 115–134.
18. Y. Tohda, M. Ariga, T. Kawashima, E. Matsumura, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 201–204.
19. Ammonium acetate serves as an excellent nitrogen source in the ring transformation using nitropyrimidinone. a) N. Nishiwaki, T. Nishimoto, M. Tamura, M. Ariga, *Synlett* **2006**, 1437–1439; b) N. Nishiwaki, K. Yamashita, M. Azuma, T.

Adachi, M. Tamura, M. Ariga, *Synthesis* **2004**, 1996–2000; c) N. Nishiwaki, M. Azuma, M. Tamura, K. Hori, Y. Tohda, M. Ariga, *Chem. Commun*. **2002**, 2170–2171.

20. Similar bicyclo[3.3.1]nonane derivatives have been isolated upon treatment of the dinitropyridone **1** with active methylene compounds. a) N. Nishiwaki, K. Kobiro, *Heterocycles* **2010**, *81*, 2139–2142; b) E. Matsumura, M. Ariga, Y. Tohda, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2413–2419.

21. Several synthetic methods for 2,8-diazabicyclo[3.3.1]nonane derivatives have been reported, however, all products are stabilized by a condesed aromatic ring except for single example.[21d] a) J.-T. Lai, P.-Y. Kuo, Y.-H. Gau, D.-Y. Yang, *Tetrahedron Lett.* **2007**, *48*, 7796–7800; b) M. Amat, M. Perez, N. Llor, C. Escolano, F. J. Luque, E. Molins, J. Bosch, *J. Org. Chem.* **2004**, *69*, 8681–8693; c) D. M. Fink, R. C. Allen, *Tetrahedron Lett.* **1992**, *33*, 2103–2106; d) N. R. Hunter, M. Z. Khan, K. Marat, O. A. L. El-Kabbani, L. T. J. Delbaere, *Can. J. Chem.* **1987**, *65*, 137–149; e) M. Hamana, Y. Fujimura, Y. Nawata, *Heterocycles* **1987**, *25*, 235–239.

22. A similar ring transformation participating a carbonyl group was also observed in the reaction of nitropyrimidinone and ketones in the presence of ammonium acetate. N. Nishiwaki, R. Sugimoto, K. Saigo, K. Kobiro, *Tetrahedron Lett.* **2013**, *54*, 956–959.

23. C. B. Baltus, N. J. Press, M. D. Antonijevic, G. J. Tizzard, S. J. Coles, J. Spencer, *Tetrahedron* **2012**, *68*, 9272–9277.

24. a) I. V. Gofman, M. Y. Goikhman, I. V. Podeshvo, E. E. Eliseeva, E. E. Bol'bat, I. V. Abalov, A. V. Yakimanskii, *Russ. J. Appl. Chem.* **2010**, *83*, 1862–1867; b) A. Xia, H. Guo, X. Qiu, M. Ding, L. Gao, *J. Appl. Polym. Sci.* **2006**, *102*, 1844–1851.

25. H. Kawahara, T. Sonoda, H. Saito, H. Arai, *Jpn. Kokai Tokkyo Koho* **2005**, JP 2005029517.

26. a) S. Leroy-Lhez, A. Parker, P. Lapouyade, C. Belin, L. Ducasse, J. Oberle, F. Fages, *Photochem. Photobio. Sci*. **2004**, *3*, 949–959; b) B. Zhang, R. Breslow, *J. Am. Chem. Soc.* **1997**, *119*, 1676–1681.

27. M. J. McPhillie, R. Trowbridge, K. R. Mariner, A. J. O'Neill, A. P. Johnson, I. Chopra, C. W. G. Fishwick, *Med. Chem. Lett.* **2011**, *2*, 729–734.

28. P. L. J. C. Castro, B. E. Terricabras, S. M. Erra, R. E. Navarro, P. S. Fonquerna, F. A. Cardus, T. M. E. Lozoya, *PCT Int. Appl.* **2009**, WO 2009021696.

29. E. A. Prill, S. M. McElvain. *Org. Synth.* **1943**, *2*, 419.

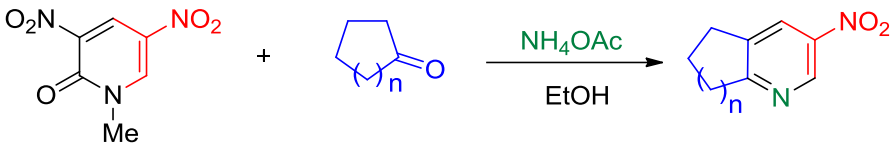
30. M. C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G. .L Cascarano, L. De Caro, C. Giacovazzo, G. Polidori, D. Siliqi, R. Spagna, *SIR2008*. **2007**.

31. Crystal Structure Analysis Package, Rigaku Corporation (2000–2010). *Crystal Structure 4.0.* Tokyo 196-8666, Japan.

32. G. M. Sheldrick, *Acta Cryst. Sect.* **2008**, *A64*, 112–122.

Chapter 3. Synthesis of Nitrated Cycloalka[*b*]pyridines

In this chapter, nitrated cycloalka[*b*]pyridines were prepared by three component ring transformation (TCRT) of dinitropyridone with cycloalkanones and NH_4OAc in high yields. Furthermore, the modifications of the condensed ring such as the size and the introduction of a double bond by only changing the cycloalkanone will also be discussed.

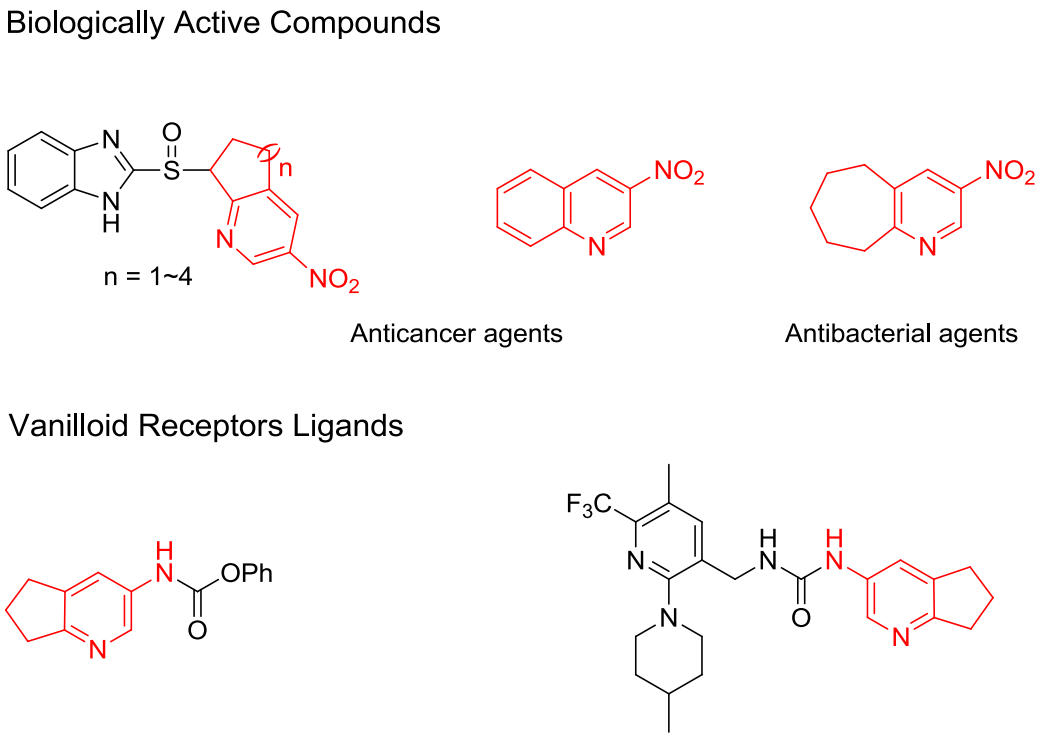


1 **2** **3**

1. Introduction

Nitro compounds consist an important class of organic compounds that are widely used in organic syntheses because of the diverse reactivities. Among them, nitrated cycloalkal[*b*]pyridines have attracted much attention of many researchers because of their unique reaction properties. These compounds have been reported as useful intermediate metacyclophanes,[1] pharmacophores[2] and biologically active compounds.[3] Thus, an efficient synthetic method for cycloalka[*b*]pyridines should also be received much attentions.

The reaction of dinitropyridone **1** with aromatic ketones in the presence of NH_4OAc furnished the nitropyridines in good to excellent yields (as discussed in chapter 2).[6] The present TCRT has a great advantage with regard to the treatability of solid NH_4OAc compared with gaseous ammonia, and extra NH_4OAc is easily removed from the reaction mixture by thermal decomposition. The successful results prompted the author to extend the scope of this method to a series of cyclic ketones **2**, which promisingly affords nitrated cycloalka[*b*]pyridines **3** which are not easily prepared by other methods.



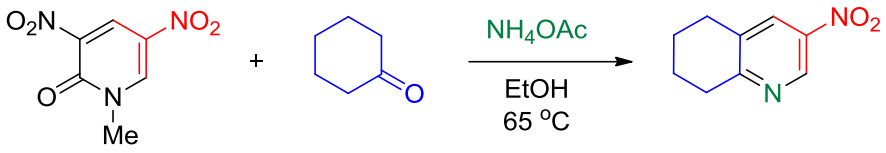
Scheme 1. Synthetic applications of nitrated cycloalka[*b*]pyridines

2. Study on the TCRT of dinitropyridone with cyclic ketones and NH_4OAc affording nitrated cycloalka[*b*]pyridines.

2.1 The optimization of reaction conditions

When the dinitropyridone **1** was reacted with cyclohexanone **2a** in the presence of 5 equiv. of NH_4OAc at 65 ^oC for 24 h, the nitrated cyclohexa[*b*]pyridine **3a**[4] was obtained in a moderate yield, which was due to a shortage of the nitrogen source caused by competitive thermal decomposition of NH_4OAc (Table 1, entry 1).[5] This problem was easily solved by increasing the amount of NH_4OAc and the yield of **3a** was increased up to 95% (Entries 2 and 3). When microwave heating was used, nitropyridine **3a** was afforded efficiently within one hour (entry 4).

Table 1. Synthesis of cyclohexa[*b*]pyridines **3** by TCRT



1 **2a** (1 equiv.) **3a**

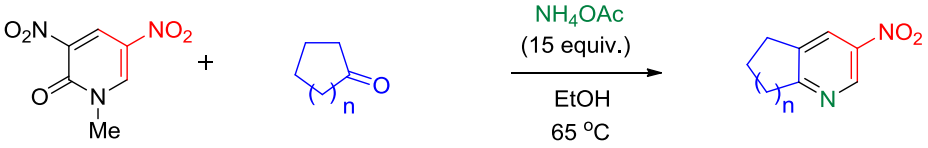
Entry	NH_4OAc (equiv.)	Time (h)	Yield (%)
1	5	24	56
2	10	24	88
3	15	24	95
4[a]	15	1	97

[a]: Microwave was used

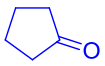
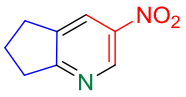
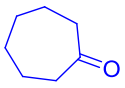
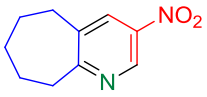
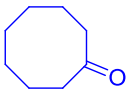
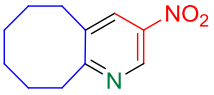
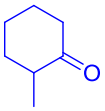
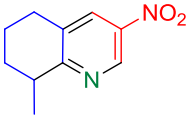
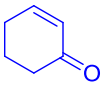
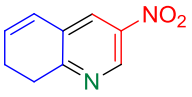
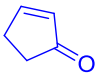
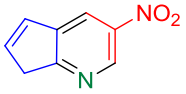
2.2 The application of TCRT to other cyclic ketones

This TCRT was then applied to other cyclic ketones **2b-g** under the optimized conditions for **2a** (Table 2). Cyclopentanone **2b** was less reactive then **2a**, thus affording cyclopentanone **3b** [7] in only 67% yield (entry 1). In such a case, microwave heating was particularly effective, and the reaction reached completion within a short time under microwave heating (entry 2). In contrast, larger cycloalkanones **2c** and **2d** underwent the TCRT efficiently to afford the corresponding cyclohepta- and cyclooctapyridines **3c**[8] and **3d**,[8] respectively in higher yields (entries 3-6). When unsymmetrical 2-methylcyclohexanone **2e** was employed, 8-methylated tetrahydroquinoline **3e** was obtained efficiently (entries 7 and 8). The reaction conditions were also applied to unsaturated cyclic ketone **2f**, thus affording 7,8-dihydroquinoline **3f**, although microwave heating was again necessary for efficient TCRT (entries 9 and 10). In contrast, cyclopentanone **2g** did not undergo TCRT despite the application of microwave heating (entry 11).

Table 2. Application of this TCRT to other cyclicketones



1 **2** (1 equiv.) **3**

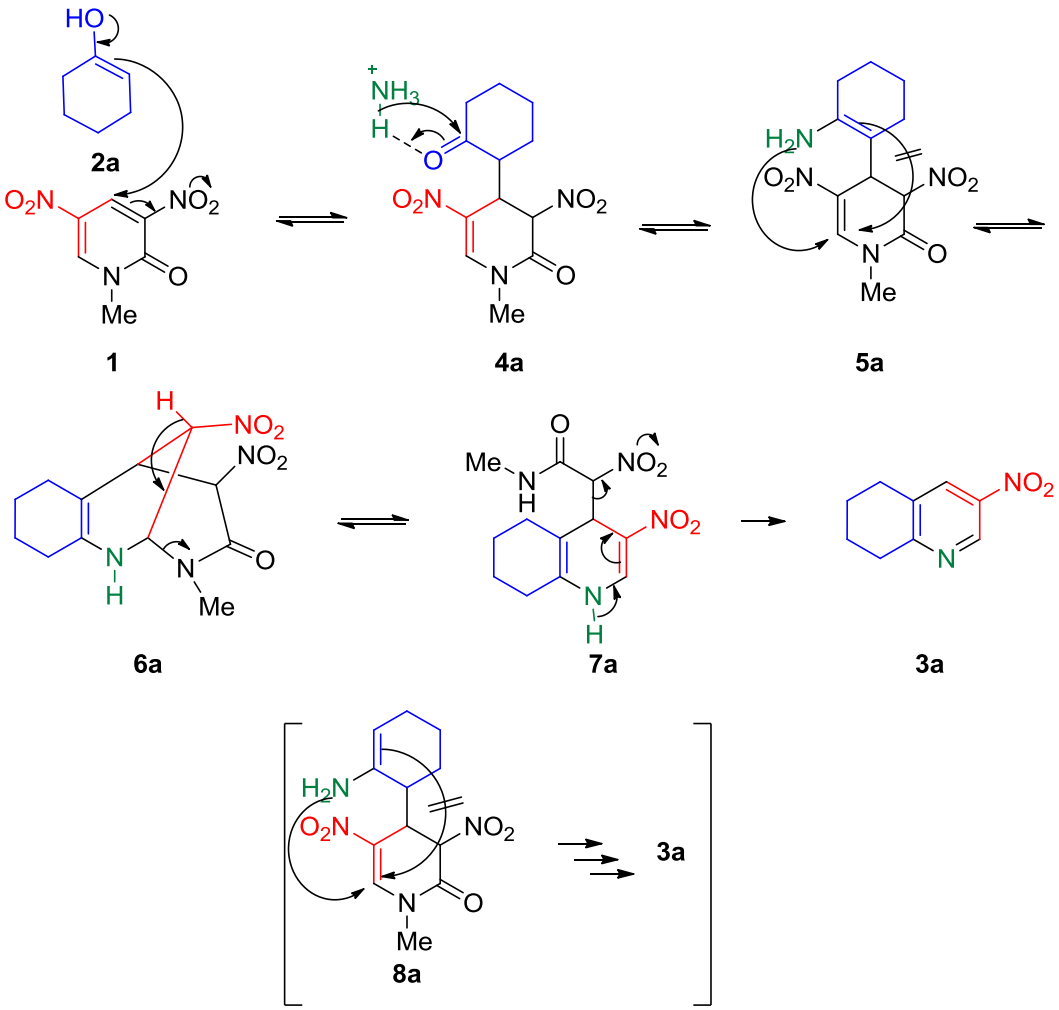
Entry	n		Ketone	Time (h)	Product	Yield (%)
1	1	**b**		24		67
2[a]				2		87
3	3	**c**		24		94
4[a]				1		91
5	4	**d**		24		85
6[a]				1		95
7	2	**e**		24		83
8[a]				2		86
9	2	**f**		24		59
10[a]				3		89
11	1	**g**		4		0

[a]: microwave heating was used

2.3 A plausible mechanism

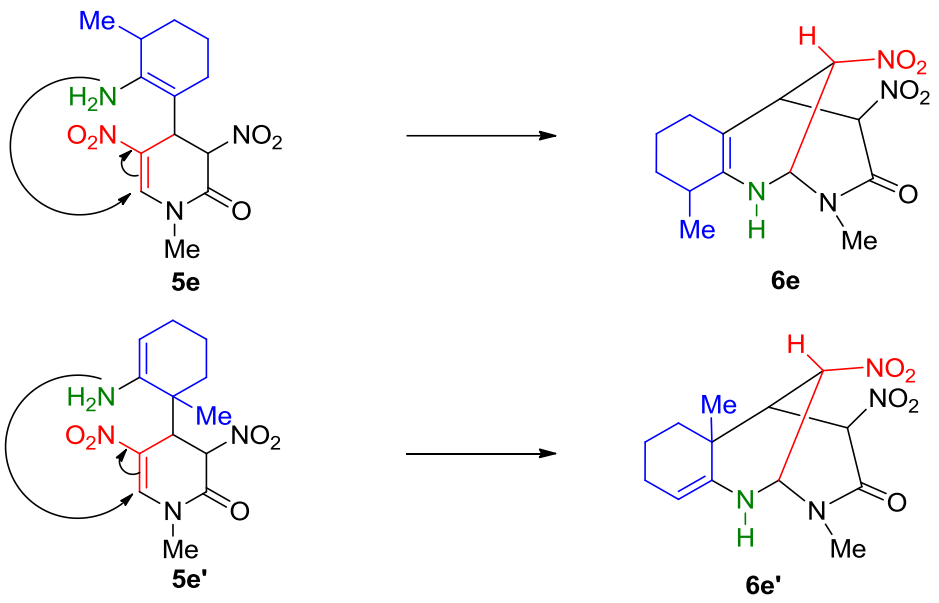
A plausible mechanism for this ring transformation is illustrated in Scheme 2. After addition of the enol form of **2a** at the 4-position of **1**, the adduct **4a** is transformed to the enanine **5a** by the reaction with ammonium ion. The intramolecular attack of the amino group at the 6-position forms the tricyclic intermediate **6a**, from which nitroacetamide is eliminated to afford the nitropyridine **3a** via aromatization of the intermediate **7a**.

