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Study on Synthesis of Polyfunctionalized Heterocyclic Compounds Using β-Keto Amides

(β−ケトアミドの特性を活かした多官能複素環化合物の合成)

Sho Hirai

1186002

A dissertation submitted to the Engineering Course,

Department of Engineering, Graduate School of Engineering,

Kochi University of Technology,

Kochi, Japan

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Assessment Committee:

Supervisor: Nishiwaki Nagatoshi

Co-Supervisor: Kazuya Kobiro

Co-Supervisor: Ryuichi Sugimoto

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Chapter 1. General Introduction

1,3-Dicarbonyl frameworks such as β-diketone, β-keto ester, β-diester, and β-keto amide are one of the important classes in organic compounds, and are widely used in synthetic chemistry. The highly acidic methylene group serves as a nucleophilic site, and the carbonyl group serves as an electrophilic site, which facilitates versatile multi-component reactions to afford polyfunctionalized compounds.[1-6] Indeed, a number of synthetic methods for heterocyclic compounds using 1,3-dicarbonyl compounds have been developed from old time, affording pyridines, pyrroles, indoles, quinolines, oxazoles, dihydropyrimidinones, pyrazoles, dihydropyridines and so on.[7-14]

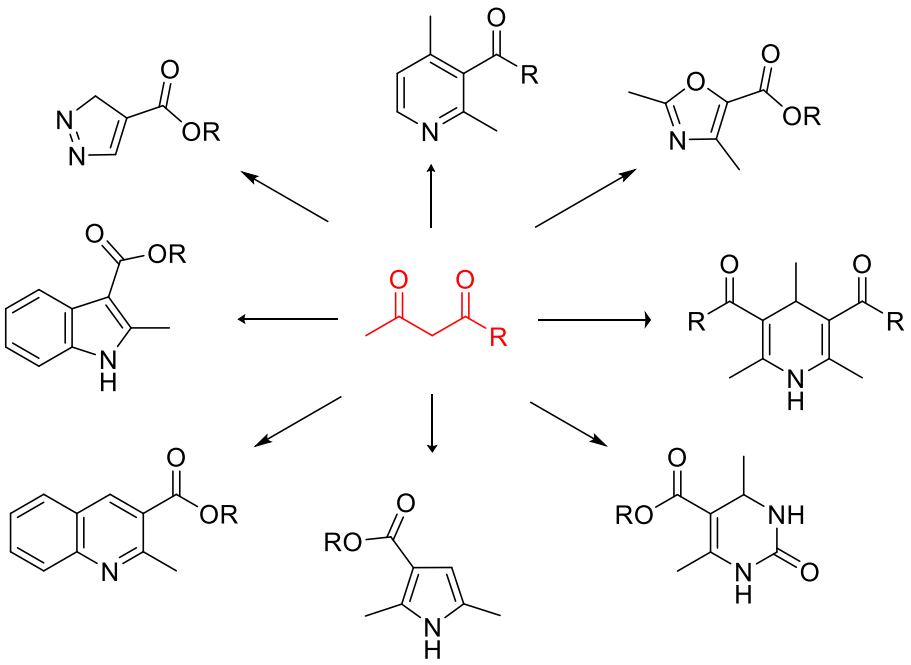


Figure 1. Illustrative use of synthesis of heterocyclic compound derived from 1,3-dicarbonyl compounds.

While 1,3-dicarbonyl compounds have been energetically investigated for a long time, novel reactivity is often discovered even now.[15-21] Although numerous reports dealing with 1,3-dicarbonyl compounds have been reported, the mainly discussed topics deal with chemistry of β-diesters β-keto esters and β-diketones. Among 1,3-dicarbonyl compounds,

β-keto amides, which have two nucleophilic sites and two electrophilic sites, are attractive synthetic reagents. Currently, however, there are fewer reports dealing with β-keto amides rather that with β-diketones or β-keto esters. This is presumably due to misconceptions about the reactivity of β-keto amides: although the amide moiety is generally less reactive than the ester moiety towards nucleophilic reagents, β-keto amides actually display high reactivity as well as β-keto esters.[22-26] Indeed, nucleophilic substitution at the amide moiety of β-keto amides is also reported.[27,28] Estimated electrophilicities by DFT method indicate that both carbonyl groups of β-keto amide are rather electrophilic compared with those of β-keto ester. Moreover, the amide group serves as nucleophilic site and can interact with reactant by forming intramolecular hydrogen bond. Hence, keto amides are expected to show hitherto unknown reactivities.

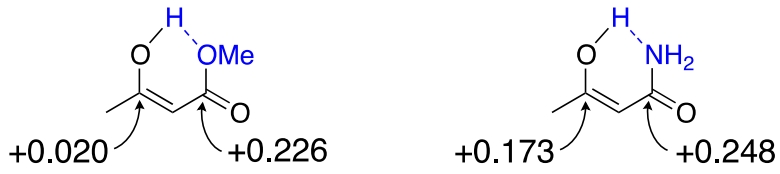
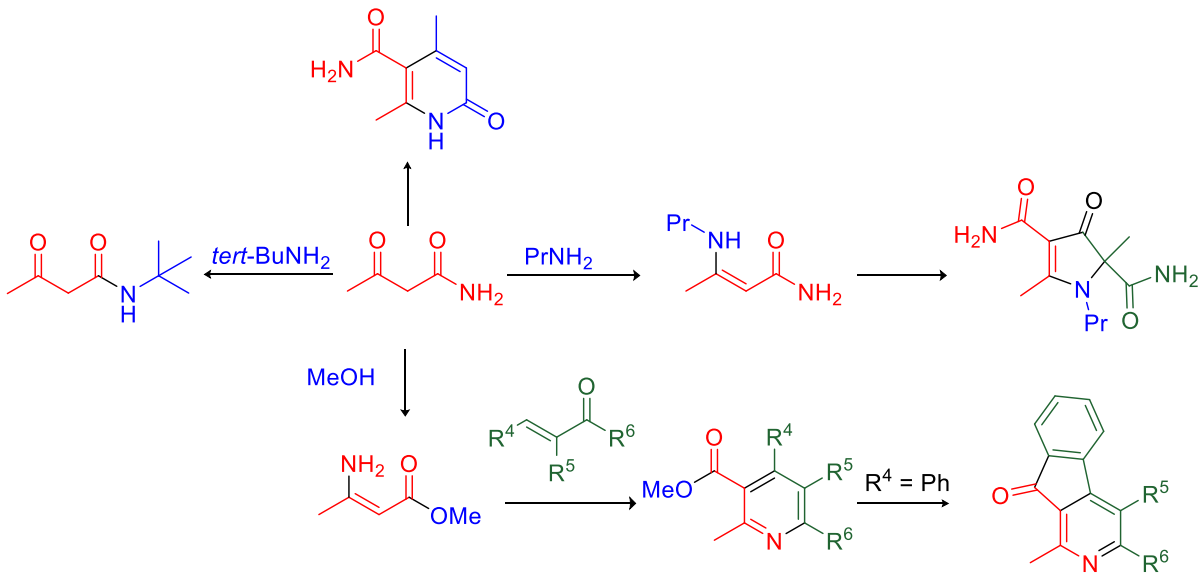


Figure 2. Estimated electrophilicities of carbonyl groups using DFT calculation using 6-31G^{+}.

Taking the structural features into my consideration, I evaluated the reactivity of β-keto amide systematically, and synthesized of aza-heterocyclic compounds using β-keto amide as a building block. In Chapter 2, I described the efficient dimerization of acetoacetamide leading to 4,6-dimethyl-2-pyridone-5-carboxamide. In Chapter 3, I surveyed the reactivity of β-keto amides with various amines. Chapter 4 deals with synthesis of bis(functinalized) pyrrolinones by the dimerization of 3-amino-2-butenamides. In Chapters 5 and 6, I described the synthesis of polysubstituted nicotinate using enamino esters and transacylation of α-arylated β-keto esters.



Scheme 1. Overview of in this thesis.

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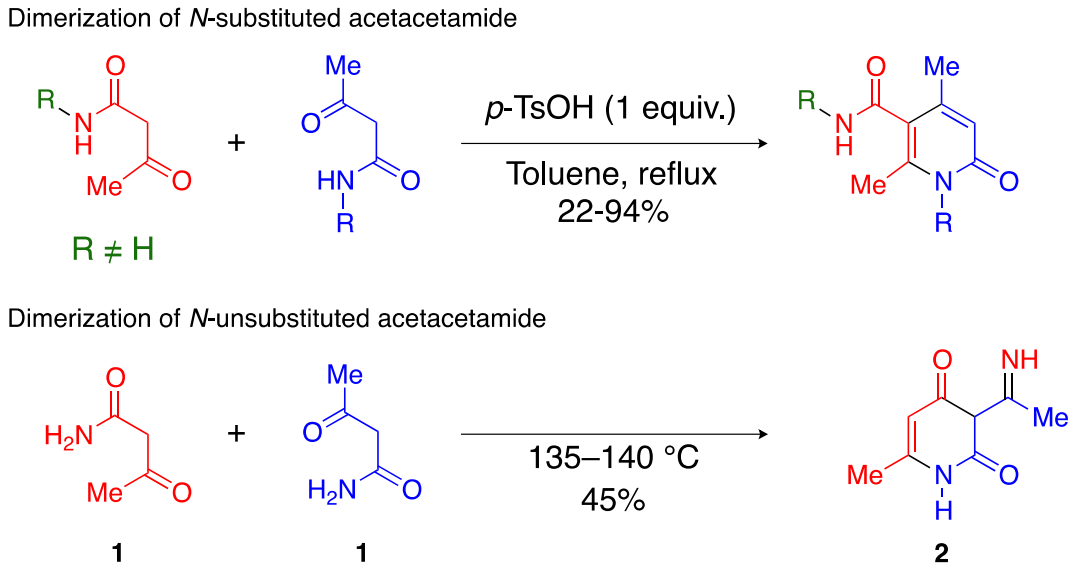
Chapter 2. Synthesis of 4,6-dimethyl-2-pyridone-5-carboxamide

1. Introduction

2-Pyridone-5-carboxamide scaffold are widely used bioactive compounds[1-3] and their synthetic intermediates (Figure 1).[4,5] While multi-step reactions were necessary to construct pyridonecarboxamide framework,[6] one-step synthesis of this structure was achieved by the dimerization of acetoacetamide derivatives. It is attractive because acetoacetamides (3-oxobutanamides) are easily prepared upon treatment of diketene with amines.[7] Therefore, a variety of *N*-substituted pyridonecarboxamides are synthesized by the dimerization of corresponding *N*-substituted acetoacetamides, in which stoichiometric amount of acid should be added (Scheme 1).[8-10] To the contrary, the dimerization of the *N*-unsubstituted acetoacetamide **1** has not been successfully achieved in a similar way. Kato *et al.* have studied this dimerization under heating, they only isolated 3-acetimidoyl-6-methylpyridine -2,4(1*H*,3*H*)-dione instead of the desired 4,6-dimethyl-2-pyridone-5-carboxamide.[11,12] From this viewpoint, I tried to efficiently synthesize 2-pyridone-5-carboxyamide **2** by dimerization of acetoacetamide **1** under mild conditions.

Figure 1. Pharmaceutical reagent about 2-pyridone-5-carboxamide.