Although another reaction path via the enamine **8a** can be considered, the same product **3a** is formed.



Scheme 2. A plausible mechanism for the formation of the condensed nitropyridine **3a**

In the case of unsymmetrical 2-methylcyclohexanone (**2e**), two kinds of intermediate, **6e** and **6e'** are possible (Scheme 3); however, the latter intermediate cannot afford the aromatized product. Therefore, only **3e** is formed via intermediate **6e**. In the reaction using cyclopentanone **2b** and cyclohexenone **2f**, the loss of the flexibility of **5b** and **5f** make the formation of tricyclic intermediates **6b** and **6f** are difficult (Figure 1). In contrast, cyclopentenone **2g** did not afford the ring transformed product **3g** because in this case, the formation of a sterically restricted intermediate is necessary.



Scheme 3. Two plausible intermediates derived from 1-mehtylcyclohexanone **2e**

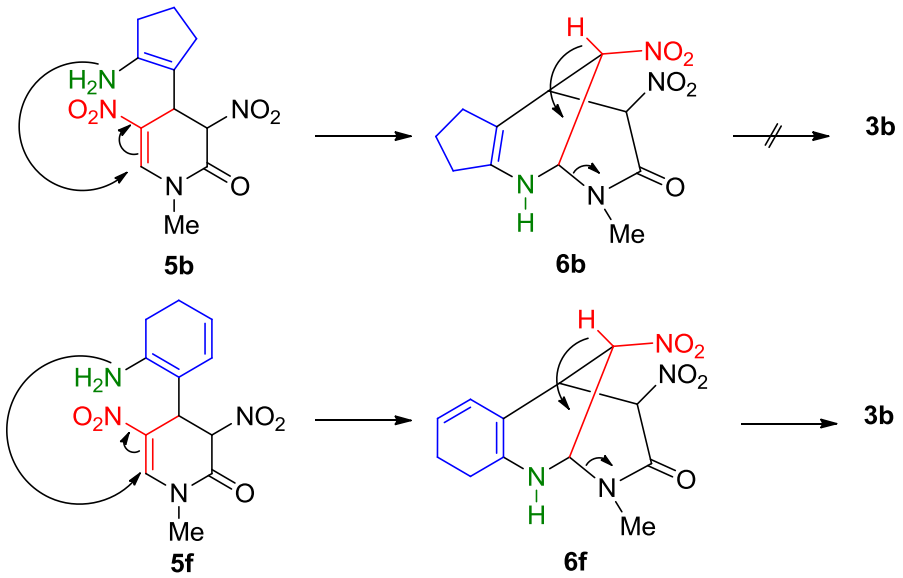


Figure 1. The intermediate **5b** and **5e**

3. Conclusions

In summary, the nitrated cycloalka[*b*]pyridines **3** were efficiently synthesized by TCRT of the dinitropyridone **1** with cyclic ketones **2** in the presence of NH_4OAc. Since the method requires only simple manipulations and mild conditions, it will be a new protocol for the synthesis of [*b*]-fused pyridine frameworks.

4. Experimental section and characterization of compounds

4.1 Experiment section

The melting points were determined on a Yanaco micro-melting-points apparatus, and were uncorrected. The ^{1}H NMR spectra were measured on a Bruker Ascend-400 at 400 MHz with TMS as an internal standard. The ^{13}C NMR spectra were measured on a Bruker Ascend-400 at 100 MHz, and assignment was performed by DEPT experiments. The IR spectra were recorded on a JASCO FT/IR-4200 spectrometer. The high resolution mass spectrum was measured on a JEOL JMS-DX303HF. Microwave heating was performed using Anton-Paar Microwave 300. All the reagents and solvents were commercially available and were used as received.

General procedure of TCRT

To a solution of the dinitropyridone **1** (50 mg, 0.25 mmol) in ethanol (5 mL), cyclohexanone **2a** (26 μL, 0.25 mmol) and NH_4OAc (289 mg, 3.75 mmol) were added, and the resultant mixture was heated at 65 °C on the oil bath for 24 h. After removal of the solvent, the residue was washed with benzene (3 × 10 mL) to afford 5,6,7,8-tetrahydro-3-nitroquinoline (**3a**) (42 mg, 0.24 mmol, 95%) as a yellow powder. The reactions of the dinitropyridone **1** with other ketones **2b-g** were performed in a similar way. When the reaction was conducted using microwave heating, the experiment was conducted in a similar way.

4.2 Characterization of compounds

*7,8-Dihydro-3-nitroquinoline **3f**.*

Yellow powder (40 mg, 89%); mp 57-59 °C. ^{1}H NMR ($CDCl_3$) δ = 2.49 (ddt, J = 2.8, 4.0. 8.4 Hz, 2H), 2.99 (t, J = 8.4 Hz, 2H), 6.57 (dt, J = 4.0, 8.0 Hz, 1H), 6.74 (ddt, J = 0.8, 2.8, 8.0 Hz, 1H), 8.16 (dd, J = 0.8, 2.8 Hz, 1H), 9.19 (d, J = 2.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ = 22.6 (CH_2), 26.5 (CH_2), 128.9 (CH), 129.3 (CH), 131.3 (C), 139.1 (CH), 141.1 (C), 143.3 (CH), 158.8 (C). IR (KBr, cm^{-1}) 1261, 1577, 1509. HRMS (EI, magnetic field) Calcd for $C_9H_8N_2O_2$: 176.0586. Found: 176.0586.

5. Reference

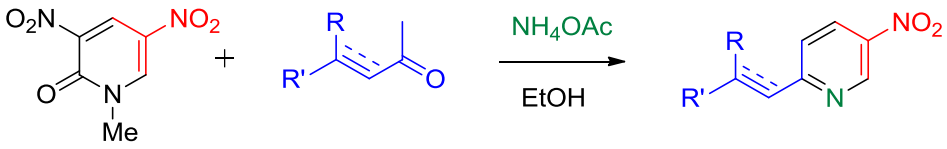
1. (a) Nishiwaki, N. in *Comprehensive Organic Synthesis*, 2nd ed., Vol. 6, 100–130, Elsevier, Oxford, UK (**2014**); (b) Balini, R.; Gabrietti, S.; Palmieri, A.; Petrini, M. *Curr. Org. Chem.* **2011**, *15*, 1482–1506; (c) Ballini, R.; Barboni, L.; Fiorini, D.; Palmieri, A.; Petrini, M. *ARKIVOC* **2006**, *vi*, 127–152; (d) Adams, J. P.; Peterson, J. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3695–3705.
2. Nishiwaki, N.; Ariga, M. in *Topics in Heterocyclic Chemistry*, *Bioactive Heterocycles* II, *Vol. 8*, Ed. by Eguchi, S., 43–72, Springer, Berlin (**2007**); (b) Tohda, Y.; Kawahara, T.; Eiraku, M.; Tani, K.; Nishiwaki, N.; Ariga, M. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2176–2186; (c) Tohda, Y.; Eiraku, M.; Nakagawa, T.; Usami, Y.; Ariga, M.; Kawashima, T.; Tani, K.; Wanatabe, H.; Mori.Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2820–2827.
3. Nishiwaki, N.; Hirao, S.; Sawayama, J.; Saigo, K. *Heterocycles* **2012**, *84*, 115–134.
4. (a) Henry, C; Haupt, A.; Turner, S. C. *J. Org. Chem.* **2009**, *74*, 1932–1938; (b) Sagitullina, G. P.; Garkushenko, A. K.; Vinokurova, Y. O.; Nyrkova, V. A.; Atavin, E. G.; Sagitullin, R. S. *Russ. J. Org. Chem.* **2009***, 45,* 1045–1049.
5. Tohda, Y.; Ariga, M.; Kawashima, T.; Matsumura, E. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 201–204.
6. The TCRT of 3-methyl-5-nitro-4-pyrimidinone with ketone in the presence of NH_4OAc efficiently proceeds to afford pyrimidines, nitropyridones and aminopyridines. (a) Nishiwaki, N.; Sugimoto, R.; Saigo, K.; Kobiro, K. *Tetrahedron*

Lett. **2013**, *54*, 956–959; (b) Nishiwaki, N.; Yamashita, K.; Azuma, M.; Adachi, T.; Tamura, M.; Ariga, M. *Synthesis* **2004**, 1996–2000; (c) Nishiwaki, N.; Azuma, M.; Tamura, M.; Hori, K.; Tohda, Y.; Ariga, M. *Chem. Commun*. **2002**, 2170–2171.

7. Le, T. S.; Asahara, H.; Kobiro, K.; Sugimoto, R.; Saigo, K.; Nishiwaki, N. *Asian. J. Org. Chem.* **2014**, *3*, 297–302.
8. Yamada, S.; Goto, T.; Yamaguchi, T.; Aihara, K.; Kogi, K.; Narita, S. *Chem. Pharm. Bull*. **1995**, *43* 421–431.
9. Yamada, S.; Goto, T.; Shimanuki, E.; Narita, S. *Chem. Pharm. Bull*. **1994**, *42*, 718–720.
10. Marcelis, A. T. M.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 2693–2702.

Chapter 4. Synthesis of 2-Alkenyl/Alkynyl 5-Nitropyridines

In this chapter, a metal-free, facile, and efficient protocol for synthesizing a series of 2-alkenyl/alkynyl-5-nitropyridines **3** was developed by using a three-component ring transformation of dinitropyridone **1** with α,β-unsaturated ketones **2** and NH_4OAc. As 2-alkenyl/alkynyl-5-nitropyridines **3** are not easily prepared by Heck or Sonogashira reactions, this method will be a supplementary to these reactions.



1 **2** **3**

1. Introduction

Among of nitroaromatic compounds, 2-alkenyl-5-nitropyridines[1-3] and 2-alkynyl-5-nitropyridines[4] are widely employed as precursors for pharmaceuticals and biologically active compounds. In addition, alkynylnitropyridines are often found in nonlinear optical materials[5] and organic semiconductors.[6]

Regulors of Vasolin Containing Protein (VCP) Antimicribial activity

Scheme 1. Synthetic application of 2-alkenyl-5-nitropyridines

Although the Heck,[7] Suzuki,[8] Stille,[3,9] and Sonogashira[10,11] reactions are used as common protocols for alkenylation/alkynylation, poisonous and expensive transition

metals should be used and a purification step to avoid metal contamination of the products is necessary. In addition, the substrates for these reactions, 2-halo-5-nitropyridines, are commonly prepared by halogenation of 5-nitro-2-pyridone.[11,12] 2-Alkenyl-5-nitropyridines are also available by condensation reactions using 5-nitropyridine-2-carbaldehydes[13] or 2-methyl-5-nitropyridines.[14] However, somewhat troublesome multi-step reactions are necessary for preparation of these starting materials. Therefore, the development of a metal-free, facile, and efficient economical methodology for the synthesis of alkenyl/alkynylpyridines is still challenging.

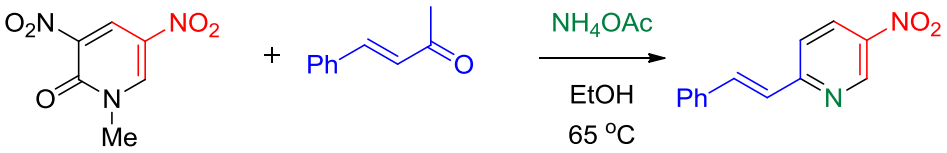
In the author's course of study on the TCRT of dinitropyridone, the scope of substrates was extended to a series of α,β-unsaturated ketones **2**, which facilitaes the introduction of an alkenyl or an alkynyl group into the nitropyridine framework without using any transition metal.

2. Study on the TCRT of dinitropyridone and α,β-unsaturated ketones and ammonium acetate affording 2-alkenyl/alkynyl 5-nitropyridines

2.1 The optimization of reaction conditions

Dinitropyridone **1** was heated with 4-phenyl-3-buten-2-one (**2a**) at 65 ˚C for 24 h in the presence of 15 equivalents of NH_4OAc. After removal of the solvent, the residue was washed with benzene (3 × 10 mL) to remove unreacted ketone **2a**, and was treated with column chromatography on silica gel (eluent: hexane/ethyl acetate = 95/5) to afford 5-nitro-2-(2-phenylethenyl)pyridine (**3a**)[7] in 21% yield (Table 1, entry 1). In this TCRT, the competitive thermal decomposition of NH_4OAc proceeds, and gaseous ammonia escapes from the reaction mixture, which depletes the nitrogen source. Thus, when all NH_4OAc is consumed by TCRT or thermal decomposition, the reaction cannot proceed further. Indeed, the low yield of nitropyridine **3a** was improved by increasing the amount of NH_4OAc, which substantially prolonged the reaction time (Table 1, entries 2 and 3). In addition, microwave heating was found to be more effective than conventional heating to increase the yield of **3a** within shorter reaction time (entry 4).

Table 1. TCRT of dinitropyridone **1** with 4-phenyl-3-buten-2-one (**2a**) and NH_4OAc

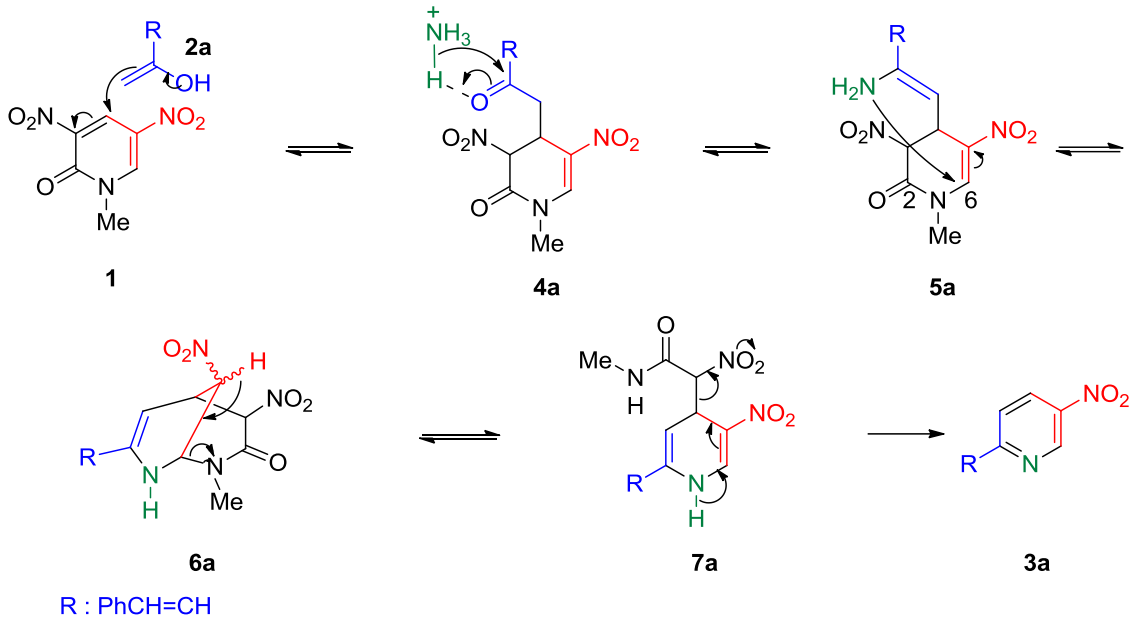


Entry	NH_4OAc (equiv.)	Time (h)	Temp. (°C)	Yield (%)	Recovery of **1** (%)
1	15	24	65	21	68
2	20	24	65	54	32
3	30	24	65	72	0
4[a]	15	4	80	82	trace

[a] Microwave heating was used.