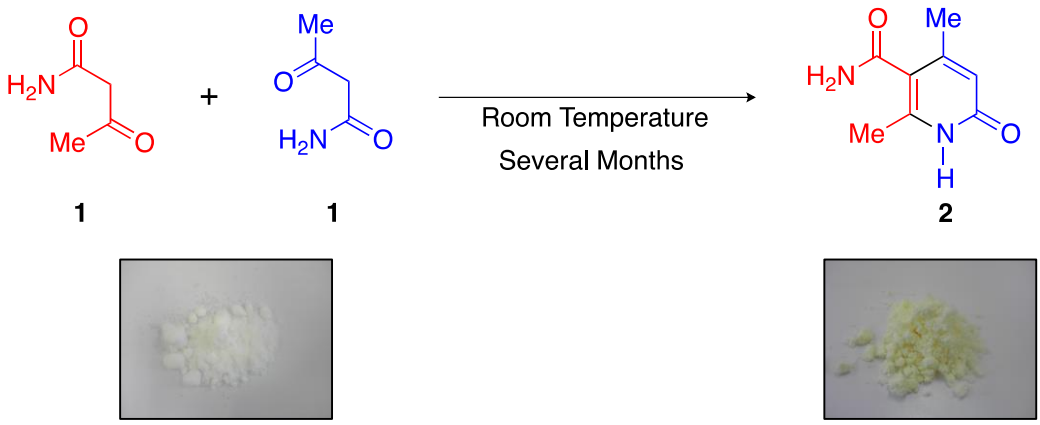


Scheme 1. Dimerization of acetoacetamides.

2. Results and Discussions

2-1. Dimerization of acetoacetamide at room temperature

When I used commercially available acetoacetamide **1**, I noticed that the structural change occurred in the bottle, which is stored for long time (Scheme 2). This product was easily purified by washing with chloroform, and was measured ^{1}H NMR using DMSO-d_6 solvent. As a result, two singlet signals were observed at 2.07 ppm (3H) and 2.15 ppm (3H) in addition to three singlet signals at 6.00 ppm (1H), 7.41 ppm (1H), 7.65 ppm (1H) and broad singlet signal at 11.39 ppm (1H). Therefore, we decided this compound to be a 4,6-dimethyl-5-carboxamide **2** based on other spectral data. Surprisingly, dimerization of acetoacetamide **1** proceeded in the bottle without any additive and any special reaction conditions.



Scheme 2. Structural change inside the reagent bottle.

At first, we monitored the reaction using ^{1}H NMR for one year whether the dimerization proceed inside the reagent bottle by only left at room temperature. When acetoacetamide **1** was stood in air at room temperature for six months, new signals were observed in the ^{1}H NMR spectrum of the resultant mixture. The compound has formed showed a couple of doublets possessing a large coupling constant (17.2 Hz). These signals indicate the presence of unequivalent geminal protons, would be assigned to a methylene group in a cyclic framework. In addition, other than signals arising from two methyl groups, five protons were also observed to be exchangeable with deuteriums by D_2O. On the basis of these data, the compound was confirmed to be the intermediate **3**. Finally, the signals of the pyridone **2** appeared after standing for one year.

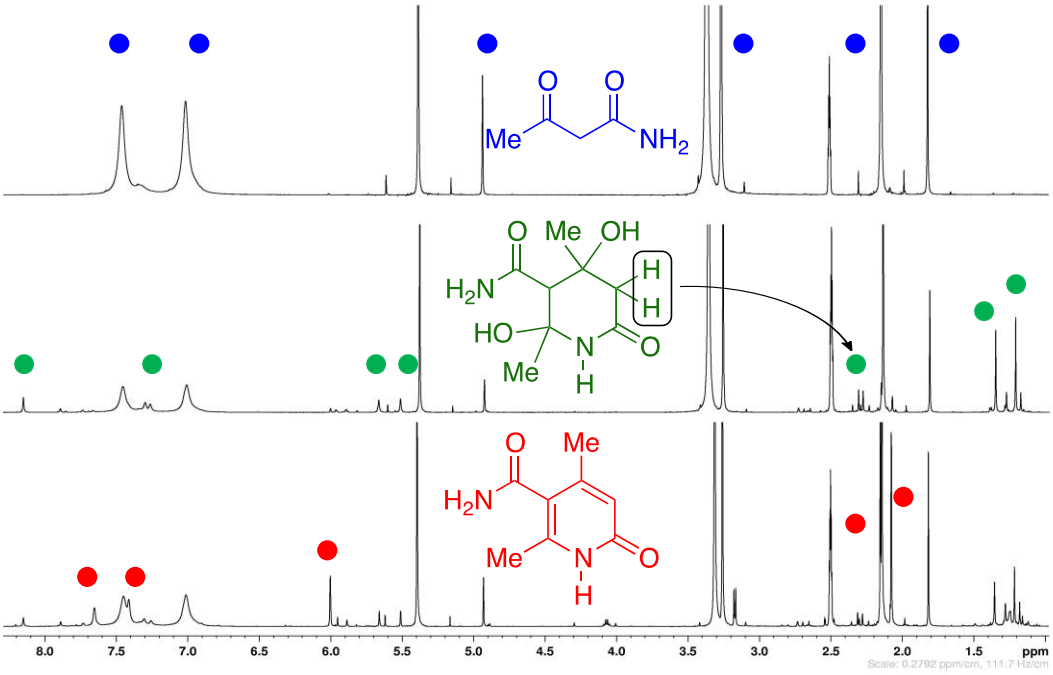
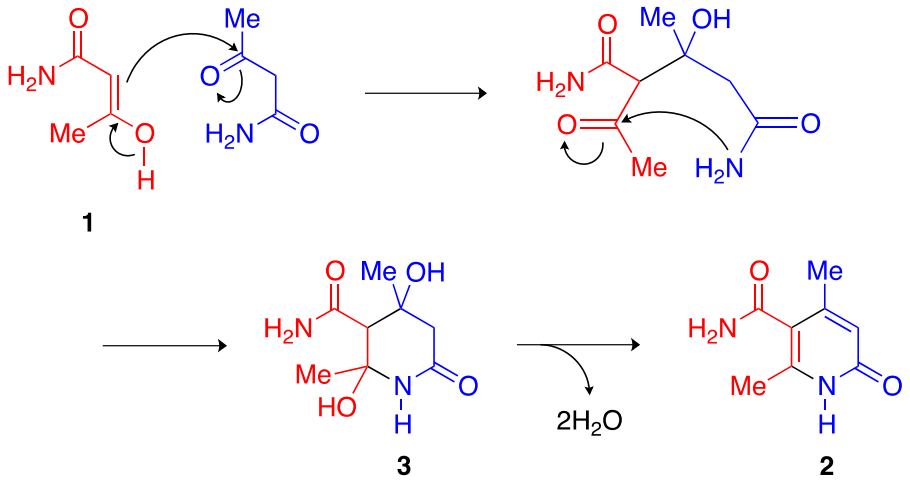


Figure 2. Monitoring of the reaction by ^{1}H NMR.

2-2. A plausible mechanism

A plausible mechanism was illustrated in Scheme 3 based on the above result. The enol form of acetoacetamide **1** attacks the ketone moiety of another acetoacetamide **1** to afford the adduct, and the following intramolecular cyclization affords piperidine intermediate **3**. Then, dehydration accompanied by aromatization proceeds to afford pyridonecarboxamide **2**. We confirmed the dimerization of acetoacetamide **1** by one-year monitoring. This fact is certainly interesting, however, this reaction cannot be practically used because it proceeds too slowly. So, I attempted to accelerate the dimerization to complete within shorter time.

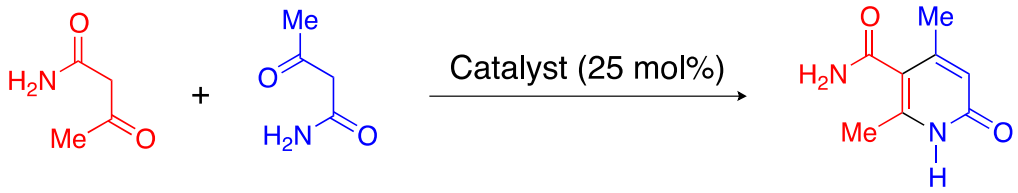


Scheme 3. A plausible mechanism.

2-3. Optimization of reaction conditions

In this section, optimization of reaction conditions was studied to use the dimerization practically. Although we tried to heat acetoacetamide **1** in several kinds of solvents, the dimerization did not proceed at all with recovery of the starting material **1**. Addition of a dehydrating agent such as molecular sieves or magnesium sulfate was not effective. On the other hand, acid catalysts promoted the dimerization reaction, and *p*-TsOH was the most effective (Table, runs 1–4). For this acid-catalyzed dimerization, non-polar benzene was found to be the most suitable, because generated water was easily separated from the reaction mixture (runs 4–9). With regard to the reaction temperature, heating at a temperature higher than 60 °C resulted in the efficient dimerization of **2** (runs 4, 10 and 11), in which **2** melted (mp 53–56 °C) and liquified. Furthermore, no solvent was required when **2** melted (run 12). This experimental fact enabled us to carry out the dimerization under milder reaction conditions, such as lower temperature (60 °C), shorter reaction time (1 h) and less amount of catalyst (5 mol%) (runs 12–18). Because a lower temperature could be employed, it is not necessary to use a sealed tube anymore. Consequently, the pyridone **2** was successfully obtained in a quantitative yield by using an opened reaction vessel, because the generated water easily went out.

Table 1. Optimization of the reaction conditions for dimerization of acetoacetamide.