2.2 A plausible mechanism

This TCRT is considered to proceed as illustrated in Scheme 2. The enol form of **2a** attacks the 4-position of dinitropyridone **1** to afford the adduct intermediate **4a**, which is then converted to enamine **5a** by reaction with ammonium ion.[15,16] The amino group of **5a** intramolecularly attacks the 6-position, leading to bicyclic product **5a**. After a ring opening reaction of **6a**, the elimination of nitroacetamide accompanied by aromatization of intermediate **7a** affords alkenylated pyridine **3a**.

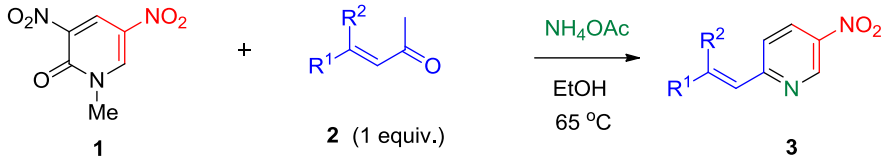


Scheme 2. A plausible mechanism for the formation of 2-ethenyl-5-nitropyridine **3a**

2.3 The application of TCRT to other vinyl ketones

The application of this TCRT to other vinyl ketones **2b-f** was also studied. Substituted styryl ketones **2b** and **2c** underwent TCRT to afford the corresponding alkenylated pyridines **3b** and **3c**, respectively (Table 2). Among styryl ketones **2a-c**, methoxy substituted ketone **2b** revealed higher reactivity because electron-rich ketone **2b** can easily approach electron-poor dinitropyridone **1**. When aliphatic ketone **2d** was employed, the reaction mixture was complex and alkenylpyridine **3d** was not detected (entries 5 and 6). The reaction of mesityl oxide **2e** also afforded a complex mixture, from which alkenylpyridine **3e** was isolated in low yield (entry 7). Although microwave heating was somewhat effective for increasing the yield of **3e**, the yield was still low because of side reactions and the instability of product **3e** (entry 8). These problems were solved by employing more bulky alkyl group to afford alkenylpyridine **3f** in high yield (entries 9 and 10).

Table 2. Synthesis of 2-alkenyl-5-nitropyridines **3**



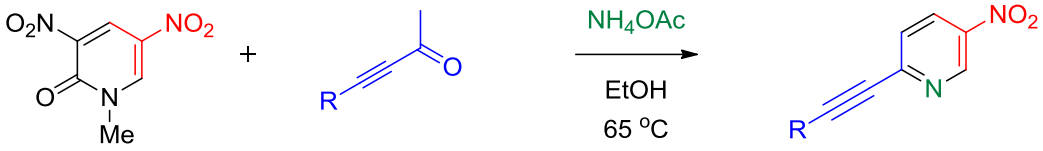
Entry	R^1	R^2		NH_4OAc (equiv.)	Time (h)	Tem. (°C)	Yield (%)
1	p-$MeOC_6H_4$	H	**b**	30	24	65	94
2[a]	p-$MeOC_6H_4$	H	**b**	15	3	80	76
3	p-ClC_6H_4	H	**c**	30	24	65	63
4[a]	p-ClC_6H_4	H	**c**	30	4	80	75
5	H	H	**d**	30	24	65	0
6[a]	H	H	**d**	30	2	80	0
7	Me	Me	**e**	30	24	65	18
8[a]	Me	Me	**e**	15	2	80	25
9	2,6,6-trimethylcyclohexenyl	H	**f**	30	24	65	68
10[a]	2,6,6-trimethylcyclohexenyl	H	**f**	30	6	80	79

[a]: Microwave heating was used.

2.4 Synthesis of 2-alkynyl-5-nitropyridines

This TCRT also facilitated alkynylation of the nitropyridine framework by using alkynyl ketones as a substrate. Both aromatic and aliphatic alkynyl ketones **8a** and **8b** underwent TCRT to afford **9a**[11,17] and **9b**, in good yields, respectively (Table 3, entries 1-4). Next, the ring transformation using trimethylsilylethynyl ketones **8c** was also possible to yield **9c**,[11] which is regarded as an equivalent of the unsubstituted ethynyl group **9d** (R = H). [17] As a results, desilylation also proceeded under the employed reaction conditions to afford a mixture of **9c** and **9d** with high total yield (entries 5 and 6).

Table 3. Synthesis of 2-alkynyl-5-nitropyridines **9**



1 **8** (1 equiv.) **9**

Entry	R		NH_4OAc (equiv.)	Time (h)	Temp. (°C)	Yield (%)
1	Ph	**a**	20	24	65	83
2[a]	Ph	**a**	15	3	80	87
3	Et	**b**	20	24	65	52
4[a]	Et	**b**	15	3	80	80
5	Me_3Si	**c**	20	24	65	ND
6[a]	Me_3Si	**c**	15	4	80	42

[a]: Microwave heating was used.

3. Conclusions

In summary, a novel method for the synthesis of alkenylated/alkynylated nitropyridines **3** and **9** was developed through the TCRT of dinitropyridone **1** with unsaturated ketones **2** and NH_4OAc. This method requires only simple manipulations during both the reaction and work-up. Moreover, this method is metal-free, which enables the omission of a purification step for removing poisonous transition metal contamination and reduces the cost of preparation. Hence, this TCRT is considered supplementary to other methods, including the Heck and Sonogashira reactions.

4. Experimental section and characterization of compounds

4.1 Experimental section

The melting points were determined on a Yanaco micro-melting-points apparatus, and were uncorrected. The ^{1}H NMR spectra were measured on a Bruker Ascend-400 at 400 MHz with TMS as an internal standard. The ^{13}C NMR spectra were measured on a Bruker Ascend-400 at 100 MHz, and assignment was performed by DEPT experiments. The IR spectra were recorded on a JASCO FT/IR-4200 spectrometer. The high resolution mass spectrum was measured on a JEOL JMS-DX303HF. All the reagents and solvents were commercially available and were used as received.

General procedure of TCRT:

To a solution of the dinitropyridone **1** (50 mg, 0.25 mmol) in ethanol (10 mL), 4-phenyl-3-buten-2-one (**2a**) (36.5 mg, 0.25 mmol) and NH_4OAc (578 mg, 7.5 mmol) were added, and the resultant mixture was heated at 65 °C for 24 h. After removal of the solvent, the residue was washed with benzene (3 × 10 mL) to remove unreacted ketone **2a** and treated with column chromatography on silica gel (eluent: hexane/ethyl acetate = 95/5) to afford 5-nitro-2-(2-phenylethenyl)pyridine (**3a**) (41 mg, 0.18 mmol, 72%) as a yellow powder. The reactions of the dinitropyridone **1** with other ketones **2b-f** or **8a-c** were performed in a similar way.

4.2 Characterization of compounds

*2-(2-Phenylethenyl)-5-nitropyridine (**3a**)*

Yellow powder (6.3 mg, 0.21 mmol, 82%). ^{1}H NMR ($CDCl_3$) δ = 7.21 (d, J = 16.0 Hz, 1H), 7.38-7.43 (m, 3H), 7.47 (d, J = 8.4 Hz, 1H), 7.62 (dd, J = 1.6, 8.4 Hz, 2H), 7.85 (d, J = 16.0 Hz, 1H), 8.43 (dd, J = 2.8, 8.4 Hz, 1H), 9.40 (d, J = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 121.6 (CH), 125.8 (CH), 127.8 (CH), 128.3 (CH), 128.9 (CH), 130.6 (CH), 135.6 (C), 138.1 (CH), 160.9 (C), 142.4 (C), 145.4 (CH), 138.9 (C).

*2-[2-(4-Methoxyphenyl)ethenyl]-5-nitropyridine (**3b**)*

Yellow powder (60.8 mg, 0.24 mmol, 94%); mp 168-170 °C. ^{1}H NMR ($CDCl_3$) δ = 3.86 (s, 3H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 16.0 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.82 (d, *J* = 16.0 Hz, 1H), 8.40 (dd, *J* = 2.4, 8.4 Hz, 1H), 9.38 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 55.4 (CH_3), 114.4 (CH), 121.2 (CH), 123.6 (CH), 128.5 (C), 129.3 (CH), 131.7 (CH), 137.8 (CH), 145.1 (C), 145.4 (CH), 160.9 (C), 161.4 (C). IR (KBr, cm^{-1}) 1343, 1508, 1569. HRMS (EI, magnetic field) Calcd for $C_{14}H_{12}N_2O_3$: 256.0848. Found: 256.0844.

*2-[2-(4-Chlorophenyl)ethenyl]-5-nitropyridine (**3c**):*

Yellow powder (49 mg, 0.19 mmol, 75%); mp 169-171 °C. ^{1}H NMR ($CDCl_3$) δ = 7.19 (d, *J* = 16.0 Hz, 1H), 7.39 (d, *J* = 6.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 6.4 Hz, 2H), 7.84 (d, *J* = 16.0 Hz, 1H), 8.46 (dd, *J* = 2.4, 8.4 Hz, 1H) 9.41 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 121.8 (CH), 126.2 (CH), 128.9 (CH), 129.2 (CH), 131.8 (CH), 134.1 (C), 135.4 (C), 136.7 (CH), 142.5 (C), 145.5 (CH), 160.6 (C). IR (KBr, cm^{-1}) 1347, 1515.

*2-(2-Methylpropen-1-yl)-5-nitropyridine (**3e**):*

Because of the instability of the product **3e**, we could not obtain pure **3e**. ^{1}H NMR ($CDCl_3$) δ = 1.13 (s, 6H), 5.03 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 8.36 (dd, *J* = 2.8, 8.4 Hz, 1H), 9.33 (d, *J* = 2.8 Hz, 1H).

*2-[2-(2,6,6-Trimethylcyclohexen-1-yl)ethenyl]-5-nitropyridine (**3f**):*

Orange liquid (54 mg, 0.20 mmol, 79%). ^{1}H NMR ($CDCl_3$) δ = 1.12 (s, 6H), 1.50-1.53 (m, 2H), 1.64-1.67 (m, 2H), 1.83 (s, 3H), 2.10 (t, *J* = 6.4 Hz, 2H), 6.58 (d, *J* = 16.0 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 16.0 Hz, 1H), 8.38 (dd, *J* = 2.8, 8.4 Hz, 1H), 9.36 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 19.0 (CH_2) 21.9 (CH_3), 28.9 (CH_3), 33.5 (CH_2), 34.3 (C), 39.8 (CH_2), 120.8 (CH), 129.8 (CH), 131.6 (CH), 134.3 (C), 137.0 (C), 138.0 (CH), 142.1 (C), 145.4 (CH), 161.6 (C). HRMS (ESI^+, magnetic field) Calcd for $C_{16}H_{21}N_2O_2$: 273.1597. Found: 273.1603.

*2-Phenylethynyl-5-nitropyridine (**9a**)*[2,3]

^{1}H NMR ($CDCl_3$) δ = 7.38-7.46 (m, 3H), 7.63 (dd, *J* = 1.6, 8.0 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 1H), 8.47 (dd, *J* = 2.4, 8.8 Hz, 1H), 9.43 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 87.7 (C), 94.9 (C), 121.1 (C), 126.9 (CH), 128.6 (CH), 130.1 (CH), 131.3 (CH), 132.4 (CH), 142.6 (C), 145.5 (CH), 148.8 (C).

*2-Butyn-1-yl--5-nitropyridine (**9b**):*

Yellow power (35 mg, 0.20 mmol, 80%); mp = 87-89 ºC ^{1}H NMR ($CDCl_3$) δ = 1.29 (t, *J* = 7.6 Hz, 3H), 2.53 (q, *J* = 7.6 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 1H), 8.41 (dd, *J* = 2.8, 8.8 Hz, 1H), 9.30 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 13.1 (CH_3), 13.3 (CH_2), 79.1 (C), 98.1 (C), 126.7 (CH), 132.1 (CH), 142.4 (C), 145.3 (CH), 149.3 (C). IR (KBr, cm^{-1}) 1353, 1516, 1590, 3038.

*2-(2-Trimethylsilyl)ethynyl-5-nitropyridine (**9c**)*[2,4,5] (total 46.2 mg, 0.21 mmol, 84%): in the reaction mixture, product **9c** was obtained in only 24% because of the elimination of -Si(CH_3)$_3$ group, leading to the formation of 2-ethynyl-5-nitropyridine (**9d**) in 60 %. After column chromatography, only compound **9d** was obtained.

^{1}H NMR ($CDCl_3$) δ = 0.26 (s, 9H), 7.55 (d, *J* = 8.8 Hz, 1H), 8.38 (dd, *J* = 2.4, 8.8 Hz, 1H), 9.30 (d, *J* = 2.4 Hz, 1H).

*2-Ethynyl-5-nitropyridine (**9d**)*[6]

^{1}H NMR ($CDCl_3$) δ = 3.46 (s, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 8.47 (dd, *J* = 2.4, 8.8 Hz, 1H), 9.42 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 81.4 (C), 82.3 (CH), 127.5 (CH), 131.4 (CH), 131.7 (C), 145.4 (CH), 147.6 (C).

5. Reference

1. Recent reports are shown in ref. 1-3: S. P. Hameed, M. Chinnapattu, G. Shanbag, P. Manjrekar, K. Koushik, A. Raichurkar, V. Patil, S. Jatheendranath, S. S Rudrapatna, S. P. Barde, Ni. Rautela, D. Awasthy, S. Morayya, C. Narayan, S. Kavanagh, R. Saralaya, S. Bharath, P. Viswanath, K. Mukherjee, B. Bandodkar, A. Srivastava, V. Panduga, J.

Reddy, K. R. Prabhakar, A. Sinha, M. B. Jiménez-Díaz, M. S. Martínez, I. Angulo-Barturen, S. Ferrer, L. M. Sanz, F. J. Gamo, S. Duffy, V. M. Avery, P. A. Magistrado, A. K. Lukens, D. F. Wirth, D. Waterson, V. Balasubramanian, P. S. Iyer, S. Narayanan, V. Hosagrahara, V. K. Sambandamurthy, S. Ramachandran, *J. Med. Chem.* **2014**, *57*, 5702.

2. V. Birault, A. J. Campbell, S. Harrison, J. Le, L. Shukla, PCT Int. Appl. WO 2013160419, **2013**; R. Frank, T. Christoph, B. Lesch, J. Lee, PCT Int. Appl. WO 2013013817, 2013; A. Kakizuka, S. Hori, T. Shudo, T. Fuchigami, PCT Int. Appl. WO 2012014994, **2012**.

3. J. L. Yap, X. Cao, K. Vanommeslaeghe, K.-Y. Jung, C. Peddaboina, P. T. Wilder, A. Nan, A. D. MacKerell, W. R. Smythe, S. Fletcher, *Org. Biomol. Chem.* **2012**, *10*, 2928

4. Recent reports: S. Hoelder, J. Blagg, S. Solanki, H. Woodward, S. Naud, V. Bavetsias, P. Sheldrake, P. Innocenti, J. Cheung, B. Atrash, PCT Int. Appl. WO 2014037750, 2014; A. G. Cole, R. A. James, Y. Shao, J. J. Letourneau, J. G. Quintero, C. M. Riviello, L Zhi, PCT Int. Appl. WO 2013025628, 2013; D. A. Coates, R. Gilmour, J. A. Martin, E. M. Martin De La Nava, PCT Int. Appl. WO 2012074761, 2012; M. Henrich, U. Abel, S. Muller, H. Kubas, U. Meyer, M. Hechenberger, V. Kauss, R. Zemribo, PCT Int. Appl. WO 2012052451, 2012.