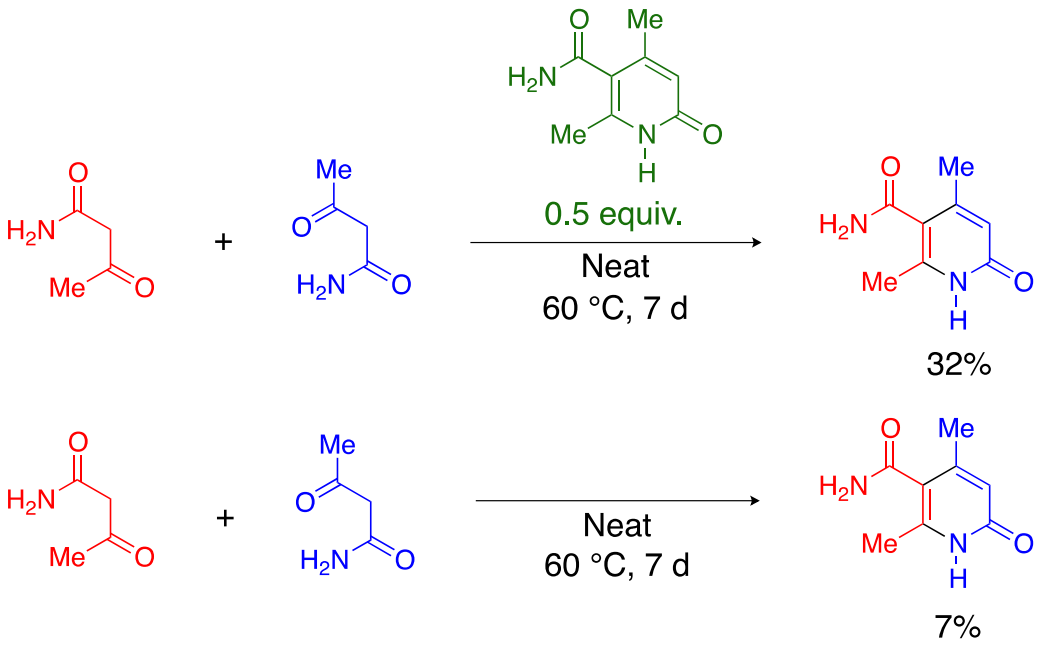


Run	Tube	Solvent	Catalyst	Temp/°C	Time/h	Yield/%
1	close	PhH	AcOH	90	12	3
2	close	PhH	12 M HCl	90	12	51
3	close	PhH	18 M H_2SO_4	90	12	72
4	close	PhH	*p*-TsOH	90	12	81
5	close	H_2O	*p*-TsOH	90	12	1
6	close	MeOH	*p*-TsOH	90	12	4
7	close	THF	*p*-TsOH	90	12	15
8	close	MeCN	*p*-TsOH	90	12	22
9	close	$CHCl_3$	*p*-TsOH	90	12	56
10	close	PhH	*p*-TsOH	60	12	76
11	close	PhH	*p*-TsOH	30	12	39
12	close	None	*p*-TsOH	90	12	96
13[a]	open	None	*p*-TsOH	90	12	quant.
14	open	None	*p*-TsOH	90	1	82
15[a]	open	None	*p*-TsOH	90	1	38
16	open	None	*p*-TsOH	60	12	quant.
17[a]	open	None	*p*-TsOH	60	12	97
18	open	None	*p*-TsOH	60	1	32

[a] 5 mol% of *p*-TsOH was used.

2-4. Self-catalyzed reaction

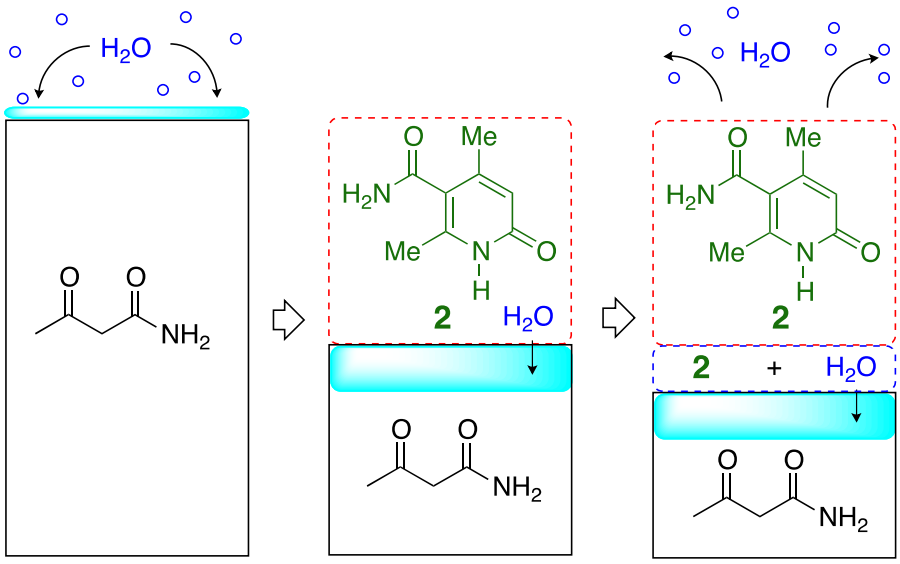
Next, I investigated how the dimerization of acetoacetamide proceeds in the bottle. When I store the reagent in the bottle, the ambient temperature should not be 60 °C and no acid such as *p*-TsOH was contained in the bottle. So I focused on the product **2**. The pyridone **2** is acidic as well as phenol, namely, the p*K*a values of unsubstituted pyridone and phenol are 17.0 and 18.0 (in DMSO), respectively.[13] Therefore, pyridonecarboxamide **2** should represent higher acidity because of possessing electron-withdrawing group. So I consider that the produced pyridone **2** serves as a self-catalyst in this dimerization to proceed in the reaction efficiently. Indeed, when the isolated pyridone **2** was added to a reaction mixture, the rate of the dimerization became faster, by which **2** was confirmed to serve as a self-catalyst (Scheme 4).



Scheme 4. The pyridone **2** served as a self-catalyst in this dimerization.

2-5. A plausible mechanism for the formation of the pyridone 2 in a purchased bottle

A plausible mechanism for the formation of the pyridone **2** in a purchased bottle of acetoacetamide **1** is provided in Scheme 5. First, **1** is partially converted into a solution because of its high hygroscopic property, in which the dimerization occurs to afford **2**. Then, the generated water penetrates inside, and generated **2** serves as an acid catalyst for the dimerization. When a bottle containing **1** is often opened, the generated water goes out as a vapor, which promotes the further condensation. Upon repeating these steps, the dimerization proceeds successively to afford pyridonecarboxamide **2** in good yield after several months.



Scheme 5. A plausible mechanism inside a bottle for dimerization of acetoacetamide **1**.

3. Conclusions

A novel method for the quantitative synthesis of pyridonecarboxamide **2** was developed through the dimerization of acetoacetamide **1** by using an acid catalyst. This method requires only simple manipulations and proceeds efficiently under mild conditions. Moreover, I found a commercially purchased acetoacetamide dimerize during storage for several months to afford pyridone **2** and the formed pyridone **2** serves as a catalyst. Thus, I recommend to check acetoacetamide **1** in a bottle before use if it is stored for a long time.

4. Experimental section and characterization of compounds

4-1. General Information

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.

4-2. Monitoring of the dimerization of acetoacetamide

Purchased acetoacetamide **1** (1 g) was extracted with $CHCl_3$ (3 × 10 mL) beforehand, and the $CHCl_3$ solution was concentrated to afford almost pure acetoacetamide **1**. Then, **1** was stood in air at room temperature for one year with monitoring the progress of the reaction by ^{1}H NMR every two weeks.

3-Oxobutanamide (1):[14] White solid, mp 52-53 °C. R_f = 0.45 (silica gel, hexane/EtOAc, 8/2), This compound exists as a mixture of keto and enol forms. The integral values for each tautomer are represented as H_k and H_e, respectively, and these isomers present in 98/2 ratio. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (s, 3H_e), 2.27 (s, 3H_k), 3.43 (s, 2H_k), 4.86 (s, 1H_e), 5.7-5.8 (br, 1H_e+1H_k), 6.9-7.0 (br, 1H_e+1H_k), 13.6-13.7 (br, 1H_e); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (CH_3), 31.1 (CH_3), 49.4 (CH_2), 90.0 (CH), 168.0 (C), 174.1 (C), 175.2 (C), 204.2 (C); IR (ATR/cm^{-1}) 3345, 2359, 1718, 1667.

4,6-Dimethyl-2-pyridone-5-carboxamide (2):[14] Pale yellow solid, mp 326-328 (dec.) °C. R_f = 0.76 (silica gel, ethanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.07 (s, 3H), 2.15 (s, 3H), 6.00 (s, 1H), 7.41 (s, 1H), 7.65 (s, 1H), 11.39 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 16.9 (CH_3), 19.4 (CH_3), 115.8 (CH), 117.0 (C), 141.6 (C), 149.1 (C), 162.0 (C), 168.3 (C); IR (ATR/cm^{-1}) 2361, 1651.

3,4,5,6-Tetrahydro-4,6-dihydroxy-4,6-dimethyl-2-pyridone-5-carboxamide (3):[15] R_f = 0.73 (silica gel, hexane/EtOAc, 8/2). Formation of **3** was confirmed by ^{1}H NMR of the reaction mixture, however, **3** was not isolated because of the conversion to **2** during the purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (s, 3H), 1.35 (s, 3H), 2.26 (d, J = 17.2 Hz, 1H), 2.33 (d, J = 17.2 Hz, 1H), 5.5–5.6 (br, 1H, exchangeable with D_2O), 5.6–5.7 (br, 1H, exchangeable with D_2O), 7.2–7.3 (br, 1H, exchangeable with D_2O), 7.3–7.4 (br, 1H, exchangeable with D_2O), 8.1–8.2 (br, 1H, exchangeable with D_2O).

4-3. Synthesis of 4,6-dimethyl-2-pyridone-5-carboxamide (2)

A mixture of acetoacetamide **1** (101.1 mg, 1 mmol) and *p*-toluenesulfonic acid (*p*-TsOH) (9.6 mg, 0.05 mmol) was heated without solvent at 60 °C for 12 h. After cooling the reaction mixture, the quantitative formation of the pyridone **2** was confirmed by ^{1}H NMR, and the yield was estimated by using CH_2Br_2 as an internal standard. The separation of *p*-TsOH was performed by recrystallization from EtOH (10 mL) to afford **2** as colorless plates (57.9 mg, yield 58% based on **1**).

4-4. Self-catalyzed dimerization

To a mixture of acetoacetamide **1** (20.2 mg, 0.2 mmol) and the pyridone **2** (8.3 mg, 0.05 mmol) was added H_2O (180 μL, 10 mmol), and the resultant mixture was heated at 90 °C for 1 week with adding H_2O every 12 h (13 × 200 μL). The yield of pyridone **2** was determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

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Chapter 3. Chemoselective Amination of β-Keto Amides

1. Introduction

1,3-Dicarbonyl compounds, which are active methylene compounds, possess both nucleophilic and electrophilic sites and therefore exhibit versatile reactivity and serve as useful building blocks for various functional materials.[1-13] Among 1,3-dicarbonyl compounds, β-keto amides, which have two nucleophilic sites and two electrophilic sites, are attractive synthetic reagents. Currently, however, there are fewer reports dealing with β-keto amides rather that with β-diketones or β-keto esters. This is presumably due to misconceptions about the reactivity of β-keto amides: although the amide moiety is generally less reactive than the ester moiety towards nucleophilic reagents, β-keto amides actually display high reactivity as well as β-keto esters.[14-19] Indeed, nucleophilic substitutions at the amide moiety of β-keto amides have been observed.[20,21] Despite the promising high reactivity of β-keto amides, to the best of our knowledge, there has been no systematic study focusing on their reactivity towards nucleophiles. This prompted us to examine the reactions of β-keto amides with various amines. These reactions afford β-amino-α,β-unsaturated amides via condensation at the ketone moiety, and allow direct synthesis of *N*-substituted β-keto amides from *N*-unsubstituted β-keto amides without the use of β-keto esters as synthetic intermediates.