5. Y. L. Si, C. G. Liu, E. B. Wang, Z. M. Su, *Theoritical Chem. Acc.* **2009**, *122*, 217; A. S. Karpov, F. Rominger, and T. J. J. Műller, *J. Org. Chem*. **2003**, *68*, 1503; R. H. Naulty, A. M. Andrew, I. R. Whittall, M. P. Cifuentes, M. G. Humphrey, S. Houbrechts, J. Maes, A. Persoons, G. A. Heath, D. C. R. Hockless, *J. Organometal. Chem.* **1998**, *563*, 137.

6. A. K. Flatt, S. M. Dirk, J. C. Henderson, D. E. Shen, J. Su, M. A. Reed, J. M. Tour, *Tetrahedron*, **2003**, *59*, 8555.

7. E. Rafiee, A. Ataei, S. Nadri, M. Joshaghani, S. Eavani, *Inorg. Chim. Acta* **2014**, *409*(PB), 302; A. Ataei, S. Nadri, E. Rafiee, S. Jamali, M. Joshaghani, *J. Mol. Cat. A: Chemical* **2013**, *366*, 30.

8. V. Birault, A. J. Campbell, S. Harrison, J. Le, L. Shukla, PCT Int. Appl. WO 2013160419, 2013; A. Saxena, H. W. Lam, *Chem. Sci.* **2011**, *2*, 2326.

9. J. L. Yap, X. Cao, K. Vanommeslaeghe, K.-Y. Jung, C. Peddaboina, P. T. Wilder, A. Nan, A. D. MacKerell, W. R. Smythe, S. Fletcher, *Org. Biomol. Chem.* **2012**, *10*, 2928;

A. Nunez, B. Abarca, A. M. Cuadro, J. Alvarez-Builla, J. J. Vaquero, *J. Org. Chem.* **2009**, *74*, 4166.

10. A. El Kadib, K. McEleney, T. Seki, T. K. Wood, C. M. Crudden, *ChemCatChem* **2011**, *3*, 1281;

11. G. P. Sagitullina, M. A. Vorontsova, A. K. Garkushenko, N. V. Poendaev, R. S. Sagitullin *Russ. J. Org. Chem.* **2010**, *46*, 1830.

12. H. Wang, K. Wen, L. Wang, Y. Xiang, X. Xu, Y. Shen, Z. Sun, *Molecules* **2012**, *17*, 4533.

13. T. C. Henninger, X. C. Xu, PCT Int. Appl. WO 2002046204, 2002.

14. P. Chand, P. L. Kotian, P. E. Morris, S. Bantia, D. A. Walsh, Y. S. Babu, *Bioorg. Med. Chem.* **2005**, *13*, 2665; J. Siu, I. R. Baxendale, S. V. Ley, *Org. Biomol. Chem.* **2004**, *2*, 160.

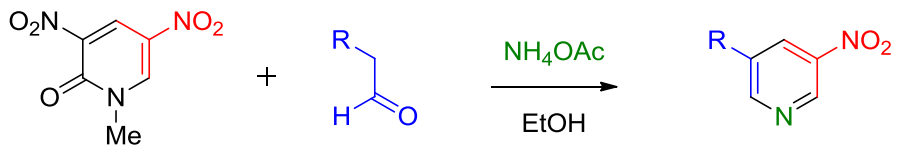
15. S. T. Le, H. Asahara; K. Kobiro, R. Sugimoto, K. Saigo, N. Nishiwaki, *Asian. J. Org. Chem.* **2014**, *3*, 297.

16. S. T. Le, H. Asahara; N. Nishiwaki, *Eur. J. Org. Chem.* **2015**, 1203; S. T. Le, H. Asahara; N. Nishiwaki, *Synthesis* **2014**, *46*, 2175.

17. A. S. Karpov, F. Rominger, T. J. J. Mueller, *J. Org. Chem.* **2003**, *68*, 1503.

Chapter 5. Synthesis of 3-Alkylated/Arylated 5-Nitropyridines

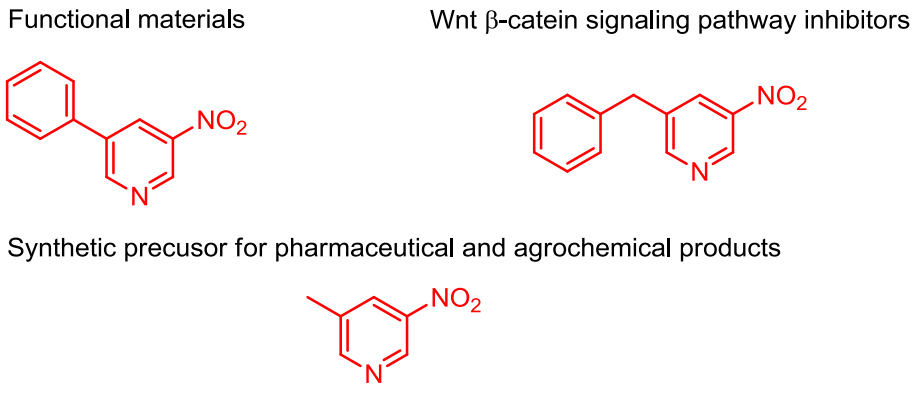
In this chapter, an alternative method for synthesis of 3-alkylated/arylated 5-nitropyridines **3** was provided which includes the three component ring transformation (TCRT) of dinitropyridone **1** with aldehydes **2** in the presence of NH_4OAc. This method facilitates the modification of the substituent at the 3-position by only changing the aldehyde. The use of solid NH_4OAc as a nitrogen source instead of ammonia improves this ring transformation as practically usable synthetic method.



1 **2** **3**

1. Introduction

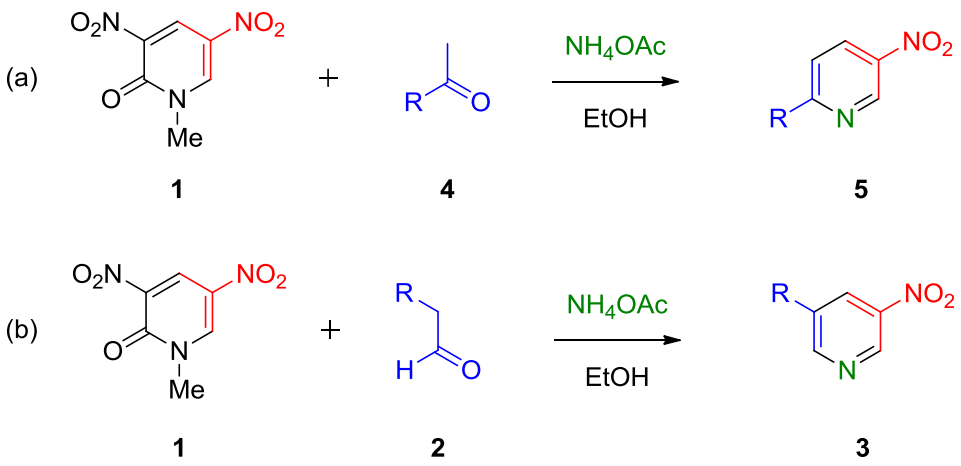
3-Alkylated/arylated 5-nitropyridines are widely used as synthetic intermediates for preparation of biologically active compounds such as cytokine inhibitors for treatment of various diseases,[1] Wnt β-catein signalling pathway inhibitors,[2] HIV integrase inhibitors,[3] and dihydroorotate dehydrogenase (DHODH) inhibitors.[4]



Scheme 1. Synthetic application of 3-Alkylated/arylated 5-nitropyridines

Despite their versatile and useful applications, versatile 3-alkylated/arylated 5-nitropyridines, that are necessary for the screening, are not easily available because β-alkylation/arylation of the pyridine framework is particularly difficult. Thus, only a few direct β-alkylation methods are known until now. One strategy is destroying the aromaticity of the pyridine ring. Indeed, Giam *et al.* reported a direct alkylation method of pyridine via the conversion to tetrakis(dihydropyridyl)aluminate with lithium aluminum hydride.[5] Tsuge *et al.* also succeeded the benzylation via the double silylation at the 1- and 4-positions.[6] With regard to direct phenylation, it has been realized by recent considerable efforts although these methods still suffer from harsh conditions or low regioselectivity.[7] So, 3-bromopyridine should be used as a substrate for alkylation using organometallic reagents/catalysts.[8] Even though β-alkylation/arylation is successfully achieved, the subsequent nitration also suffer from low reactivity of the pyridine framework.

Meanwhile, the ring transformation has revealed high synthetic utility to obtain nitrated compounds. Diels-Alder-type ring transformation has been widely used, among which van der Plas *et al.* succeeded synthesis of 3-nitro-5-phenylpyridine using nitropyrimidine and an enamine.[9] On the other hand, nucleophilic ring transformation using 1-methyl-3,5-dinitro-2-pyridone (**1**) has also been employed since Ariga and his co-workers reported at first time.[10] Especially, TCRT of dinitropyridone **1** with ketones **4** in the presence of NH_3 as a nitrogen source is an excellent method to synthesize 2-substituted (or 2,3-disubstituted) 5-nitropyridines **5**, which are practically used by many researchers[11] and pharmaceutical companies.[12] However, this method requires NH_3 solution beforehand, and ammonolysis of pyridone **1** sometimes competitively occurs. In order to solve these problems, the TCRT was conducted using easily treatable solid NH_4OAc as a nitrogen source instead of NH_3, by which nitropyridines **5** (Scheme 1, method a)[13] and nitroanilines[14] were efficiently synthesized. With regard to TCRT of **1** with aldehydes **2** in the presence of NH_3, only a few examples[15] are known which is presumably due to the side reactions caused by reactive aldehydes **2**. It is considered that 3-substituted 5-nitropyridines **3** will be surely available by this protocol using NH_4OAc; the TCRT of dinitropyridone **1** with aldehyde **2** in the presence of NH_4OAc (Sheme 1, method b).



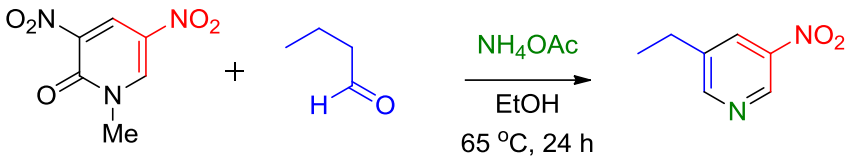
Scheme 2. TCRT of dinitropyridone

2. Study on the TCRT of dinitropyridone with aldehyde and NH_4OAc affording 3-alkyl/aryl-5-nitropyridines

2.1 The optimization of reaction conditions

Dinitropyridone **1** was allowed to react with butanal (**2a**) in the presence of 5 equiv. of NH_4OAc at 65 °C for 24 h in ethanol. After removal of the solvent, the residue was extracted with benzene (10 ml × 3) to afford nitropyridine **3a**[15c] in almost pure form, however, the yield was only 26% (Table 1, entry 1). It is noticed that the competitive thermal decomposition of NH_4OAc also proceeded, and TCRT cannot proceed anymore due to the lack of a nitrogen source when all amount of NH_4OAc was consumed by TCRT or thermal decomposition.[13,14] Thus, the use of larger amount of NH_4OAc increased the actual reaction time accompanying the increase of the yield of nitropyridine **3a** (entries 2-3). In order to shorten the reaction time, microwave heating was used, which was efficient for the TCRT of **1** with ketones **4**. However, the yield of **3a** became rather lower because high reactivity of aldehyde **2a** caused side reactions such as aldol and Chichibabin[16] reactions to give a complex reaction mixture (entry 4).

Table 1. The TCRT of dinitropyridone **1** with butanal (**2a**) and NH_4OAc



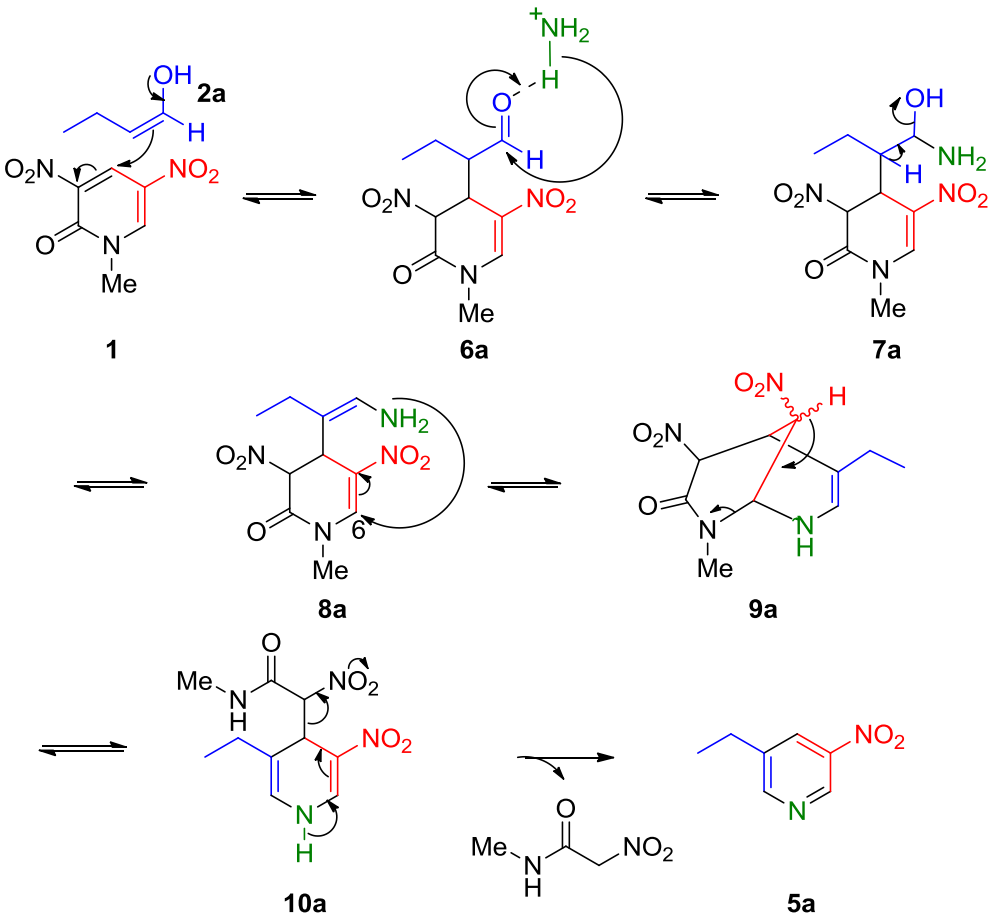
1 **2a** **3a**

Entry	NH_4OAc (equiv.)	Yield (%)	Recovery of **1** (%)
1	5	26	66
2	10	75	20
3	15	86	0
4[a]	15	24	65

[a]: Microwave heating was used

2.2 A plausible mechanism

This TCRT is considered to proceed as illustrated in Scheme 2. The enol form of **4a** attack to the 4-position of **1** giving adduct **6a**, which is converted to enamine **8a** as a result of the reaction with ammonium ion. The nucleophilic attack of the amino group to the 6-position of enamine **8a** giving nitropyridine **5a** by the formation of bicyclic intermediate **9a**, which undergoes the ring opening reaction and aromatization accompanied by the elimination of good leaving group nitroacetamide via **10a**.



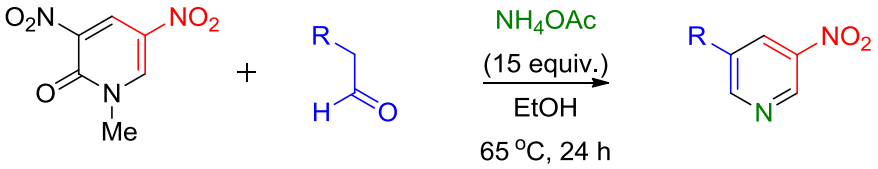
Scheme 3. A plausible mechanism

2.3 The TCRT of dinitropyridone with different kinds of aldehyde in the presence of NH_4OAc

To exame the scope of this method, the reaction of **1** with several kinds of aldehydes **2b-f** were performed under the optimized conditions (Table 2). The TCRT using propanal (**2b**) similarly proceeded to afford 3-methyl-5-nitropyridine (**3b**)[17] in 52% yield although it is diminished by the competitive self-condensation of **2b** (entry 1). The self-condensation could be avoided when bulkier aldehyde **2c** was used, which resulted in 3-isopropylpyridine (**3c**)[15c] up to 71% yield (entry 2). In the case of more sterically hindered aldehydes **2d** and **2e**, the corresponding nitropyridines **3d**[18] and **3e**[19] the efficiency of the TCRT decreased (entries 3 and 4). This disadvantage was overcome by use of microwave

heating and the yield of **3e** increased up to 68% (entry 5). It was also possible to introduce a phenyl group to the pyridine ring to give **3f**[9] when phenylacetaldehyde **2f** was employed (entries 6 and 7).

Table 2. TCRT of **1** with other aldehydes **2** and NH_4OAc

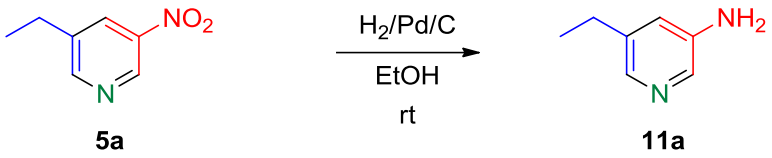


1 **2** **3**

Entry	R		Yield (%)	Recovery of **1** (%)
1	Me	**b**	52	-
2	*i*-Pr	**c**	71	16
3	Bn	**d**	34	21
4	*t*-Bu	**e**	29	63
5[a]	*t*-Bu	**e**	68	-
6	Ph	**f**	47	44
7[a]	Ph	**f**	75	-

[a]: Microwave heating was used

Next, the conversion of the nitropyridine **3a** to aminopyridine **11a** was studied because aminopyridines are widely used as synthetic intermediates for biologically active compounds because the amino group facilitates further chemical conversion.[20] 5-Amino-3-ethyl-5-nitropyridine **11a**[21] was obtained in 82% yield upon treatment of **3a** under hydrogen atmosphere at room temperature in the presence of Pd/C catalyst (Scheme 4).



Scheme 4. Synthetic application of synthesized compound **5a**

3. Conclusions

In summary, we have successfully developed a facile and efficient method for synthesis of 3-substituted 5-nitropyridines, which are not easily prepared by other methods. This method requires only simple manipulations, single step reaction, and mild conditions. Furthermore, the alkyl/aryl group at the 3-position can be easily modified by only chaining aldehydes. These features improve the synthetic value of this method, and it will be alternative approach to 3-substituted-5-pyridine frameworks.

4. Experimental section and characterization of compounds

4.1 Experimental section

General procedure of TCRT

To a solution of the dinitropyridone **1** (50 mg, 0.25 mmol) in ethanol (5 ml), were added butanal (**2a**) (46 µl, 0.5 mmol) and NH_4OAc (289 mg, 3.75 mmol), and then the resultant mixture was heated at 65 °C for 24 h. After removal of the solvent, the residue was extracted with benzene (10 ml × 3) to afford almost pure nitropyridine **3a** (33.4 mg, 0.22 mmol, 86%) as yellow powder. The TCRT reactions of the dinitropyridone **1** with other aldehydes **2b-f** were performed in a similar way.

4.2 Characterization of compounds

*3-Enthyl-5-nitropyridine (**5a**)*

Yellow powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (t, *J* = 7.6 Hz, 3H), 2.82 (q, *J* = 7.6 Hz, 2H), 8.30 (dd, *J* = 2.0, 2.4 Hz, 1H), 8.76 (d, *J* = 2.0 Hz, 1H), 9.26 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8 (CH_3), 25.7(CH_2), 129.9 (CH), 140.4 (C), 142.5 (CH), 144.2 (C), 154.8 (CH).

*3-Methyl-5-nitropyridine (**5b**)*

Yellow powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.50 (s, 3H), 8.29 (dd, *J* = 1.2, 2.4 Hz, 1H), 8.74 (d, *J* = 1.2 Hz, 1H), 9.26 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.9 (CH_3), 131.1 (CH), 134.4 (C), 142.4 (CH), 155.42 (CH), one C was not observed.

*3-(1-Methylethyl)-5-nitropyridine (**5c**)*

Yellow powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (d, *J* = 6.8 Hz, 6H), 3.07-3.12 (m, 1H), 8.32 (dd, *J* = 2.0, 2.4 Hz, 1H), 8.78 (d, *J* = 2.0 Hz, 1H), 9.27 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7 (CH_3), 31.6 (CH), 128.6 (CH), 142.6 (CH), 144.5 (C), 145.0 (C), 153.9 (CH);

*3-Phenyl-5-nitropyridine (**5d**)*

Yellow powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50-7.57 (m, 3H), 7.64 (d, *J* = 7.6 Hz, 2H), 8.66 (dd, *J* = 2.0, 2.4 Hz, 1H), 9.13 (d, *J* = 2.0 Hz, 1H), 9.40 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 127.3 (CH), 128.3 (C), 128.9 (CH), 129.4 (CH), 129.5 (CH), 135.2 (C), 143.3 (CH), 149.5 (C), 153.1 (CH).

*3-(1,1-Dimethylethyl)-5-nitropyridine (**5e**)*

Yellow powder, boiling point 248 – 250 ^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H), 8.46 (dd, *J* = 2.4, 2.4 Hz, 1H), 8.97 (d, *J* = 2.4 Hz, 1H), 9.27 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.8 (CH_3), 34.1 (C), 127.8 (CH), 142.1 (CH), 144.2 (C), 147.5 (C), 152.8 (CH); IR (KBr, cm-1) 1353, 1532; HRMS. Calcd for $C_9H_{12}N_2O_2$: 180.0899. Found: 180.0899.

*2-Phenyl-5-nitropyridine (**5f**)*

White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.11 (s, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 8.24 (dd, *J* = 1.6, 2.4 Hz, 1H), 8.79 (d, *J* = 1.6 Hz, 1H), 9.29 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.6 (CH_2), 127.2 (CH), 128.8 (CH), 129.1 (CH), 130.9 (CH), 137.9 (C), 142.9 (CH), 155.1 (CH), two C could not be observed.

*5-Enthyl-3-pyridineamine (**11a**)*

Yellow powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, *J* = 7.6 Hz, 3H), 2.53 (q, *J* = 7.6 Hz, 2H), 4.43 (s, 2H), 6.84 (s, 1H), 7.85 (s, 1H), 7.94 (s, 1H); (these protons should appeare as dd, d, and d but actual signals appeared as singlet.

*The conversion of 3-ethyl-5-nitropyridine (**5a**) to 5-amino-3-ethylpyridine (**11a**)*

To a solution of nitropyridine **5a** (70 mg, 0.46 mmol) in ethanol (5 ml), was added Pd/C powder (5 wt% Pd, 50 mg), and the reaction was carried at room temperature for 40 h under hydrogen atmosphere. After removal of Pd/C powder and solvent by filtration and vacuum pressure, respectively, the residue was extracted with chloroform (10 ml × 3) to give 5-amino-3-ethylpyridine (**11a**)[21] (46 mg, 0.38 mmol, 82%) as yellow powder.

5. Reference

1. Hao, M. H.; Xiong, Z.; Aungst, R. A.; Davis, A. L.; Cogan, D.; Goldberg, D. R. *U. S. Pat.* **2005**, 050245536.
2. Hood, J.; Sunil, K. *PCT Int. Appl.* **2013**, 2013040215.
3. Johns, B. A.; Spaltenstein, A. *PCT Int. Appl.* **2007**, 2007019101.
4. Castro, P. L.; Julio, C.; Terricarbras, B. E.; Erra, S. M.; Navarro, R. E.; Fonquerna, P. S.; Cardus, F. A.; Lozoya, T. M. E. *PCT Int. Appl.* **2009**, 2009021696.
5. Giam, C. S.; Abbott, S. D. *J. Am. Chem. Soc.* **1971**, *93*, 1294−1296.
6. Tsuge, O.; Kanemasa, S.; Naritomi, T.; Tanaka, J. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1497−1504.

7. Recent papers: (a) Bhakuni, B. S.; Yadav, A.; Kumar, S.; Kumar, S. *New J. Chem.* **2014**, *38*, 827−836; (b) Cheng, Y.; Gu, X.; Li, P. *Org. Lett.* **2013**, *15*, 2664−2667; (c) Dai, F.; Gui, Q.; Liu, J.; Yang, Z.; Chen, X.; Guo, R.; Tan, Z. *Chem. Commun.* **2013**, *49*, 4634−4636; (d) Wen, J.; Zhang, R.-Y.; Chen, S.-Y.; Zhang, J.; Yu, X.-Q. *J. Org. Chem.* **2012**, *77*, 766−771; (e) Ye, M.; Gao, G.-L.; Edmunds, A. J. F.; Worthington, P. A.; Morris, J. A.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19090−19093; (f) Kobayashi O.; Uraguchi, D.; Yamakawa, T. *Org. Lett.* **2009**, *11*, 2679−2682; (g) Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673−4676.

8. Recent papers: (a) Everson, D. A.; Bunomo, J. A.; Weix, D. J. *Synlett* **2014**, *25*, 233−238; (b) Wu, Y.; Li, L.; Li, H.; Gao, L.; Xie, H.; Zhang, Z.; Su, Z.; Hu, C.; Song, Z. *Org. Lett.* **2014**, *16*, 1880−1883; (c) St. Denis, J. D.; Scully, C. C. G.; Lee, C. F.; Yudin, A. K. *Org. Lett.* **2014**, *16*, 1338−1341; (d) Bernhardt, S.; Shen, Z.-L.; Knochel, P. *Chem. Eur. J.* **2013**, *19*, 828−833; (e) Fleury-Brégeot, N.; Presset, M.; Beaumard, F.; Colombel, V.; Oehlrich, D.; Rombouts, F.; Molander, G. A. *J. Org. Chem.* **2012**, *77*, 10399−10408; (f) Chang, S.-T.; Li, Q.; Chiang, R.-T.; Gau, H.-M. *Tetrahedron* **2012**, *68*, 3956−3962.

9. Marcelis, A. T. M.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 2693−2702.

10. (a) Matsumura, E.; Ariga, M.; Tohda, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2413−2419; (b) Nishiwaki, N.; Ariga, M. in *Topics in Heterocycl. Chem.*, Vol. 8, *Bioactive Heterocycles II*, Ed. by Eguchi, S. pp. 43–72, Springer, Berlin (**2007**), and references are cited in.

11. Recent papers: (a) Schultz, T.; Turner, S. C.; Braje, W. M. *Synthesis* **2010**, 1339–1343; (b) Sagitullina, G. P.; Garkushenko, A. K.; Vinokurova, Y. O.; Nyrkova, V. A.; Atavin, E. G.; Sagitullin, R. S. *Russ. J. Org. Chem.* **2009**, *45*, 1045–1049; (c) Guiadeen, D.; Kothandaraman, S.; Yang, L.; Mills, S. G.; MacCoss, M. *Tetrahedron Lett.* **2008**, *49*, 6368–6370; (d) Shah, U.; Lankin, C. M.; Boyle, C. D.; Chackalamannil, S.; Greenlee, W. J.; Neustadt, B. R.; Cohen-Williams, M. E.; Higgins, G. A.; Ng, K.; Varty, G. B.; Zhang, H.; Lachowicz, J. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4204–4209.

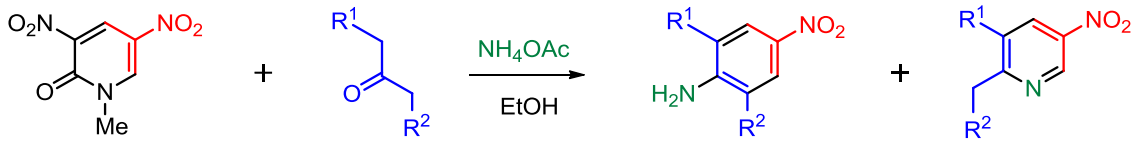
12. Recent patents: (a) Bell, I. M.; Fraley, M.; Biftu, T.; Zhu, C.; Nair, A. *PCT Int. Appl.* **2013**, 2013169565; (b) Frank, R.; Christoph, T.; Lesch, B.; Lee, J. *PCT Int. Appl.* **2013**, 2013013816; (c) Sheth, U.; Fanning, T. T. D.; Numa, M.; Binch, H.; Hurley, D. J.;

Zhou, J.; Hadida, R.; Sara, S.; Hazlewood, A. R.; Silla, A.; Vairagoundar, R.; Van Goor, F. F.; Grootenhuis, P. D. J.; Botfield, M. C. *PCT Int. Appl.* **2011**, 2011072241.

13. Le, S. T.; Asahara, H.; Nishiwaki, N. *Chem. Lett.* **2015**, DOI: 10.1246/cl.150045; (b) Le, S. T.; Asahara, H.; Nishiwaki, N. *Synthesis* **2014**, 2175–2178; (c) Le, T. S.; Asahara, H.; Kobiro, K.; Sugimoto, R.; Saigo, K.; Nishiwaki, N. *Asian J. Org. Chem.* **2014**, *3*, 297–302.
14. Le, T. S.; Asahara, H.; Nishiwaki, N. *Eur. J. Org. Chem.* **2015**, 1203–1206.
15. (a) Henry, C.; Haupt, A.; Turner, S. C. *J. Org. Chem.* **2009**, *74*, 1932–1938; (b) Kelly, M. G.; Kaub, C. J.; Kincaid, J.; Janagani, S.; Wu, G.; Wei, Z.-L.; Sahasrabudhe, K.; Duncton, M.; Upasani, R. B.; Fang, Y.; Cox, M. *PCT Int. Appl.* **2007**, 2007100758; (c) Tohda, Y.; Eiraku, M.; Nakagawa, T.; Usami, Y.; Ariga, M.; Kawashima, T.; Tani, K.; Watanabe, H.; Mori, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2820–2827.
16. Bulgakov, R. G.; Kuleshov, S. P.; Makhmutov, A. R.; Dzhemilev, U. M. *Russ. J. Org. Chem.* **2007**, *43*, 1417–1418.
17. Nishiwaki, N.; Tohda, Y.; Ariga, M. *Synthesis* **1997**, 1277–1280.
18. Hood, J.; Kc, S. K. *PCT. Int. Appl.* **2013**, 2013040215.
19. Description about **5e** was found in the following patent, however, the preparative method is not given. Furuyama, H.; Kurihara, H.; Terao, T.; Nakagawa, D.; Tanabe, S.; Kato, T.; Yamamoto, M.; Sekine, S.; Mashiko, T.; Inuki, S.; Ueda, S. *PCT Int. Appl.* **2014**, 2014109414.
20. Chemical conversions of 3-alkyl-5-aminopyridines are shown: (a) Qiu, D.; Jin, L.; Zheng, Z.; Meng, H.; Mo, F.; Wang, X.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2013**, *78*, 1923–1933; (b) Joshi, G.; Adimurthy, S. *Ind. Eng. Chem. Res.* **2011**, *50*, 12271–12275; (c) Umezawa, N.; Matsumoto, N.; Iwama, S.; Kato, N.; Higuchi, T. *Bioorg. Med. Chem.* **2010**, *18*, 6340–6350; (d) Jensen, H. H.; Lyngbye, L.; Jensen, A.; Bols, M. *Chem. Eur. J.* **2002**, *8*, 1218–1226; (e) Kyba, E. P.; Liu, S.-T.; Chockalingam, K.; Reddy, B. R. *J. Org. Chem.* **1988**, *53*, 3513–3521.
21. Flynn, D. L.; Petillo, P. A.; Kaufman, M. D.; Booth, R. J. *PCT Int. Appl.* **2012**, 2012019015.

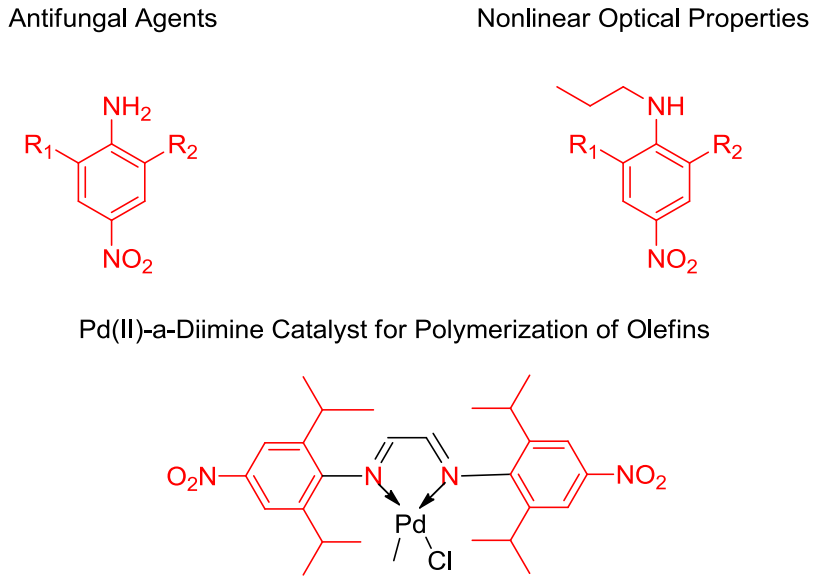
Chapter 6. Synthesis of *N*,*N*,2,6-Tetrasubstituted Nitroanilines

This chapter deals with the ring transformation (TCRT) of dinitropyridone with aliphatic ketones in the presence of NH_4OAc as a nitrogen source, which afforded various kinds of 2,6-disubstituted-4-nitroanilines. Not only the benzene ring but also the amino group of the nitroalinine framework could be easily modified by only changing a ketone and a nitrogen source, namely, *N*,*N*,2,6-tetrasubstituted 4-nitroanilines were synthesized in good to excellent yields.