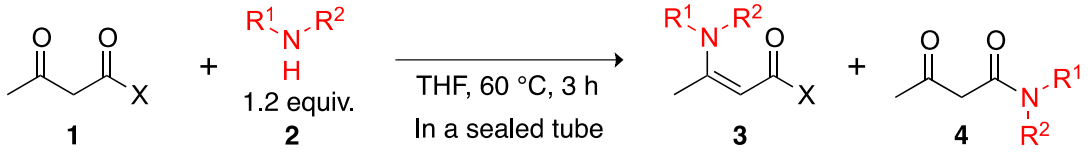
2. Results and Discussions

2-1. Reaction of acetoacetamides 1 with amines 2 at low temperature

Acetoacetamide **1A** was reacted with various amines **2** (Table 1). To a solution of acetoacetamide **1A** in THF, 1.2 equivalents of propylamine **2a** were added, and the resultant mixture was heated at 60 °C for 3 h. After removal of the solvent, the residue was extracted with hot hexane to afford 3-propylamino-2-butenamide (**3Aa**) in 84% yield as a pure form (Entry 1). The reaction did not go to completion because the volatile amine evaporated from the reaction mixture. This was solved by using a sealed tube, which increased the yield of **3Aa** to 97% (Entry 2). The primary amines, isobutylamine **2b** and benzylamine **2c**, reacted readily at the ketone moiety to afford the corresponding amides **3Ab** and **3Ac**, respectively (Entries 3 and 4).

The reaction was influenced by the steric bulk of the amine. While *sec*-butylamine **2d** furnished **3Ad** in moderate yield, bulkier *tert*-butylamine **2e** gave no reaction under the same conditions (Entries 5 and 6). For the less nucleophilic aromatic amine *p*-anisidine **2f**, β-aminated enamide **3Af** was similarly obtained in high yield, although a longer reaction time was necessary (Entries 7 and 8). The secondary amines, pyrrolidine **2g** and diethylamine **2h**, displayed different reactivities. While enamide **3Ag** was readily formed by the reaction of **1A** with **2g**, no product was observed for diethylamine **2h** (Entries 9 and 10), presumably due to steric hindrance by the flexible alkyl groups. The β-amination also proceeded when an *N*-substituent was present on the amide moiety, affording enamides **3Bb** and **3Cb** in high yields upon treatment of **1B** and **1C** with isobutylamine **2b** (Entries 11 and 12). These results suggest that the ketone moiety is not activated by the intramolecular hydrogen bond with the amide N–H.

Table 1. Reaction of acetoacetamides **1** with amines **2** at lower temperature (60 °C).



Entry	Substrate		Amine		Product		Yield(%)	
	X		R^1	R^2			**3**	**4**
1[a]	NH_2	**1A**	Pr	H	**2a**	**Aa**	84	0
2	NH_2	**1A**	Pr	H	**2a**	**Aa**	97	0
3	NH_2	**1A**	*iso*-Bu	H	**2b**	**Ab**	94	0
4	NH_2	**1A**	$PhCH_2$	H	**2c**	**Ac**	95	0
5	NH_2	**1A**	*sec*-Bu	H	**2d**	**Ad**	76	0
6	NH_2	**1A**	*tert*-Bu	H	**2e**	**Ae**	0	0
7	NH_2	**1A**	*p*-$MeOC_6H_4$	H	**2f**	**Af**	31	0
8[b]	NH_2	**1A**	*p*-$MeOC_6H_4$	H	**2f**	**Af**	86	0
9	NH_2	**1A**	$-(CH_2)_4-$		**2g**	**Ag**	92	0
10	NH_2	**1A**	Et	Et	**2h**	**Ah**	0	0
11	NHPr	**1B**	*iso*-Bu	H	**2b**	**Bb**	91	0
12	NMe_2	**1C**	*iso*-Bu	H	**2b**	**Cb**	92	0

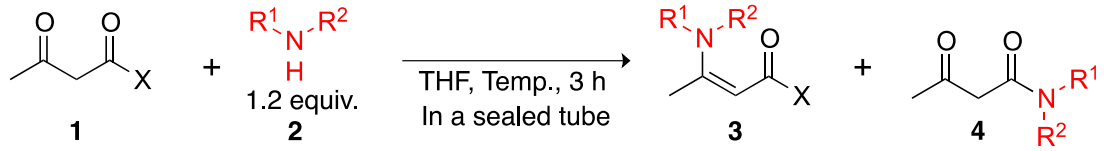
[a] Open vessel, [b] Reaction time was 24 h.

2-2. Reaction of acetoacetamides 1 with amines 2 at high temperature

At higher temperatures, β-keto amide **1A** exhibited different reactivity (Table 2). When acetoacetamide **1A** was reacted with **2** equivalents of propylamine **2a** at 130 °C, enamide **3Aa** was obtained quantitatively without any observation of further reaction, indicating that **3Aa** does not react with amine **2a**, even under harsh conditions (Entry 1). Contrastingly, bulkier *sec*-butylamine **2d** underwent substitution at the amide moiety to afford *N*-substituted acetoacetamide **4Ad** in addition to enamide **3Ad** (Entry 2). For *tert*-butylamine **2e**, **4Ae** was obtained as the sole product, although product decomposition occurred competitively (Entry 3). Since butanamide **5** could be recovered following treatment with *tert*-butylamine **2e** under the same conditions, the amide carbonyl group of **1A** must be activated by the β-carbonyl group (Scheme 1). When **1A** was reacted with the acyclic secondary amines, diethylamine **2h** and diisopropylamine **2i**, *N*-substituted acetoacetamides **4Ah** and **4Ai** were formed,

respectively (Entries 4 and 5). The substitution was not impeded by a dimethylamino group, and **4Ch** was obtained in high yield (Entry 6). The reaction of β-keto ester **1D** with a bulky amine gave similar results. While enamide **3Db** was formed when **1D** was treated with isobutylamine **2b** at low temperature, no reaction was observed when **1D** was treated with *tert*-butylamine **2e** under the same conditions (Entries 7 and 8). Conversely, substitution by **2e** at the ester moiety proceeded at a higher temperature (Entry 9).

Table 2. Reaction of acetoacetamides **1** with amines **2** at higher temperature (130 °C).



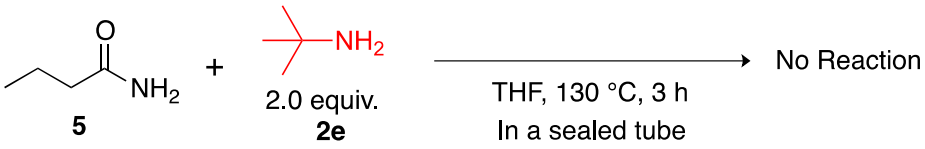
Entry	Substrate		Amine			Temp.(°C)	Product	Yield(%)	
	X		R^1	R^2				**3**	**4**
1[a]	NH_2	**1A**	Pr	H	**2a**	130	**Aa**	99	0
2[a]	NH_2	**1A**	*sec*-Bu	H	**2d**	130	**Ad**	61	30
3[a]	NH_2	**1A**	*tert*-Bu	H	**2e**	130	**Ae**	0	65
4[a]	NH_2	**1A**	Et	Et	**2h**	130	**Ah**	0	99
5[a]	NH_2	**1A**	*iso*-Pr	*iso*-Pr	**2i**	130	**Ai**	0	73
6[a]	NMe_2	**1C**	Et	Et	**2h**	130	**Ch**	0	92
7	OEt	**1D**	*iso*-Bu	H	**2a**	60	**Da**	92	0
8	OEt	**1D**	*tert*-Bu	H	**2e**	60	**De**	0	0
9[a]	OEt	**1D**	*tert*-Bu	H	**2e**	130	**De**	0	45

[a] 2.0 equiv. of amine were used.

2-3. The chemoselectivity between 3 and 4 depending on the steric hindrance

To rationalize the dependence of the chemoselectivity between **3** and **4** on the steric bulk of the amine, heats of formation of **3Aa**, **3Ae**, **4Aa**, and **4Ae** were calculated by DFT method using B3LYP/6-31G*. Each compound has several possible conformations, among which the most stable are shown in Figure 1.[22,23] In the conversion of acetoacetamide **1A** to either a β-aminobutenamide or an *N*-substituted acetoacetamide, water or ammonia splits off, respectively. Therefore, the DFT calculation was performed at approximately the heat of

formation of each product, with water or ammonia present. In the reaction of **1A** with propylamine **2a**, enamide **3Aa** is more stable than acetoacetamide **4Aa**, whereas in the reaction of **1A** with *tert*-butylamine **2e**, acetoacetamide **4Ae** is more stable than enamide **3Ae** (Figure 1).



Scheme 1. Study on the role of the β-carbonyl group.

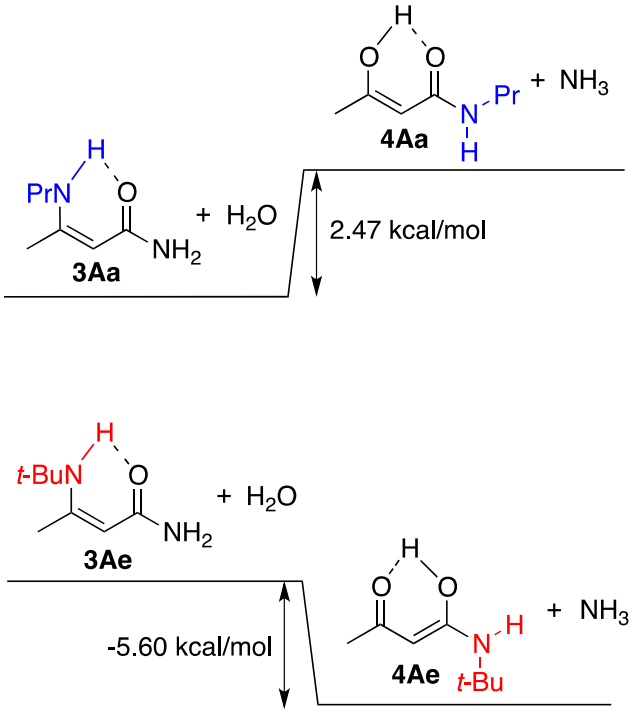


Figure 1. Estimated heat of formation of enamides **3** and *N*-substituted amides **4**.

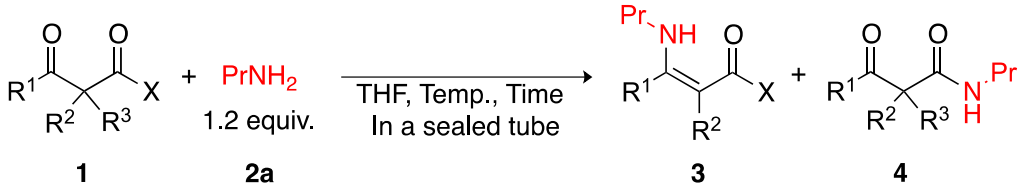
2-3. Reaction of α-substituted acetoacetamides 1 with propylamine 2a

Based on experimental results, it was determined that the steric bulk around the ketone moiety influenced the chemoselectivity (Table 3). While 3-oxohexanamide **1E** reacted readily with propylamine **2a** to afford the corresponding enamide **3Ea** in 96% yield, bulkier

keto amide **1F** gave no reaction at 60 °C (Entries 1 and 2). At a higher temperature, however, substitution at the amide moiety afforded *N*-propylacetoacetamide **4Fa** (Entry 3). These results indicate that the ketone moiety is more easily attacked because of the higher electrophilicity. Additionally, steric bulk of the amine or ketone moiety destabilizes enamide **3**, such that amide **4** is formed instead.