1. Introduction

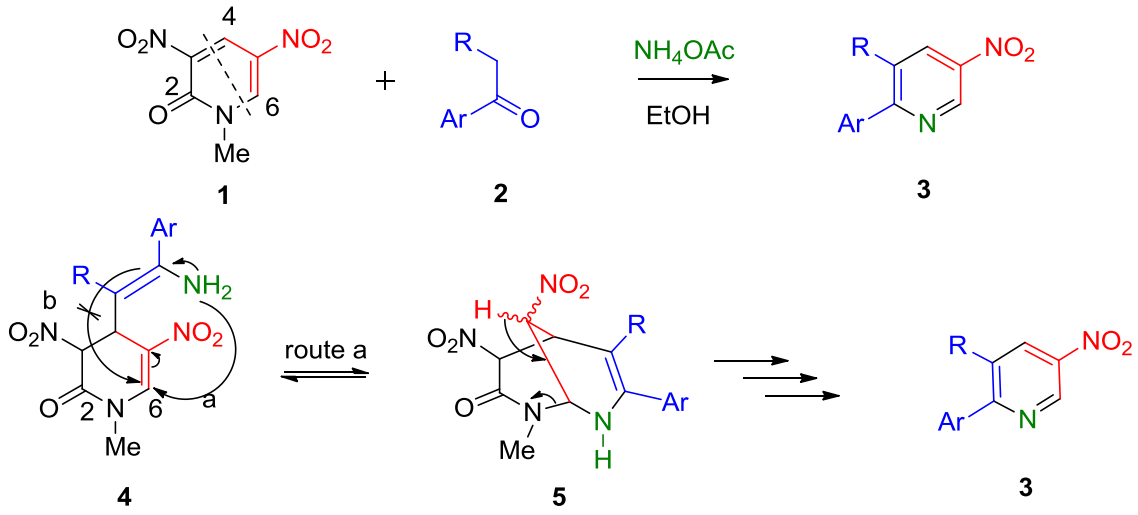
2,6-Disubstituted 4-nitroanilines are useful synthetic intermediates for functional materials such as inhibitors of cholesterol acyl transferase,[1] π-conjugated polymers,[2] and key intermediate for synthesis of antimicrobial activities compounds[3] and β-diketiminate ligand.[4] Moreover, the push-pull electronic property is crucial for developing potential organic nonlinear optical materials. Generally, 2,6-disubstituted 4-nitroanilines **8** are prepared from the corresponding anilines by nitration under harsh conditions, in which protection and deprotection of the amino group are necessary.[5] Furthermore, the preparation of 2,6-disubstituted anilines is also restricted due to the limitations of Friedel-Crafts alkylation;[6] 1) monoalkylated product undergoes further alkylation to afford polyalkylated products, 2) it is difficult to introduce two different alkyl groups, 3) primary alkyl groups longer than the ethyl group cannot be introduced, 4) a phenyl and a vinyl groups cannot be introduced, and 5) aminated and nitrated benzenes do not facilitate the alkylation. Therefore, the development of an efficient synthetic method for 2,6-disubstituted 4-nitroanilines still remains a significant challenging.



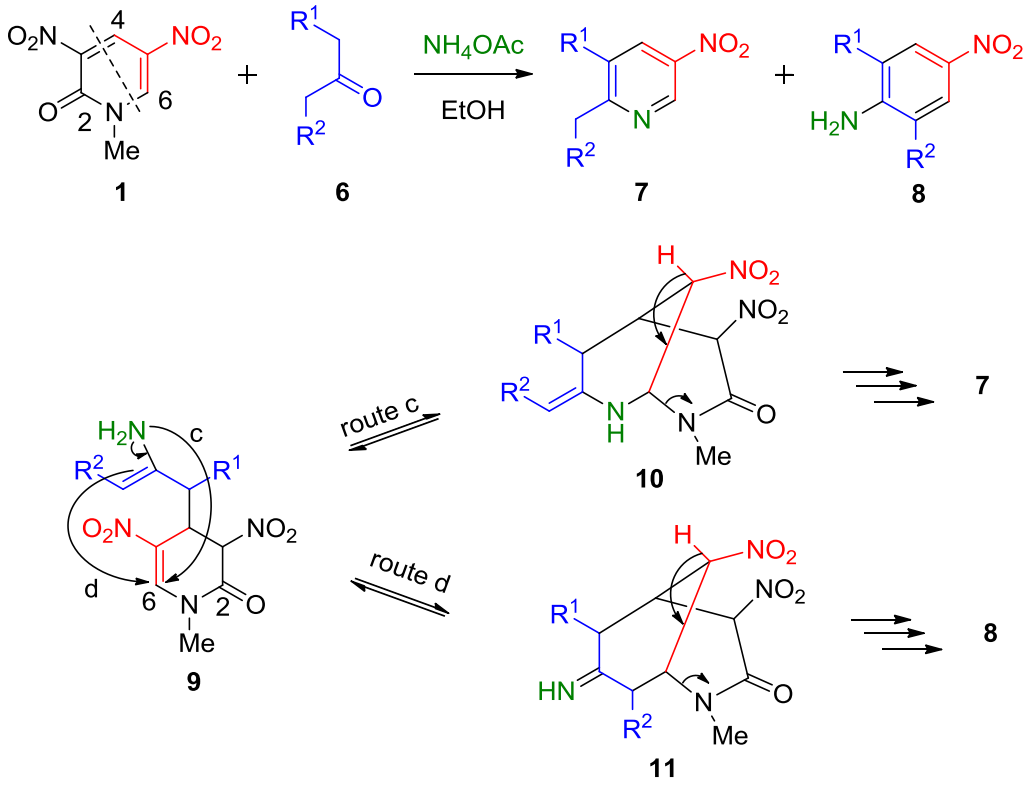
Scheme 1. Synthetic applications of nitroaniline derivatives

As discussed in chapter, the TCRT of dinitropyridone **1** with aromatic ketones **2** in the presence of NH_4OAc affording nitropyridines from good to excellent yields (Scheme 2). This reaction is initiated by the nucleophilic attack of the enol form of **2** followed by conversion to enamine **4**. When the amino group of enamine **4** attacks the 6-position (route a), 2-arylated 5-nitropyridines **3** are formed via bicyclic intermediates **5** (Scheme 2).[7] However, the β-carbon of enamine **4** cannot attack the 6-position (route b) because it would form a sterically strained four membered ring.

On considering this reaction mechanism, it is predicted that another ring transformation would occur when aliphatic ketones **6** having two α-hydrogens, viz. α- and α‘-, are employed instead of aromatic ketones **2** (Scheme 3). In this ring transformation, both the amino group and the β-carbon can attack the 6-position in the case of enamine **9**, which leads to the formation of nitropyridines **7** (route c) or nitroanilines **8** (route d).



Scheme 2. TCRT of dinitropyridone **1** with aromatic ketones **2** in the presence of NH_4OAc, leading to the formation of 6-arylated nitropyridines **3**.



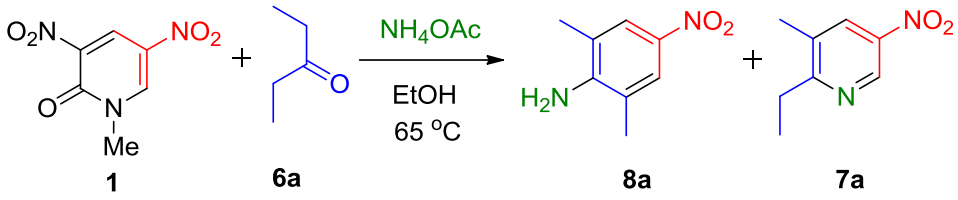
Scheme 3. TCRT of dinitropyridone **1** with aliphatic ketones **6** in the presence of NH_4OAc, affording disubstituted nitropyridines **7** and nitroalines **8**.

2. Study on TCRT of dinitropyridone with aliphatic ketones and NH_4OAc affording nitroaniline derivatives

2.1 The optimization of reaction conditions

When dinitropyridone **1** was allowed to react with 3-pentanone (**6a**) in the presence of 5 equiv. of NH_4OAc in ethanol at 65 ^oC for 24 h, nitroaniline **8a**[7] was obtained in 50% yield accompanied by 44% yield of nitropyridine **7a**[7] as a result of two kinds of TCRTs (Table 1, entry 1). When 10 equiv. of NH_4OAc were used, the ratio of **8a** to **7a** was considerably increased without decreasing the total yield (entry 2), which indicates the presence of equilibrium between intermediates **10** and **11**, kinetically and thermodynamically controlled intermediates, respectively, which can interconvert via enamine **9**. In the present TCRT, competitive thermal decomposition NH_4OAc also proceeded to afford ammonia which went out from reaction mixture as a gas. When all NH_4OAc was consumed, the TCRT could not proceed anymore due to the lack of the nitrogen source. Thus, increasing of the amount of NH_4OAc prolonged actual reaction time, which resulted in the predominance of nitroaniline **8a**. However, no more change was observed even though larger amounts of NH_4OAc were used (entry 3). It was also found that heating for 24 h is necessary for the completion of the TCRT (entries 4-6).

Table 1. Optimization of reaction conditions for the TCRT

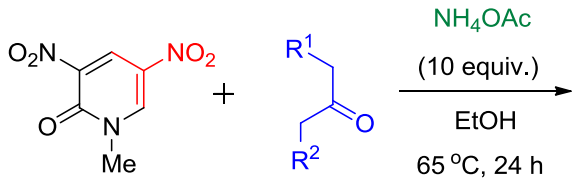


Entry	NH_4OAc (equiv.)	Time (h)	Yield (%)	
			8a	**7a**
1	5	24	50	44
2	10	24	83	13
3	15	24	86	13
4	10	18	70	14
5	10	12	64	13
6	10	6	55	13

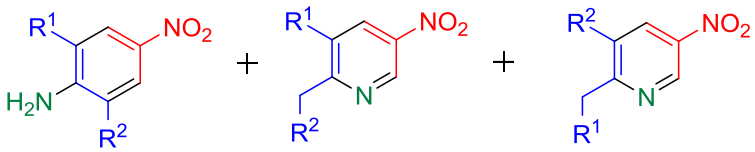
2.2 Synthesis of 2,6-disubstitued 4-nitroanilines

Application of this TCRT to other ketones **6b-i** was studied under the conditions optimizited for **6a** (Table 2). When acetone (**6b**) was used as a substrate, two kinds of TCRT proceeded similarly to afford nitroaniline **8b**[7] in 51% and nitropyridine **7b**[7] in 47% yields, respectively (entry 2). It was possible to modify the 2- and 6- positions of the nitroaniline framework by only changing the ketone **6** (entries 3-9). Notably, this TCRT facilitates the introduction of a propyl or a phenyl group into the benzene ring, which cannot be achived by Friedel–Crafts reaction. As a result, symmetrical and unsymmetrical nitroanilines **8f-i**[7] were easily prepared although the yield of **8i** was low which is presumably becauce steric repulsion by phenyl groups prevent the formation of **11i** (entries 6-9).

Table 2. Application of this TCRT to other aliphatic ketones



1 **6** (1 equiv.)



8 **7** **7'**

Entry	R^1	R^2		Yield (%)		
				8	**7**	**7'**
1	Me	Me	**a**	83	13	0
2	H	H	**b**	51	47	0
3	Et	H	**c**	66	10	8
4	i-Pr	H	**d**	58	0	31
5	Pr	H	**e**	83	9	6
6	Et	Et	**f**	67	24	0
7	Pr	Pr	**g**	74	22	0
8	C_6H_5	Pr	**h**	62	24	13
9	C_6H_5	C_6H_5	**i**	8	81	0

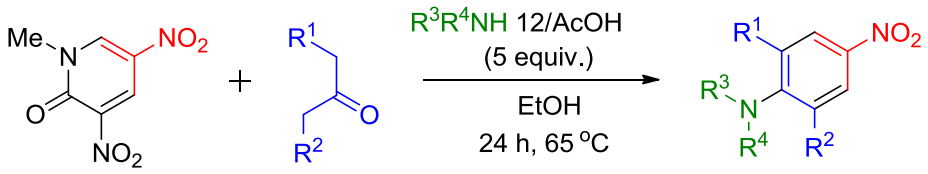
2.3 Synthesis of *N*,*N*,2,6-tetrasubstituted 4-nitroanilines

As mentioned above, two kinds of TCRTs competitively occurred to form 5-nitropyridines **7** and 4-nitroanilines **8**. In these reactions, NH_4OAc serves as both a nitrogen source and ketone **6** activator. We believe that a combination of amine **12** and acetic acid, used instead of NH_4OAc, can carry out these roles, thus achieving the

modification of the benzene ring as well as the amino group of the nitroaniline framework. In this case, only nitroanilines **13** will be formed as a TCRT product, because the aromatization of the intermediate, which is required for the formation of nitropyridines, is prevented by the *N*-substituents (R^3 and R^4).

Propylamine **12A** was added to a solution of dinitropyridone **1**, 3-pentanone (**6a**), and acetic acid in ethanol, and the resulting solution was heated at 65 ^oC for 24 h. After the usual work-up, 2,6-dimethyl-4-nitro-*N*-propylaniline (**13Aa**) was obtained in 99% yield (Table 3, entry 1). This method was applied to the secondary amines, pyrrolidine **12B** and diethylamine **12C**, to afford *N*,*N*,2,6-tetrasubstituted 4-nitroanilines **13Ba** and **13Ca**, respectively, in excellent yields (entries 2 and 3). Methyl ketones **6b-d** also underwent this TCRT using a combination of either propylamine or pyrrolidine with acetic acid to afford the corresponding nitroanilines **13** in moderate to excellent yields (entries 4-9). Moreover, these reactions could induce modifications at the 2- and 6-positions using ketones **6e-h**, by which a propyl or a phenyl could be introduced to the nitroaniline framework (entries 10-15).

Table 3. TCRT of dinitropyridone **1** with aliphatic ketones **6** using the mixture of amine **12** and acetic acid.



1 **6** **13**

Entry	Ketone **6**			Amine **12**		Product	Yield
	R^1	R^2		R^3	R^4		(%)
1	Me	Me	**a**	Pr	H	**13Aa**	99
2	Me	Me	**a**	-$(CH_2)_4$-		**13Ba**	98
3	Me	Me	**a**	Et	Et	**13Ca**	98
4	Et	H	**b**	Pr	H	**13Ab**	83
5	Et	H	**b**	-$(CH_2)_4$-		**13Bb**	68
6	Pr	H	**c**	Pr	H	**13Ac**	77
7	Pr	H	**c**	-$(CH_2)_4$-		**13Bc**	87
8	Pr	H	**c**	Et	Et	**13Cc**	51
9	*i*-Pr	H	**d**	Pr	H	**13Ad**	83
10	Et	Et	**e**	Pr	H	**13Ae**	69
11	Et	Et	**e**	-$(CH_2)_4$-		**13Be**	68
12	Pr	Pr	**f**	Pr	H	**13Af**	81
13	Pr	Pr	**f**	-$(CH_2)_4$-		**13Bf**	59
14	C_6H_5	Pr	**g**	Pr	H	**13Ag**	80
15	C_6H_5	C_6H_5	**h**	Pr	H	**13Ah**	32

3. Conclusions

In summary, we have developed a new preparative method for 2,6-disubstituted 4-nitroanilines **8** and **13** by the TCRT of dinitropyridone **1** with aliphatic ketones **6** in the presence of NH_4OAc. In this reaction, a number of ketones **6** are usable as substrates, which facilitate the modification of the nitroaniline framework. In addition, this TCRT requires only simple experimental manipulations and mild reaction conditions, which is advantageous from the viewpoint of practical use. These features facilitate the construction of a library of compounds that are not easily available by other methods. Furthermore, modification of the amino group was successfully achieved by using a combination of amine **12** and acetic acid. Consequently, the tailor-made synthesis of *N*,*N*,2,6-tetrasubstituted 4-nitroanilines **8** and **13** became possible on demand.

4. Experiment section and characterization of compounds

4.1 Experimental section

General information

The melting points were determined on a Yanaco micro-melting-points apparatus, and were uncorrected. The dinitropyridone **1** was synthesized according to literature procedures. All the reagents and solvents were commercially available and used as received. The ^{1}H NMR spectra were measured on a Bruker Ascend-400 at 400 MHz with TMS as an internal standard. The ^{13}C NMR spectra were measured on a Bruker Ascend-400 at 100 MHz, and assignments of ^{13}C NMR spectra were performed by DEPT experiments. The IR spectra were recorded on a JASCO FT/IR-4200 spectrometer. The mass spectra and the high resolution mass spectra were measured on a JEOL JMS-DX303HF.

*The reaction of dinitropyridone **1** with aliphatic ketones **6** in the presence of NH_4OAc:*

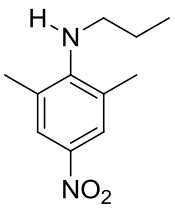
To a solution of the dinitropyridone **1** (50 mg, 0.25 mmol) in ethanol (5 mL), were added 3-pentanone **6a** (26 µL, 0.25 mmol) and NH_4OAc (96.3 mg, 1.25 mmol), and then the resultant mixture was heated at 65 °C for 24 h. After removal of the solvent, the residue was washed with benzene (3 × 10 mL) to remove unreacted ketone **6a**, which affords a mixture of the nitropyridine **7a** and the nitroaniline **8a**. The separation of products was performed by column chromatography on silica gel (eluent: hexane/ethyl acetate = 95/5) to afford **7a** (18.3 mg, 0.11 mmol, 44%) and **8a** (20.8 mg, 0.13mmol, 50%), respectively. The TCRT reactions of the dinitropyridone **1** with other ketones were performed in a similar way.

*The reaction of dinitropyridone **1** with aliphatic ketones **6** in the presence of the combination of amine **12** and acetic acid:*

Propylamine (**12A**, 103 µl, 1.25 mmol) was added to a solution of dinitropyridone **1** (50 mg, 0.25 mmol), 3-pentanone **6a** (26 µL, 0.25 mmol)) and acetic acid (72 µl, 1.25 mmol) in ethanol (5 ml), and the resultant solution was heated at 65 ^{o}C for 24 h. After removal of the solvent, the residue was washed with benzene (3 × 10 mL) to afford 2,6-dimethyl-4-nitro-*N*-propylaniline **13Aa** (51.5 mg, 0.245 mmol, 99%) as a yellow powder. The reactions of the dinitropyridone **1** with other ketones **6b-e** and/or other amines were performed in a similar way.

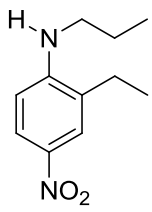
4.2 Characterization Data

*2,6-Dimethyl-4-nitro-N-propylaniline (**13Aa**)*



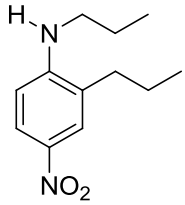
Yellow powder; mp 64–66 ˚C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01 (t, J = 7.2 Hz, 3H), 1.61 (tq, J = 6.8, 7.2 Hz, 2H), 2.30 (s, 6H), 3.26 (t, J = 6.8 Hz, 2H), 3.68-3.79 (br, 1H), 7.86 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.3 (CH_3), 19.4 (CH_3), 24.5 (CH_2), 49.3 (CH_2), 125.1 (CH), 125.3 (C), 139.5 (C), 152.7 (C); IR (KBr, cm^{-1}) 3426, 1591, 1386; HRMS (EI, magnetic field) Calcd for $C_{11}H_{16}N_2O_2$: 208.1212. Found: 208.1213.

*2-Ethyl-4-nitro-N-propylaniline (**13Ab**)*



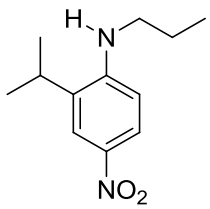
Yellow powder; mp 66–68 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (t, J = 7.6 Hz, 3H), 1.30 (t, J = 6.8 Hz, 3H), 1.75 (tq, J = 7.6, 7.6 Hz , 2H), 2.47 (t, J = 7.6 Hz, 2H), 3.24 (q, J = 6.8 Hz, 2H), 4.28-4.49 (br, 1H), 6.53 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 2.8 Hz, 1H), 8.01 (dd, J = 2.8, 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.5 (CH_3), 12.1 (CH_3), 22.4 (CH_2), 23.2 (CH_2), 45.3 (CH_2), 107.9 (CH), 123.8 (CH), 124.5 (CH), 126.2 (C), 137.6 (C), 151.0 (C); IR (KBr, cm^{-1}) 3403, 1591, 1382; HRMS (EI, magnetic field) Calcd for $C_{11}H_{16}N_2O_2$: 208.1212. Found: 208.1211.

*4-Nitro-N, 2-dipropylaniline (**13Ac**)*



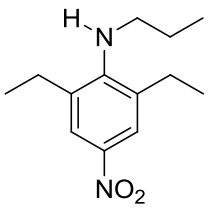
Yellow powder; mp 60–62 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.02 (t, J = 7.2 Hz, 3H), 1.03 (t, J = 7.2 Hz, 3H), 1.71 (m, 4H), 2.42 (t, J = 7.2 Hz, 2H), 3.24 (tq, J = 7.2, 8.0 Hz, 2H), 4.29-4.38 (br, 1H), 6.54 (d, J = 9.2 Hz, 1H), 7.95 (d, J = 2.4 Hz, 1H), 8.05 (dd, J = 2.4, 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.5 (CH_3), 14.0 (CH_3), 20.9 (CH_2), 22.4 (CH_2), 32.6 (CH_2), 45.3 (CH_2), 108.1 (CH), 124.5 (CH), 124.8 (C), 124.9 (CH), 139.5 (C), 151.1 (C); IR (KBr, cm^{-1}) 3402, 1530, 1383; HRMS (EI, magnetic field) Calcd for $C_{12}H_{18}N_2O_2$: 222.1368. Found: 222.1370.

*2-(1-Methyl)ethyl-4-nitro-N-propylaniline (**13Ad**)*



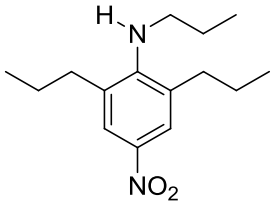
Yellow powder; mp 64–65 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01 (t, J = 7.2 Hz, 3H), 1.29 (d, J = 6.8 Hz, 6H), 1.76 (tq, J = 6.8, 7.2 Hz , 2H), 2.80 (sep., J = 6.8 Hz, 1H), 3.24 (t, J = 6.8 Hz, 2H), 4.48-4.58 (br, 1H), 6.54 (dd, J = 2.4, 9.6 Hz, 1H), 8.01 (d, J = 2.4 Hz, 1H), 8.03 (d, J = 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.5 (CH_3), 21.8 (CH_3), 22.3 (CH_2), 45.3 (CH_2), 108.4 (CH), 121.6 (CH), 124.2 (CH), 131.0 (C), 137.7 (C), 150.5 (C); IR (KBr, cm^{-1}) 3415, 1527, 1308; HRMS (EI, magnetic field) Calcd for $C_{12}H_{18}N_2O_2$: 222.1368. Found: 222.1369.

*2,6-Diethyl-4-nitro-N-propylaniline (**13Ae**)*



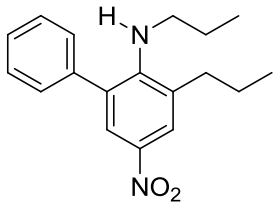
Yellow powder; mp 71–73 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.6 Hz, 6H), 1.64 (tq, J = 7.2, 7.2 Hz, 2H), 2.66 (q, J = 7.6 Hz, 4H), 3.10 (t, J = 7.2 Hz, 2H), 3.64-3.78 (br, 1H), 7.90 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.4 (CH_3), 13.7 (CH_3), 24.4 (CH_2), 25.1 (CH_2), 50.4 (CH_2), 122.8 (2CH), 132.6 (C), 140.7 (C), 151.9 (C); IR (KBr, cm^{-1}) 3419, 1588, 1324;

*4-Nitro-N,2,6-tripropylaniline (**13Af**)*



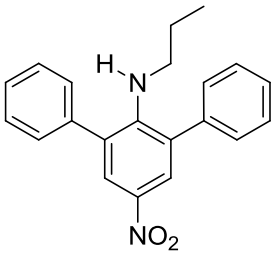
Yellow powder; mp 72–74 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01 (t, J = 7.2 Hz, 6H), 1.01 (t, J = 7.2 Hz, 3H), 1.60-1.72 (m, 6H), 2.61 (t, J = 7.6 Hz, 4H), 3.12 (t, J = 7.2 Hz , 2H), 7.88 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.4 (CH_3), 14.0 (CH_3), 22.6 (CH_2), 24.3 (CH_2), 34.4 (CH_2), 54.4 (CH_2), 123.6 (CH), 131.2 (C), 140.4 (C), 152.1 (C); IR (KBr, cm^{-1}) 3419, 1588, 1324; HRMS (EI, magnetic field) Calcd for $C_{15}H_{24}N_2O_2$: 264.1836. Found: 264.1836.

*4-Nitro-6-phenyl-N,2-dipropylaniline (**13Ag**)*



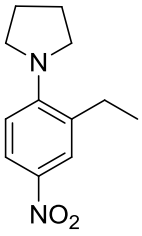
Yellow powder; mp 67–69 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.72 (t, J = 7.6 Hz, 3H), 1.05 (t, J = 7.2 Hz, 3H), 1.36 (tq, J = 7.2, 7.6 Hz , 2H), 1.72 (tq, J = 7.2, 7.6 Hz , 2H), 2.61 (t, J = 7.6 Hz , 2H), 2.71 (t, J = 7.2 Hz , 2H), 3.62-3.95 (br, 1H), 7.33-7.44 (m, 5H), 7.90 (d, J = 2.4 Hz , 1H), 7.98 (d, J = 2.4 Hz , 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.1 (CH_3), 14.1 (CH_3), 22.1 (CH_2), 23.9 (CH_2), 34.1 (CH_2), 43.4 (CH_2), 124.5 (CH), 125.9 (CH), 127.6 (CH), 128.1 (CH), 128.5 (CH), 129.3 (C), 129.6 (C), 139.1 (C), 139.7 (C), 151.1 (C); IR (KBr, cm^{-1}) 3415, 1586, 1321; HRMS (EI, magnetic field) Calcd for $C_{18}H_{22}N_2O_2$: 298.1681. Found: 298.1682.

*4-Nitro-2,6-diphenyl-N-propylaniline (**13Ah**)*



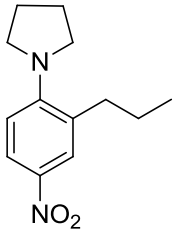
Yellow powder; mp 69–71 ˚C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.52 (t, J = 7.2 Hz, 3H), 1.15 (tq, J = 7.2, 7.2 Hz, 2H), 2.17 (s, 1H), 2.46 (t, J = 7.2 Hz, 2H), 7.39-7.46 (m, 10H), 8.02 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.8 (CH_3), 23.4 (CH_2), 48.8 (CH_2), 126.5 (CH), 128.0 (CH), 128.9 (CH), 129.1 (CH), 129.5 (C), 138.8 (C), 138.9(C), 150.4 (C); IR (KBr, cm^{-1}) 3393, 1487, 1321; HRMS (EI, magnetic field) Calcd for $C_{18}H_{22}N_2O_2$: 332.1525. Found: 332.1529.

*2-Ethyl-4-nitro-1-pyrrolidinobenzene (**13Bb**)*



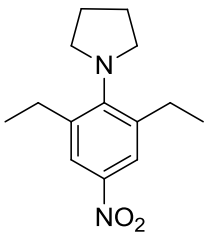
Yellow powder; mp 79–81 ˚C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, J = 7.6 Hz, 3H), 1.98-2.01 (m, 4H), 2.79 (q, J = 7.6 Hz , 2H), 3.42-3.46 (m, 4H), 6.66 (d, J = 9.2 Hz, 1H), 7.93 (dd, J = 2.8, 9.2 Hz, 1H), 7.99 (d, J = 2.8 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5 (CH_3), 25.7 (CH_2), 27.1 (CH_2), 51.2 (CH_2), 113.7 (CH), 123.1 (CH), 126.6 (CH), 130.4 (C), 138.7 (C), 153.7 (C); IR (KBr, cm^{-1}) 1597, 1309; HRMS (EI, magnetic field) Calcd for $C_{12}H_{16}N_2O_2$: 220.1212. Found: 220.1211.

*4-Nitro-2-propyl-1-pyrrolidinobenzene (**13Bc**)*



Yellow powder; mp 74–76 ˚C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, J = 7.6 Hz, 3H), 1.64 (tq, J = 7.6, 7.6 Hz, 2H), 1.94-2.00 (m, 4H), 2.73 (t, J = 7.6 Hz, 2H), 3.20-3.45 (m, 4H), 6.56 (d, J = 9.2 Hz, 1H), 7.94 (dd, J = 2.4, 9.2 Hz, 1H), 7.97 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (CH_3), 23.2 (CH_2), 25.7 (CH_2), 36.4 (CH_2), 51.1 (CH_2), 113.6 (CH), 123.1 (CH), 127.3 (CH), 128.6 (C), 138.4 (C), 153.6 (C); IR (KBr, cm^{-1}) 1517, 1340.

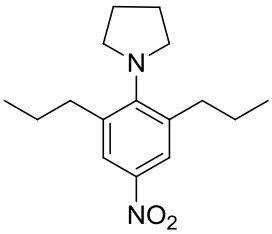
*2,6-Diethyl-4-nitro-pyrrodinobenzene (**13Be**)*



Yellow powder; mp 75–77 ˚C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, J = 7.2 Hz, 6H), 2.00-2.04 (m, 4H), 2.69 (q, J = 7.2 Hz , 4H), 3.19-3.21 (m, 4H), 7.94 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8 (CH_3), 24.9 (CH_2), 26.4 (CH_2), 51.4 (CH_2), 121.9 (CH),

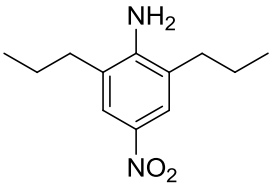
145.0 (C), 145.6 (C), 151.7 (C); IR (KBr, cm^{-1}) 1517, 1340; HRMS (EI, magnetic field) Calcd for $C_{14}H_{20}N_2O_2$: 248.1525. Found: 248.1524.

*4-Nitro-2,6-dipropyl-1-pyrrolidinobenzene (**13Bf**)*



Yellow powder; mp 76–78 ˚C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99 (t, J = 7.2 Hz, 6H), 1.67 (tq, J = 7.6, 7.6 Hz, 4H), 2.00-2.04 (m, 4H), 2.59 (t, J = 7.6 Hz , 4H), 3.17-3.20 (m, 4H), 7.91 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3 (CH_3), 23.8 (CH_2), 26.4 (CH_2), 34.1 (CH_2), 51.6 (CH_2), 122.4 (CH), 144.2 (C), 144.7 (C), 152.0 (C); IR (KBr, cm^{-1}) 1516, 1341; HRMS (EI, magnetic field) Calcd for $C_{16}H_{24}N_2O_2$: 276.1838. Found: 276.1839.

*4-Nitro-2,6-dipropylaniline (**8g**)*



Yellow powder; mp 93–95 ˚C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (t, J = 7.6 Hz, 6H), 1.74 (tq, J = 7.6, 7.6 Hz, 4H), 2.49 (t, J = 7.6 Hz , 4H), 4.27-4.31 (br, 2H), 7.89 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (CH_3), 21.1 (CH_2), 33.2 (CH_2), 123.3 (CH), 125.1 (C), 138.6 (C), 148.3 (C); IR (KBr, cm^{-1}) 3494, 3396, 1592, 1482; HRMS (EI, magnetic field) Calcd for $C_{12}H_{18}N_2O_2$: 222.1368. Found: 222.1693.

5. Reference

1. Diels-Alder type ring transformation: (a) J. D. Kirkham, R. J. Butlin, J. P. A. Harrity, *Angew. Chem. Int. Ed.* **2012**, *51*, 6402; (b) C. Sabot, E. Oueis, X. Brune, P. Y. Renard, *Chem. Commun.* **2012**, *48*, 768; (c) E. D. Anderson, D. L. Boger, *Org. Lett*. **2011**, *13*, 2492; (d) T. Delaunay, P. Genix, M. Es-Sayed, J. P. Vors, N. Monterio, G. Balme, G. *Org. Lett*. **2010**, *12*, 3328; (e) C. Wu, Y. Fang, R. C. Larock, F. Shi, *Org. Lett.* **2010**, *12*, 2234; (f) T. Miura, M. Yamauchi, M. Murakami, M. *Chem. Commun.* **2009**, 1470; (g) Y. Yoshino, T. Kurahashi, S-J. Matsubara, *J. Amer. Chem. Soc.* **2009**, *131*, 7494; (h) H. Xie, L. Zu, H. R. Oueis, H. Li, J. Wang, W. Wang, W. *Org. Lett*. **2008**, *10*, 1923. ANROR type ring transformation: (a) H. G. Bonacorso, J. Navarini, L. M. F. Porte, E. P. Pittaluga, A. F. Junges, A. R. Mayer, M. A. P. Martins, N. Zanatta, *J. Fluor. Chem.*

2013, *151*, 38; (b) P. A. Koutentis, M. Koyioni, S. S. Michaelidou, *Org. Biomol. Chem.* **2013**, *11*, 621; (c) A. Rykowski, E. Wolinska, D. Branowska, H. C. van der Plas, *ARKIVOC* **2004**, *iii*, 74; (c) G. Hajós, Z. Riedl, G. Kollenz, G. *Eur. J. Org. Chem.* **2001**, 3405; (d) H. C. van der Plas, *J. Heterocycl. Chem.* **2000**, *37*, 427.