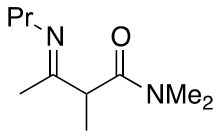
When α-methylacetoacetamide **1G** was allowed to react with **2a** at 60 °C for 2 days, condensation occurred readily at the ketone moiety, with the product **3Ga** obtained in a tautomeric imine form instead of the enamine form (Entry 4). α-Methylacetoacetamide **1G** did not undergo substitution at the amide moiety under harsh conditions (Entry 5). Contrastingly, α,α-dimethylacetoacetamide **1H** gave no reaction under either condition (Entries 6 and 7). These results suggest that β-keto amide **1** is activated by intramolecular hydrogen bonding with the enol O–H, although steric hindrance by the methyl groups should also be considered. From the reaction of *p*-methoxybenzoylacetoacetamide **1I** at 120 °C, both products **3Ia** and **4Ia** were obtained (Entry 8). Further, by heating enamide **3Ia** at 120 °C for 1 day, it was converted to the more stable amide **4Ia** (Scheme 2).

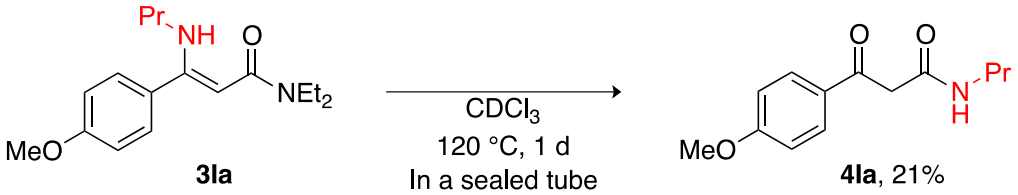
Table 3. Reaction of Substituted acetoacetamides **1** with propylamine **2a**.



1 **2a** **3** **4**

	Substrate					Temp. (°C)	Time (h)	Product	Yield(%)	
	R^1	R^2	R^3	X					**3**	**4**
1	Pr	H	H	NEt_2	**1E**	60	3	**Ea**	96	0
2	*tert*-Bu	H	H	NEt_2	**1F**	60	48	**Fa**	0	0
3	*tert*-Bu	H	H	NEt_2	**1F**	120	6	**Fa**	0	97
4	Me	Me	H	NMe_2	**1G**	60	48	**Ga**	90[a]	0
5	Me	Me	H	NMe_2	**1G**	120	3	**Ga**	32[a]	0
6	Me	Me	Me	NMe_2	**1H**	60	48	**Ha**	0	0
7	Me	Me	Me	NMe_2	**1H**	120	3	**Ha**	0	0
8	*p*-$MeOC_6H_4$	H	H	NEt_2	**1I**	120	6	**Ia**	18	56

[a] β-Iminoamide  **3Ga** was formed instead of enamide.



3Ia **4Ia**, 21%

Scheme 2. Conversion of enamide **3Ia** to keto amide **4Ia**.

3. Conclusion

I have demonstrated that β-keto amide **1** has high reactivity comparable to that of β-keto esters. Both carbonyl groups reacted readily with various amines to afford either β-aminobutenamide **3** or *N*-substituted acetoacetamide **4**. The chemoselectivity is dependent on the steric bulk of both the amine and the keto amide: less hindered amines underwent β-amination at low temperatures, whereas bulkier amines underwent substitution at the amide

moiety at higher temperatures. These results provide systematic insight into the reactivity of β-keto amide **1**, which is useful for researchers exploring elaborate syntheses.

4. Experimental section and characterization of compounds

4-1. General information

1,3-dicarbonyl compound **1A–1D** and amine **2a–2i** were purchased from commercial suppliers, and were used without further purification. Preparation of other β-ketoamide **1E–1I** referred to a literature procedure respectively.[24-26]

4-2. General Procedure for the preparation of β-aminoacrylamide 3Aa:

To a solution of acetoacetamide **1A** (50.5 mg, 0.5 mmol) in THF (0.5 mL), propylamine **1a** (49.3 mL, 0.6 mmol) was added, and the resultant mixture was heated at 60 °C for 3 h. The residue after removal of the solvent was almost pure 3-propylamino-2-butenamide (**3Aa**, 68.1 mg). Further purification was achieved by extraction with hot hexane (2 mL × 3) followed by concentration to give product **3Aa** (66.4 mg, 0.47 mmol, 94%) as yellow oil.

3-Propylamino-2-butenamide (3Aa): Yellow oil, R_f = 0.38 (silica gel, hexane/EtOAc = 9/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.2 Hz, 3H), 1.57 (tq, *J* = 7.2, 7.2 Hz, 2H), 1.88 (s, 3H), 3.14 (dt, *J* = 7.2, 7.2 Hz, 2H), 4.31 (s, 1H), 4.6–4.7 (br, 2H), 9.1–9.2 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (CH_3), 19.4 (CH_3), 24.0 (CH_2), 44.8 (CH_2), 83.1 (CH), 160.6 (C), 172.9 (C); IR (ATR/cm^{-1}) 3470, 3333, 3205, 2962, 1651, 1614; HRMS (ESI/TOF) *m/z cald.* for $C_7H_{14}N_2O$ $[M + H]^+$ 143.1179, found 143.1176.

3-(2-Methyl-1-propyl)amino-2-butenamide (3Ab): Yellow oil, R_f = 0.28 (silica gel, hexane/EtOAc = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.8 Hz, 6H), 1.77 (triple septet, *J* = 6.8, 6.8 Hz 1H), 1.85 (s, 3H), 2.98 (dd, *J* = 6.8, 6.8 Hz, 2H), 4.31 (s, 1H), 4.6–4.7 (br, 2H), 9.2–9.3(br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5 (CH_3), 20.2 (CH_3), 29.6 (CH), 50.7 (CH_2), 83.1 (CH), 160.6 (C), 173.0 (C); IR (ATR/cm^{-1}) 3478, 3339, 3206, 2959, 1643, 1614; HRMS (ESI/TOF) *m/z calcd.* for $C_8H_{16}N_2O$ $[M + H]^+$ 157.1335, found 157.1332.

3-Benzylamino-2-butenamide (3Ac):[27] Yellow solid, mp 74-76 °C. R_f = 0.37 (silica gel, hexane/EtOAc = 9/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (s, 3H), 4.40 (s, 1H), 4.42 (s, 2H),

4.7–4.8 (br, 2H), 7.2–7.3 (m, 3H), 7.3–7.4 (m, 2H), 9.5–9.6 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4 (CH_3), 46.7 (CH_2), 84.5 (CH), 126.7 (CH), 127.3 (CH), 128.8 (CH), 139.4 (C), 160.5 (C), 172.9 (C); IR (ATR/cm^{-1}) 3325, 3198, 1645, 1610, 690.

3-(2-Butyl)amino-2-butenamide (3Ad): Orange oil, R_f = 0.35 (silica gel, hexane/EtOAc = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.50 (dt, *J* = 7.2, 7.2 Hz, 2H), 1.88 (s, 3H), 3.39 (dtq, *J* = 9.6, 7.2, 7.2 Hz, 1H), 4.27 (s, 1H), 4.6–4.7 (br, 2H), 9.0–9.1 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6 (CH_3), 19.5 (CH_3), 22.0 (CH_3), 31.1 (CH_2), 50.0 (CH), 83.0 (CH), 159.7 (C), 172.9 (C); IR (ATR/cm^{-1}) 3472, 3339, 3208, 2966, 1651, 1614; HRMS (ESI/TOF) *m/z calcd.* for $C_8H_{16}N_2O$ $[M + H]^+$ 157.1335, found 157.1335.

3-(4-Methoxyphenyl)amino-2-butenamide (3Af):[28] Colorless solid, mp 118–120 °C. R_f = 0.58 (silica gel, hexane/EtOAc = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (s, 3H), 3.80 (s, 3H), 4.53 (s, 1H), 4.7–4.8 (br, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 10.8–10.9 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2 (CH_3), 55.6 (CH_3), 85.9 (CH), 114.3 (CH), 126.9 (CH), 132.7 (C), 157.4 (C), 158.6 (C), 172.6 (C); IR (ATR/cm^{-1}) 3460, 3335, 3225, 1682, 1624, 669.

3-(Pyrrolidin-1-yl)but-2-enamide (3Ag): Brown oil, R_f = 0.49 (silica gel, hexane/EtOAc = 9/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.8-2.0 (m, 4H), 2.48 (s, 3H), 3.2–3.3 (m, 4H), 4.37 (s, 1H), 4.7–4.8 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5 (CH_3), 25.3 (CH_2), 47.8 (CH_2), 85.0 (CH), 158.1 (C), 171.5 (C); IR (ATR/cm^{-1}) 3348, 3204, 2976, 1626, 1543; HRMS (ESI/TOF) *m/z calcd.* for $C_8H_{14}N_2O$ $[M + H]^+$ 155.1179, found 155.1176.

3-(2-Methyl-1-propyl)amino-*N*-propyl-2-butenamide (3Bb): Pale yellow oil, R_f = 0.49 (silica gel, hexane/EtOAc = 9/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 6H), 1.49 (tq, *J* = 6.8, 6.8 Hz, 2H), 1.76 (triple septet, *J* = 6.4, 6.4 Hz, 1H), 1.84 (s, 3H), 2.96 (dd, *J* = 6.4, 6.4 Hz, 2H), 3.17 (td, *J* = 6.8, 6.8 Hz, 2H), 4.23 (s, 1H), 4.7–4.8 (br, 1H), 9.1–9.2 (br, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6 (CH_3), 19.6 (CH_3), 20.4 (CH_3), 23.5 (CH_2), 29.6 (CH), 40.8 (CH_2), 50.7 (CH_2), 84.4 (CH), 158.7 (C), 171.2 (C); IR (ATR/cm^{-1}) 3306, 2957, 1624, 1539; HRMS (ESI/TOF) *m/z calcd.* for $C_{11}H_{22}N_2O$ $[M + H]^+$ 199.1805, found 199.1805.

***N*,*N*-Dimethyl-3-(2-methyl-1-propyl)amino-2-butenamide (3Cb):** Yellow oil, R_f = 0.32 (silica gel, hexane/EtOAc = 9/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.4 Hz, 6H), 1.77 (triple septet, *J* = 6.4, 6.4 Hz, 1H), 1.90 (s, 3H), 2.92 (s, 6H), 2.98 (dd, *J* = 6.4, 6.4 Hz, 2H), 4.52 (s, 1H), 9.6–9.7 (br, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 20.2 (CH_3), 20.4 (CH_3), 29.6 (CH_3), 36.1 (CH_3), 50.8 (CH_2), 81.1 (CH), 159.6 (C), 171.6 (C); IR (ATR/cm^{-1}) 2953, 1608. HRMS (ESI/TOF) *m/z calcd.* for $C_{10}H_{20}N_2O$ $[M + H]^+$ 185.1648, found 185.1647.

***N*-(2-Butyl)-3-oxobutanamide (4Ad):**[29] Pale yellow oil, R_f = 0.46 (silica gel, hexane/EtOAc = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.2 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.48 (dq, *J* = 7.2, 7.2 Hz, 2H), 2.26 (s, 3H), 3.38 (s, 2H), 3.91 (dtq, *J* = 8.4, 7.2, 6.8 Hz, 1H), 6.6–6.7 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.4 (CH_3), 20.4 (CH_3), 29.6 (CH_2), 31.2 (CH_3), 46.9 (CH), 50.1 (CH_2), 164.8 (C), 205.0 (C); IR (ATR/cm^{-1}) 3291, 1717, 1645.

***N*-*tert*-Butyl-3-oxobutanamide (4Ae):**[30] Colorless solid, mp 44–45 °C. R_f = 0.56 (silica gel, hexane/EtOAc = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 9H), 2.21 (s, 3H), 3.28 (s, 2H), 6.6-6.7 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7 (CH_3), 31.0 (CH_3), 51.1 (CH_2), 51.4 (C), 164.7 (C), 205.0 (C); IR (ATR/cm^{-1}) 3319, 1720, 1667.

***N*,*N*-Diethyl-3-oxobutanamide (4Ah):**[30] Yellow oil, R_f = 0.52 (silica gel, hexane/EtOAc = 1/1). This compound exists as a mixture of keto and enol forms. The integral values for each tautomer are represented as H_k and H_e, respectively, and these isomers present in 68/32 ratio. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, *J* = 7.2 Hz, $3H_k$ + $3H_e$), 1.17 (t, *J* = 7.2 Hz, $3H_k$ + $3H_e$), 1.95 (s, $3H_e$), 2.28 (s, $3H_k$), 3.28 (q, *J* = 7.2 Hz, $2H_k$ + $2H_e$), 3.39 (q, *J* = 7.2 Hz, $2H_k$ + $2H_e$), 3.49 (s, $2H_k$), 5.05 (s, $1H_e$), 14.9–15.0 (br, $1H_e$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1 (CH_3), 14.4 (CH_3), 22.1 (CH_3), 30.3 (CH_3), 40.4 (CH_2), 42.8 (CH_2), 50.2 (CH_2), 87.2 (CH), 165.9 (C), 171.4 (C), 174.8 (C), 203.0 (C); IR (ATR/cm^{-1}) 3474, 2976, 1718, 1637.

***N*,*N*-Bis(1-methylethyl)-3-oxobutanamide (4Ai):**[31] Orange oil, R_f = 0.64 (silica gel, hexane/EtOAc = 1/1). This compound exists as a mixture of keto and enol forms. The integral values for each tautomer are represented as H_k and H_e, respectively, and these isomers present in 84/16 ratio. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6.8 Hz, $6H_k$ + $6H_e$), 1.39 (d, *J* = 6.8 Hz, $6H_k$ + $6H_e$), 1.93 (s, $3H_e$), 2.25 (s, $3H_k$), 3.47 (s, $2H_k$), 3.82 (septet, *J* =

6.8 Hz, 1H_k + 1H_e), 5.07 (s, 1H_e), 15.2–15.3 (br, 1H_e); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6 (C_kH_3 + C_eH_3), 20.9 (C_kH_3 + C_eH_3), 22.3 (C_eH_3), 30.0 (C_kH_3), 46.2 (C_kH + C_eH), 49.9 (C_kH + C_eH), 52.6 (C_kH_2), 165.5 (C_k), 172.0 (C_e), 203.2 (C_k + C_e), one signal of a tertiary carbon (C_eH) was not observed; IR (ATR/cm^{-1}) 2968, 1717, 1631.

Ethyl 3-(2-Methyl-1-propyl)amino-2-butenoate (3Db):[32] Yellow oil, R_f = 0.89 (silica gel, hexane/EtOAc = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, *J* = 6.8 Hz, 6H), 1.24 (t, *J* = 6.8 Hz, 3H), 1.79 (triple septet, *J* = 6.8, 6.8 Hz 1H), 1.89 (s, 3H), 3.01 (dd, *J* = 6.8, 6.8 Hz, 2H), 4.08 (q, *J* = 6.8 Hz, 2H), 4.42 (s, 1H), 8.6–8.7 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8 (CH_3), 19.6 (CH_3), 20.3 (CH_3), 29.5 (CH), 50.8 (CH_2), 58.4 (CH_2), 82.0 (CH), 162.2 (C), 170.8 (C); IR (ATR/cm^{-1}) 2961, 1647, 1606.

***N,N*-Diethyl-3-propylamino-2-hexenamide (3Ea):** Pale yellow oil, R_f = 0.54 (silica gel, hexane/EtOAc = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 6.8 Hz, 3H), 1.13 (t, *J* = 6.8 Hz, 6H), 1.5–1.7 (m, 4H), 2.14 (t, *J* = 6.8 Hz, 2H), 3.12 (dt, *J* = 6.8, 6.8 Hz, 2H), 3.31 (q, *J* = 6.8 Hz, 4H), 4.50 (s, 1H), 9.5–9.6 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8 (CH_3), 14.1 (CH_3), 14.1 (CH_3), 22.0 (CH_2), 24.0 (CH_2), 35.3 (CH_2), 44.5 (CH_2), 80.8 (CH), 163.0 (C), 170.5 (C); IR (ATR/cm^{-1}) 2963, 1606; HRMS (ESI/TOF) *m/z calcd.* for $C_{13}H_{26}N_2O$ $[M + H]^+$ 227.2118, found 227.2110.

4-Aza-*N,N*,2,3-tetramethyl-3-heptenamide (3Ga): Formation of **3Ga** was confirmed by ^{1}H NMR of the reaction mixture, however, **3Ga** was not isolated because of the decomposition to **1Ga** and **2a** during the purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.2 Hz, 3H), 1.30 (d, *J* = 7.2 Hz, 3H), 1.65 (dq, *J* = 7.2, 7.2 Hz, 2H), 1.78 (s, 3H), 2.95 (s, 3H), 3.05 (s, 3H), 3.23 (t, *J* = 7.2 Hz, 2H), 3.64 (q, *J* = 7.2 Hz, 1H).

4,4-Dimethyl-3-oxo-*N*-propylheptanamide (4Fa): Colorless oil, R_f = 0.50 (silica gel, hexane/EtOAc = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.16 (s, 9H), 1.53 (tq, *J* = 7.2, 7.2 Hz, 2H), 3.22 (dt, *J* = 7.2, 7.2 Hz, 2H), 3.46 (s, 2H), 7.1-7.2 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (CH_3), 22.8 (CH_2), 26.0 (CH_3), 41.4 (CH_2), 43.5 (CH_2), 45.3 (C), 165.9 (C), 212.9 (C); IR (ATR/cm^{-1}) 3310, 1715, 1645; HRMS (ESI/TOF) *m/z calcd.* for $C_{10}H_{19}NO_2$ $[M + Na]^+$ 208.1308, found 208.1307.

***N,N*-Diethyl-3-(4-methoxyphenyl)-3-propylamino-2-butenamide (3Ia):** Yellow oil, R_f = 0.57 (silica gel, hexane/EtOAc = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 6H), 1.48 (tq, *J* = 7.2, 7.2 Hz, 2H), 2.95 (dt, *J* = 7.2, 7.2 Hz, 2H), 3.8–3.9 (br, 4H), 3.83 (s, 3H), 4.62 (s, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 9.4–9.5 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6 (CH_3), 14.1 (CH_3), 23.5 (CH_2), 24.5 (CH_2), 46.4 (CH_2), 55.4 (CH_3), 84.9 (CH), 113.7 (CH), 129.4 (CH), 130.4 (C), 160.0 (C), 162.8 (C), 169.9 (C); IR (ATR/cm^{-1}) 3306, 3070, 2965, 1681, 1601; HRMS (ESI/TOF) *m/z calcd*. for $C_{17}H_{26}N_2O_2$ $[M + H]^+$ 291.2067, found 291.2064.

3-(4-Methoxyphenyl)-3-oxo-*N*-propylbutanamide (4Ia): Colorless oil, R_f = 0.39 (silica gel, hexane/EtOAc = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.2 Hz, 3H), 1.53 (tq, *J* = 7.2, 7.2 Hz, 2H), 3.24 (dt, *J* = 7.2, 7.2 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.1-7.2 (br, 1H), 7.97 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (CH_3), 22.8 (CH_2), 41.5 (CH_2), 45.2 (CH_2), 55.7 (CH_3), 114.2 (CH), 129.4 (C), 131.2 (CH), 164.4 (C), 166.0 (C), 194.8 (C); IR (ATR/cm^{-1}) 3308, 2968, 1680, 1651; HRMS (ESI/TOF) *m/z calcd.* for $C_{13}H_{17}NO_3$ $[M + H]^+$ 236.1281, found 236.1276.

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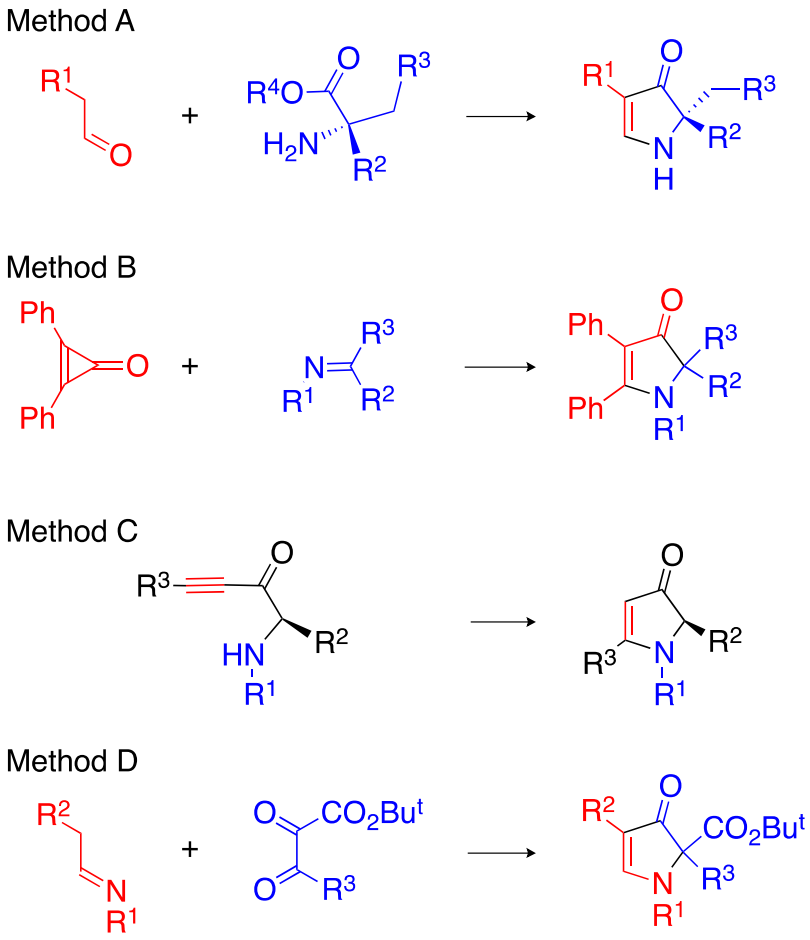
Chapter 4. Synthesis of pyrrolinone

1. Introduction

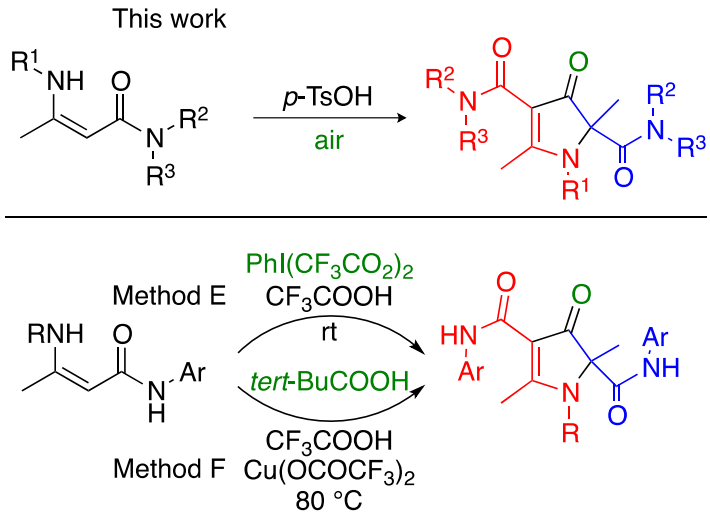
Pyrroline-4-ones are one of the attractive frameworks because these scaffolds are widely found in optical materials[1] and biologically active compounds such as HIV-1 protease inhibitors,[2] antimalarials,[3] and antimicrobials.[4] Despite the highly valuable and versatile applications, only a few synthetic methods have been reported for pyrrolinones. The most common approach to synthesize pyrrolinones is condensation of α-amino acid esters with aldehydes, facilitating stereo-controlled synthesis (Scheme 1, Method A).[5] The formal [3+2] cycloaddition reactions of diphenylcyclopropenones with imines (Method B) and α-diazoimines with ketenes have also been used for this purpose.[6] The transition-metal-catalyzed intramolecular cyclization of α-aminoynones and the condensation of imines with vicinal tricarbonyl compounds are acceptable methods (Methods C and D).[7,8] However, these methods suffer from some drawbacks such as low availability of the starting materials and narrow substrate scope. Furthermore, it is difficult to introduce multiple functional groups into the pyrrolinone framework. Thus, the development of a facile method for multifunctionalized pyrrolinones remains one of the challenging projects.