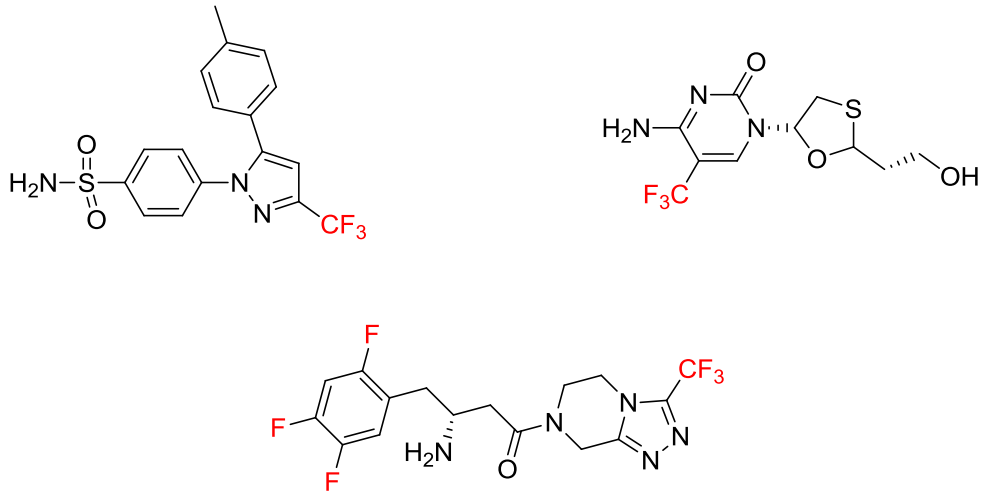
2. Nucleophilic type ring transformation: (a) C. Henry, A. Haupt, S. C. Turner. *J. Org. Chem.* **2009**, *74*, 1932; (b) G. P. Sagitullina, A. K. Garkushenko, Y. O. Vinokurova, V. A. Nyrkova, E. G. Atavin, R. S. Sagitullin. *Russ. Org. Chem.* **2009**, *45*, 1045; (c) Y. Tohda, T. Kawahara, M. Eiraku, K. Tani, N. Nishiwaki, M. Ariga. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2176.
3. (a) T. S. Le, H. Asahara; K. Kobiro, R. Sugimoto, K. Saigo, N. Nishiwaki, *Asian. J. Org. Chem.* **2014**, *3*, 297; (b) T. S. Le, H. Asahara, N. Nishiwaki, *Synthesis.* **2014**, 2175.
4. N. Nishiwaki, S. Hirao, J. Sawayama, K. Saigo, *Heterocycles* **2012**, *84*, 115.
5. Similar reaction mechanism was proposed for the ring transformation of the nitropyrimidinone: N. Nishiwaki, R. Sugimoto, K. Saigo, K. Kobiro. *Tetrahedron. Lett*. **2013**, *54*, 956.
6. H. Saka, M. Muraoka, S. Onuma. *Jpn. Kokai Tokkyo Koho*, **2002**-173476.
7. F. Chimenti, A. Boasco, D. Secci, P. Chimenti, A. Granese, A. *Synth. Commun*. **2004**, *34*, 2549.
8. C. M. Jamkhandi, J. I. Disouza. *J. Pharm. Sci*. **2013**, *5*, 225.
9. N. M. Rajendran, A. Haleel, N. Reddy, N. Dastagiri. *Organometallics* .**2014**, *33*, 217.
10. (a) F. J. Carver, C. A. Hunter, D. J. Livingstone, J. F. McCabe, E. M. Seward. *Chem. Eur. J*. **2002**, *8*, 2848; (b) S. Al-Khafaji, N. Cardinale, J. R. Hanson. *J. Chem. Res. Synopese.* **2003**, *388*, 701.
11. (a) P. Vollhardt, K. P. C. Vollhardt, N. E. Schore. *Organic Chemistry Sturcture and Function*. 5th ed. New York: W. H. Freeman and Company**, 2007**; (b) L. G. Wade. Jr. *Organic Chemistry*. 6th ed. New Jersey: Pearson Prentice Hall, **2006**.
12. For known compounds **7** and **8**; **8a**: T. Fehrentz, C. A. Kuttruff, F. M. E. Huber, M. A. Kienzler, P. Mayer, D. Trauner, *Chem. Bio. Chem.* **2013**, *14*, 1157; **8b**: T. Axenrod, C. M. Watnick, M. J. Wieder, S. Duangthai, G. A. Webb, H. J. C. Yeh, S. Bulusu, M. M. King, *Org. Mag. Res.* **1982**, *20*, 11; **8c**: E. A. Kuo, P. T. Hambleton, D. P. Kay, P. L. Evans, S. S. Matharu, E. Little, N. McDowall, C. B. Jones, C. J. R.

Hedgecock, *J. Med. Chem.* **1996**, *39,* 4608; **8d**: M. Birch, G. E. M. Sibley, D. Law, J. D. Oliver, *PCT Int. Appl.* WO **2009**-144473; **8e**: G. Baddeley, J. Kenner, *J. Chem. Soc.* **1935**, 303; **8f**: K. Minksztym, A. Jarczewski, *J. Mole. Struc.* **2004**, *691,* 203; **8h**, **7d**, **7f** and **7g**: N. Nishiwaki, H. Tatsumichi, M. Tamura, M. Ariga, *Lett. Org. Chem*. **2006**, *3*, 629; **8i**: D. Meinhard, M. Wegner, G. Kipiani, A. Hearley, P. Reuter, S. Fischer, O. Marti, B. Rieger, *J. Amer. Chem. Soc*. **2007**, *129*, 9182; **7a**: Y. Tohda, M. Eiraku, T. Nakagawa, Y. Usami, M. Ariga, T. Kawashima, K. Tani, H. Watanabe, Y. Mori, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2820; **7b**: Y. Liu, P. Ren, K. Jessen, X. Guo, C. Rommel, T. Wilson, E. Troy, *PCT Int. Appl*. WO **2014**-151147; **7c**: A. S. Jorgensen, P. Jacobsen, L. B. Christiansen, P. S. Bury, A. Kanstrup, S. M. Thorpe, L. Naerum, K. Wassermann, *Bioorg. Med. Chem. Lett.* **2000**, *10,* 2383; **7e**: W. Gruber, *Can. J. Chem*. **1953**, *31*, 1181; **7h**: ref. 2a; **7i**: P. Barczynski, H. C. van der Plas, *Reu. Trav. Chim. Pays-Bas***, 1978**, *97*, 256.

Chapter 7. Development of a New Substrate for Three Component Ring Transformation

1. Introduction

The synthesis of fluoro compounds has rapidly gained increasing attention during the past decades because of their many applications in the agrochemical[1] and pharmaceutical industries.[2] Indeed, CF_3 is often found in small molecule drug such as sitagliptin (Januvia), celecoxib (Celebrex), and emtricitabine (Atripla) because it can improve the binding affinity, physicochemical properties and metabolic stabibilty of molecule (Scheme 1).[3] Thus, an efficient synthetic method for fluorinated organic compounds should also be received much attentions.



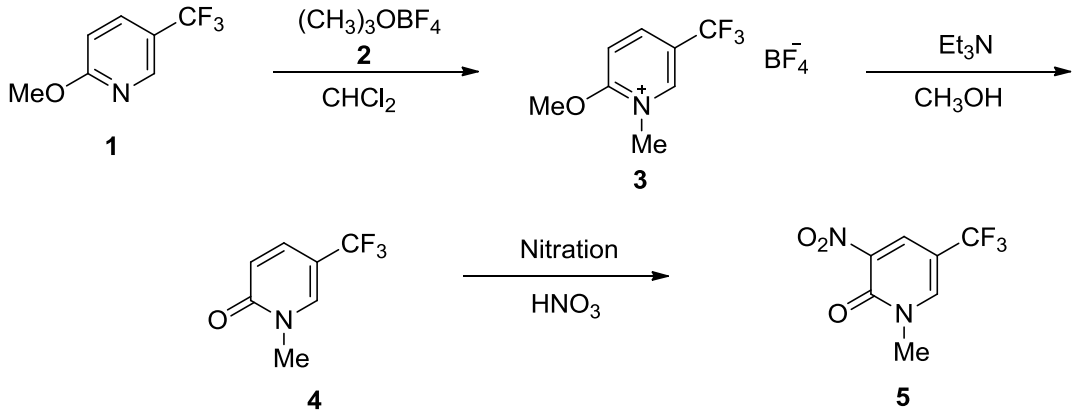
Scheme 1. Several top-selling drugs contain CF_3 group

As mentioned so far, the three component ring transformation (TCRT) of dinitropyridone becomes a powerful method for synthesis of various kinds of nitro compounds such as arylated nitropyridines, nitrated cycloalka[*b*]pyridines, nitroanilines and so on. The successful results promoted the author to develop a new substrate for this

TCRT, by which a nitro group at 5-position of dinitropyridone is replaced by CF_3 group, namely, 3-nitro-5-trifluoromethyl-*N*-methylpyridone will be developed.

2. The preparation of the new substrate

3-Nitro-5-trifluoromethyl-*N*-methyl-2-pyridone (**5**) was prepared with a few steps as descript in the literature.[4] The new substrate was synthesized as illustrated in Scheme 2.



2.1 The preparation of 2-methoxy-5-trifluoromethyl-*N*-methylpyridinium tetrafluoroborate

At first, trimethyloxonium tetrafluorobonate **2** was added to 3-methoxyl-5-trifluoromethylpyridine **1** in CH_2Cl_2. Then, the resultant mixture was kept at room temperature for 22 h. The solid trimethoxonium tetrafluoroborate gradually dissolved, the solution clarified, and a new precipitate gradually formed. Finally, the obtained solid was rinsed with hexane to remove any unreacted starting materials and the solvent was removed by pipette and residual was dried in vacuo to provide the 2-Methoxy-5-trifluoromethyl-*N*-methylpyridinium tetrafluoroborate **3** in 98% yield.

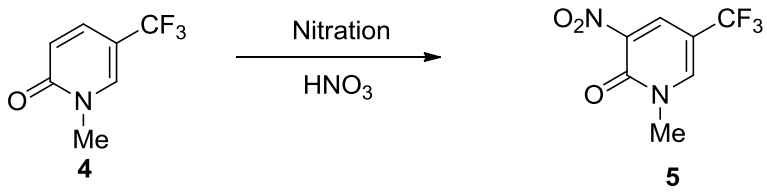
2.2 The preparation of 5-Trifluoromethyl-*N*-methylpyridone tetrafluoroborate

To a vial containing a stir bar, obtained solid **3** and methanol, trimethylamine was sequentially added. The resultant mixture was stirred at room temperature for 24 h. After removing the solvent by vacuum, the residue was purified by column chromatography (hexane: EtOAc = 95: 5) to afford 5-trifluoromethyl-*N*-methyl-2-pyridone **4** in 87% yield as a colourless wax.

2.3 The preparation of 3-Nitro-5-trifluoromethyl-*N*-methyl-2-pyridone

The nitration of compound **4** was performed upon treatment with nitric acid (Table 1). It is noticed that the nitration did not proceed when normal nitric acid was used (entries 1 and 2). On the other hand, fuming nitric acid was found to be more useful and the efficiency of the reaction was improved by conducting nitration with larger time (entries 3-5). Finally, a new substrate for TCRT, namely, 3-nitro-5-trifluoromethyl-*N*-methylpyridone **5** was developed.

Table 1. The nitration of 5-trifluromethyl-*N*-methylpyridone **4**



4 **5**

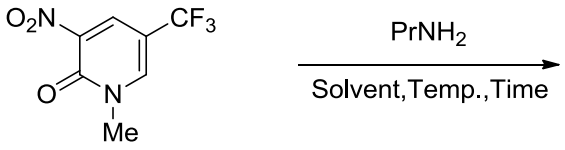
Entry	HNO_3	Temp.(^oC)	Time (h)	Yield (%)
1	Nomal	35	40	No reaction
2	Nomal	60	24	Trace
3	Fuming	60	6	Trace
4	Fuming	60	15	25
5	Fuming	60	24	46

3. The reaction of 3-nitro-5-trifluoromethyl-*N*-methylpyridone

3.1 The aminolysis of 3-nitro-5-trifluoromethyl-*N*-methyl-2-pyridone

The electron deficiency and electrophilicity of substrate **5** was estimated before beginning the study on TCRT reactions by the reaction with amine such as polyamine (Table 2). Unfortunately, the reaction of **5** with propylamine did not proceed at any reaction conditions as shown in Table 2. These fact indicate that the substrate **5** is less electrophilic than dinitropyridone, by which the reaction of the substrate **5** with nucleophilic reagents occur with difficulty.

Table 2. The aminolysis of **5**



5

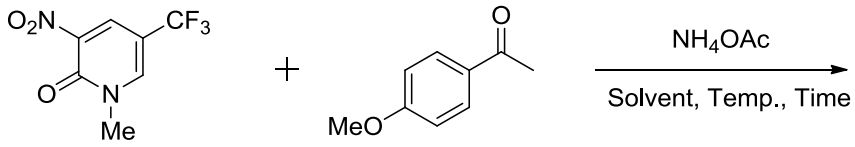
Entry	Slovent	Time (h)	Temp.(^{o}C)	Result	Recovery of **5** (%)
1	pyridine	5	50	No reaction	93
2	CH_3OH	5	50	No reaction	92
3	CH_3OH	24	65	No reaction	68
4[a]	CH_3OH	3	80	No reaction	94
5[a]	CH_3OH	3	100	No reaction	88
6[a]	CH_3OH	1	150	Not detected	-

[a]: microwave heating was used

3.2 The reaction of 3-nitro-5-trifluoromethyl-*N*-methyl-2-pyridone with with *p*-methoxyacetophenone in the presence of NH_4OAc

Compound **5** was also allowed to react with electron-rich p-methoxyacetophenone in the presence of NH_4OAc under different reaction conditions as shown in table 3. However, the reaction did not proceed even though larger amount of NH_4OAc were employed or under microwave heating conditiond.

Table 3. The reaction of 3-nitro-5-trifluoromethyl-*N*-methyl-2-pyridone **5** with with *p*-methoxyacetophenone in the presence of NH_4OAc.



5

Entry	Slovent	NH_4OAc (equiv.)	Time (h)	Temp.(^oC)	Recovery of **5**	Result
1	EtOH	15	24	65	98	No reaction
2	EtOH	15	24	80	97	No reaction
3	EtOH	30	3	80	97	No reaction
4[a]	EtOH	30	3	80	93	No reaction
5[a]	CH_3OH	30	3	80	98	No reaction
6[a]	$CHCl_3$	30	3	80	98	No reaction

[a]: microwave heating was used

4. Conclusion

Although a new substrate for TCRT was developed, however, any useful results have not been obtained until the date.

5. Reference

1. (a) Kirk, K. L. *Curr.Top. Med. Chem*. **2006**, *6*, 1447−1456; (b) Isanbor, C.; O'Hagan, D. J. *Fluorine Chem*. **2006**, *127*, 303−319; (c) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881−1886; (d) Schlosser, M. *Angew. Chem., Int. Ed*. **1998**, *37*, 1496−1513; (e) Gouverneur, V.; Muller, K. *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applicati0ns*; Imperial College Press: London, **2012**; (f) Zhang, X. J.; Lai, T. B.; Kong, R. Y.; *Top. Curr. Chem*. **2012**, *308*, 365-404.
2. (a) Maienfish, P.; Hall, R. G. *Chimia* **2004**, *58*, 93−99. (b) Dhara, M. G.; Banerjee, S. *Prog. Polym. Sci*. **2010**, *35*, 1022−1077. (c) Cametti, M.; Crousse, B.; Metrangolo, P.; Milani, R.; Resnati, G. *Chem. Soc. Rev*. **2012**, *41*, 31−42. (d) Li, Y. *Acc. Chem. Res*. **2012**, *45*, 723−733.
3. (a) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, **2004**;. (b) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, UK, **2006**.
4. Zhang, X.; Wang, J.; Wan. Z, *Org. Lett.*, **2015**, *17* , 2086–2089