In the last chapter, we reported a systematic study on the regioselective amination of acetoacetamides (3-oxobutanamides) was discussed.[9] The reaction with less hindered amines involved condensation at the β-keto moiety, affording 3-amino-2-butenamides while the reaction with bulky amines involved substitution at the amide moiety. Aminobutenamides may serve as useful building blocks in the organic synthesis because of both multifunctionality and the biased electron density of the carbon−carbon double bond also known as push-pull alkene.[10] During my studies on chemical conversion of aminated enamides, polysubstituted pyrrolinone were obtained when exposed to air at room temperature. A similar dimerization of enamides has been reported by two groups: hypervalent iodine(III)-mediated cyclization (Scheme 2, Method E) and Cu(II)-catalyzed oxidative tandem cyclization (Scheme 2, Method F).[11,12] Although bis(functionalized) pyrrolinones can be prepared in good yields by these protocols, highly toxic trifluoroacetic acid is used in both the cases, and substituents can be present on the amide function of aryl groups. Contrary to these methods, the present dimerization proceeded at room temperature

without using any special reagent. This advantageous feature encouraged me to study this reaction in detail for developing a practical method for the synthesis of polyfunctionalized pyrrolinones.



Scheme 1. Commonly used synthetic methods for pyrrolin-4-ones.



Scheme 2. Tree kinds of dimerization of β-amino-α,β-unsaturated amides.

2. Results and Discussions

2-1. Dimerization of 3-amino-2-butenamide at room temperature

The substrates, 3-amino-2-butenamides **1**, were easily prepared in 76−97% yields by heating acetoacetamide with amines such as propylamine isobutylamine, *sec*-butylamine and benzylamine at 60 °C for 3 h in THF. When 3-propylamino-2-butenamide (**1a**) was exposed to air at room temperature for 3 days, crystalline precipitates were obtained in the chloroform solution. Based on spectral data, this crystalline product was determined to be 1-propyl-2,5-dimethyl-3-oxo-2,3-dihydro-1*H*-pyrrole-2,4-dicarboxiamide (**2a**), a dimeric product of **1a**, and the structure was finally confirmed by X-ray crystallography (Figure 1). This structure indicates that the dimerization involved the oxidation of the pyrroline framework and 1,2-migration of the methyl group.

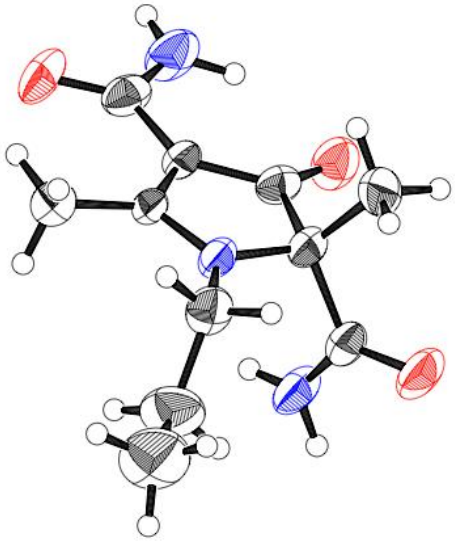


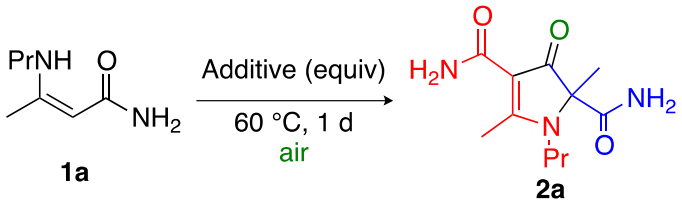
Figure 1. ORTEP diagram of the molecular structure of **2a**.

2-2. Optimization of reaction conditions

First, we optimized the reaction conditions using butenamide **1a** as the model substrate. Among several solvents such as hexane, benzene, chloroform, ethyl acetate, and acetonitrile, nonpolar benzene was effective for the dimerization (Table 1 entries 1−6). Although this reaction proceeded even in the absence of any additives, the addition of *p*-toluenesulfonic acid (*p*-TsOH) significantly accelerated the reaction. Notably, the amount of *p*-TsOH was crucial for this dimerization, and 0.5 equiv. *p*-TsOH afforded pyrrolinone **2a** in the best yield (entries 7−11, Figure 1). When ≤ 0.5 equiv. of *p*-TsOH was used, the starting material **1a** was recovered. In contrast, acetoacetamide, the hydrolized product of **1a**, was obtained when more than 0.5 equiv. of *p*-TsOH in the reactions.

When **1a** was treated with 0.5 equiv. *p*-TsOH in benzene at 60 °C for 1 day under nitrogen atmosphere, the dimerization did not proceed at all (entry 12), indicating that the oxygen present in air serves as the oxidant to furnish pyrrolinone **2a**. Moreover, the reaction delivered pyrrolinone in a good yield even in the presence of an excess amount of a radical scavenger [(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO)], indicating that this reaction possibly proceeds with the ionic mechanism (entry13).

Table 1. Optimization of reaction conditions for synthesis of pyrrolin-4-ones **7Aa**.



Entry	Solvent	Additive/equiv.	Yield/%
1	Hexane	—	12
2	Benzene	—	24
3	Chloroform	—	17
4	Ethyl Acetate	—	9
5	Acetonitrile	—	3
6	Methanol	—	6
7	Benzene	*p*-TsOH (0.2)	45
8	Benzene	*p*-TsOH (0.4)	70
9	Benzene	*p*-TsOH (0.5)	92
10	Benzene	*p*-TsOH (0.7)	48
11	Benzene	*p*-TsOH (1.0)	0
12[a]	Benzene	*p*-TsOH (0.5)	Trace
13	Benzene	*p*-TsOH (0.5)/TEMPO (5.0)	80

[a] Under N.

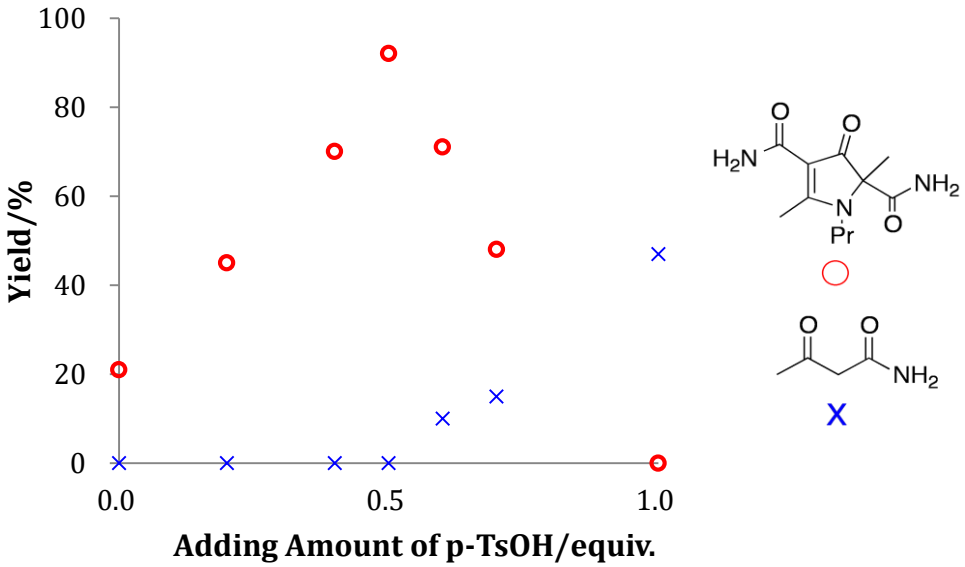
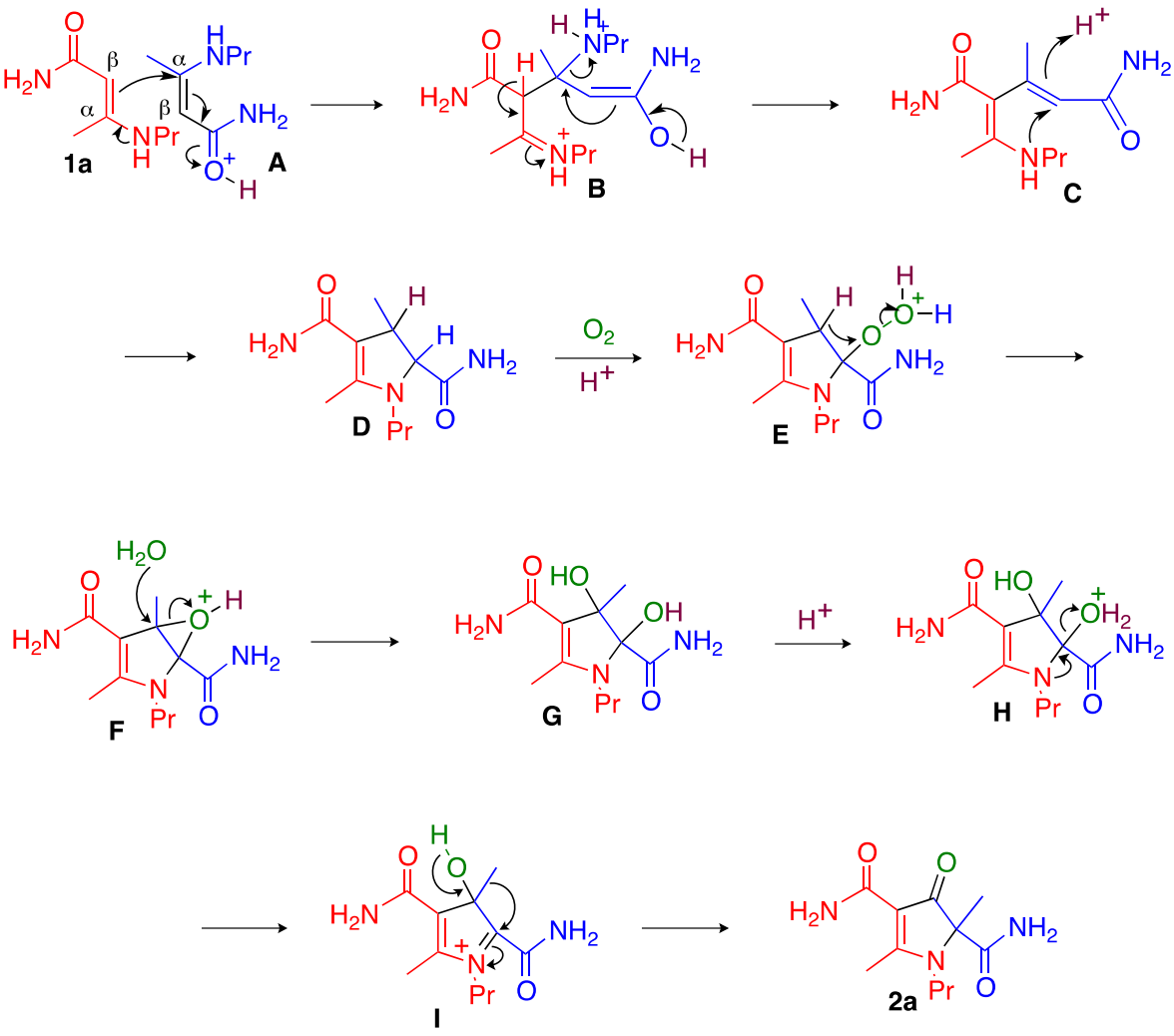


Figure 2. The yield **2a** (○) and acetoacetamide (×) depending on the amount of *p*-TsOH.

2.3. A Plausible Mechanism

Based on the abovementioned experimental facts, a plausible mechanism is illustrated in Scheme 3. First, the β-carbon of enamide **1a** attacks the α-carbon of another protonated enamide **A** to afford intermediate **B**. At this time, equimolar amounts of unprotonated and protonated enamides, **1a** and **A**, are necessary. The former maintains the nucleophilicity, and the latter improves the electrophilicity. After the elimination of an amine, the intramolecular cyclization affords a five-membered product **D**. Then, **D** is oxidized by molecular oxygen in the air,[13] and epoxide **F** is formed by dehydration. The subsequent ring-opening reaction by water affords 1,2-diol **G**. Finally, the 1,2-migration of the methyl group[14] affords the final product 2-pyrrolin-4-one **2a**.

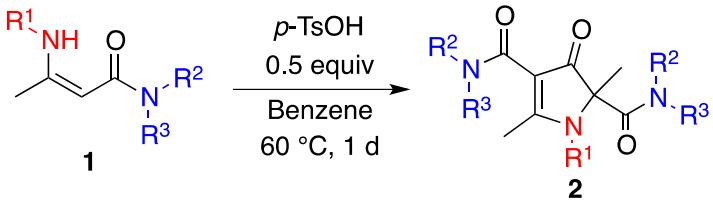


Scheme 3. A plausible mechanism.

2-4. Scope of limitation

Other enamides **1a–e** were subjected to this dimerization using the optimized reaction conditions (Table 2). *N*-Unsubstituted enamides **1a–c** ($R^2 = R^3 = H$) efficiently afforded the corresponding pyrrolinones **2a–c** in excellent yields, respectively (entries 1–3). On the other hand, bulkiness on the amide function suppressed the dimerization, leading to pyrrolinones **2d** and **2e** in lower yields under the same conditions (entries 4 and 5). The obtained pyrrolinones **2a–e** could not be prepared by alternative procedures.

Table 2. Scope of limitation.



Entry	R^1	R^2	R^3	Product	Yield/% **2**	Recovery/% **1**
1	Pr	H	H	**2a**	92	0
2	*i*-Bu	H	H	**2b**	96	0
3	$PhCH_2$	H	H	**2c**	93	0
4	Pr	Me	H	**2d**	35	31
5	Pr	Me	Me	**2e**	21	22

3. Conclusion

In conclusion, I have successfully developed a facile and efficient method for the synthesis of polysubstituted pyrrolinones by the dimerization of α-amino-2-butenamides **1** by treating with 0.5 equiv. *p*-TsOH under mild reaction conditions with simple manipulations. Moreover, the substituents at the 1-position of pyrrolinone **2** and the amide function can be easily modified by changing enamide **1**. This is advantageous for the construction of a new compound library. Only simple experimental manipulations are required, and this reaction proceeded without special reagents such as metal catalysts and oxidants. Hence, this reaction is expected to be a useful tool for the synthesis of versatile pyrrolinones.

4. Experimental section and characterization of compounds

4-1. General Information

Unless otherwise noted, all reagents were commercial supplied and were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker DPX-400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ using tetramethylsilane as an internal standard. ^{1}H NMR spectroscopic data is reported as follows: chemical shift (δ, ppm), chemical shift mutiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, integration, coupling constant (Hz). ^{13}C NMR spectroscopic data is reported in terms of chemical shift (δ, ppm). Infrared spectra were recorded with a Horiba FT-200 IR spectrometer, and data are reported in frequency of absorption (wavenumbers). High resolution mass spectra were obtained with a AB SCIEX TripleTOF 4600 mass spectrometer. Melting points were recorded with a Stanford Research Systems MPA100 melting point apparatus.

4-2. Typical procedure for synthesis of pyrrolinones

To a solution of 3-aminobutanamide **1** (0.5 mmol) in benzene (1.0 mL), *p*-toluenesulfonic acid (0.25 mmol) was added, and the resultant mixture was heated at 60 °C for 1 d. After concentration, the residue was washed with acetonitrile (2 mL × 3) to remove *p*-toluenesulfonic acid, and dried in vacuo to afford corresponding pyrrolinone product **2**.

2,3-Dihydro-2,5-dimethyl-3-oxo-1-propylpyrrole-2,4-dicarboxamide (2a): White solid, mp 240–244 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3H), 1.45 (s, 3H), 1.5–1.7 (m, 2H), 2.66 (s, 3H), 3.1–3.3 (m, 1H), 3.4-3.6 (m, 1H), 6.6–6.7 (br, 1H), 7.1–7.2 (br, 1H), 7.2–7.3 (br, 1H), 7.5–7.6 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1 (CH_3), 14.1 (CH_3), 18.7 (CH_3), 22.4 (CH_2), 45.6 (CH_2), 76.0 (C), 100.7 (C), 165.0 (C), 166.4 (C), 180.5 (C), 193.8 (C); IR (ATR/cm^{-1}) 1697, 1636, 1521; HRMS (ESI/TOF) *m/z* calcd. for $C_{11}H_{17}N_3O_3$ $[M + Na]^+$ 262.1162, found 262.1170.

2,3-Dihydro-2,5-dimethyl-1-(2-methylpropyl)-3-oxopyrrole-2,4-dicarboxamide (2b): White solid, mp 234–237 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (dd, J = 7.2, 7.2 Hz, 6H), 1.45 (s, 3H), 1.96 (ddqq, J = 8.0, 8.0, 8.8, 8.9 Hz, 1H), 2.65 (s, 3H), 3.09 (dd, J = 7.2, 14.8 Hz, 1H), 3.43 (dd, J = 7.2, 14.8 Hz, 1H), 6.7–6.8 (br, 1H), 7.1–7.2 (br, 1H), 7.3–7.4 (br, 1H), 7.5–7.6 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8 (CH_3), 18.8 (CH_3), 19.9 (CH_3),

20.1 (CH_3), 27.7 (CH), 51.2 (CH_2), 76.3 (C), 101.2 (C), 165.0 (C), 166.5 (C), 181.5 (C), 194.2 (C); IR (ATR/cm^{-1}) 3271, 1701, 1636, 1522; HRMS (ESI/TOF) *m/z* calcd. for $C_{12}H_{19}N_3O_3$ $[M + Na]^+$ 276.1319, found 276.1323.

1-Benzyl-2,3-dihydro-2,5-dimethyl-3-oxopyrrole-2,4-dicarboxamide (2c): Pale yellow solid, mp 241–244 °C (dec.). ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 3H), 2.47 (s, 3H), 4.69 (d, *J* = 16.8 Hz, 1H), 4.80 (d, *J* = 16.8 Hz, 1H), 6.6–6.7 (br, 1H), 6.8–6.9 (br, 1H), 7.2–7.3 (m, 3H), 7.2–7.3 (br, 1H), 7.3–7.4 (m, 2H), 7.5–7.6 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 21.7 (CH_3), 44.0 (CH_2), 89.1 (C), 99.1 (C), 126.6 (CH), 127.1 (CH), 128.6 (CH), 137.3 (C), 165.2 (C), 178.9 (C), 196.6 (C), one signal of a quaternary carbon was not observed presumably due to overlapping with another signal; IR (ATR/cm^{-1}) 3347, 1661, 1520; HRMS (ESI) *m/z* calcd. for $C_{15}H_{17}N_3O_3$ $[M + H]^+$ 288.1342, found 288.1351.

2,3-Dihydro-2,5-diethyl-2,4-bis(*N*-methylcarbamoyl)-3-oxo-1-propylpyrrole (2d): Yellow solid, mp 182–185 °C (dec.). ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.2 Hz, 3H), 1.61 (s, 3H), 1.6–1.7 (m, 1H), 1.7–1.8 (m, 1H), 2.76 (s, 3H), 2.78 (d, *J* = 4.8 Hz, 3H), 2.86 (d, *J* = 4.8 Hz, 3H), 3.6–3.7 (m, 1H), 3.8–3.9 (m, 1H), 7.0–7.1 (br, 1H), 7.9–8.0 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (CH_3), 14.8 (CH_3), 22.7 (CH_3), 23.8 (CH_2), 25.2 (CH_3), 26.5 (CH_3), 46.9 (CH_2), 74.4 (C), 102.4 (C), 164.7 (C), 166.9 (C), 180.2 (C), 195.0 (C); IR (ATR/cm^{-1}) 3314, 1682, 1651, 1520; HRMS (ESI) *m/z* calcd. for $C_{13}H_{21}N_3O_3$ $[M + Na]^+$ 290.1475, found 290.1481.

2,3-Dihydro-2,5-diethyl-2,4-bis(*N*,*N*-dimethylcarbamoyl)-3-oxo-1-propylpyrrole (2e): Yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.2 Hz, 3H), 1.30 (s, 3H), 1.4–1.6 (m, 2H), 2.00 (s, 3H), 2.6–2.7 (br, 6H), 2.91 (s, 6H), 3.4-3.5 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1 (CH_3), 11.8 (CH_3), 21.8 (CH_2), 23.5 (CH_3), 35.8 (CH_3), 36.6 (CH_3), 41.2 (CH_2), 57.0 (C), 113.0 (C), 139.1 (C), 164.4 (C), 166.6 (C), 176.6 (C); IR (ATR/cm^{-1}) 3455, 2324, 1695 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{25}N_3O_3$ $[M + Na]^+$ 318.1788, found 318.1790.

5. References

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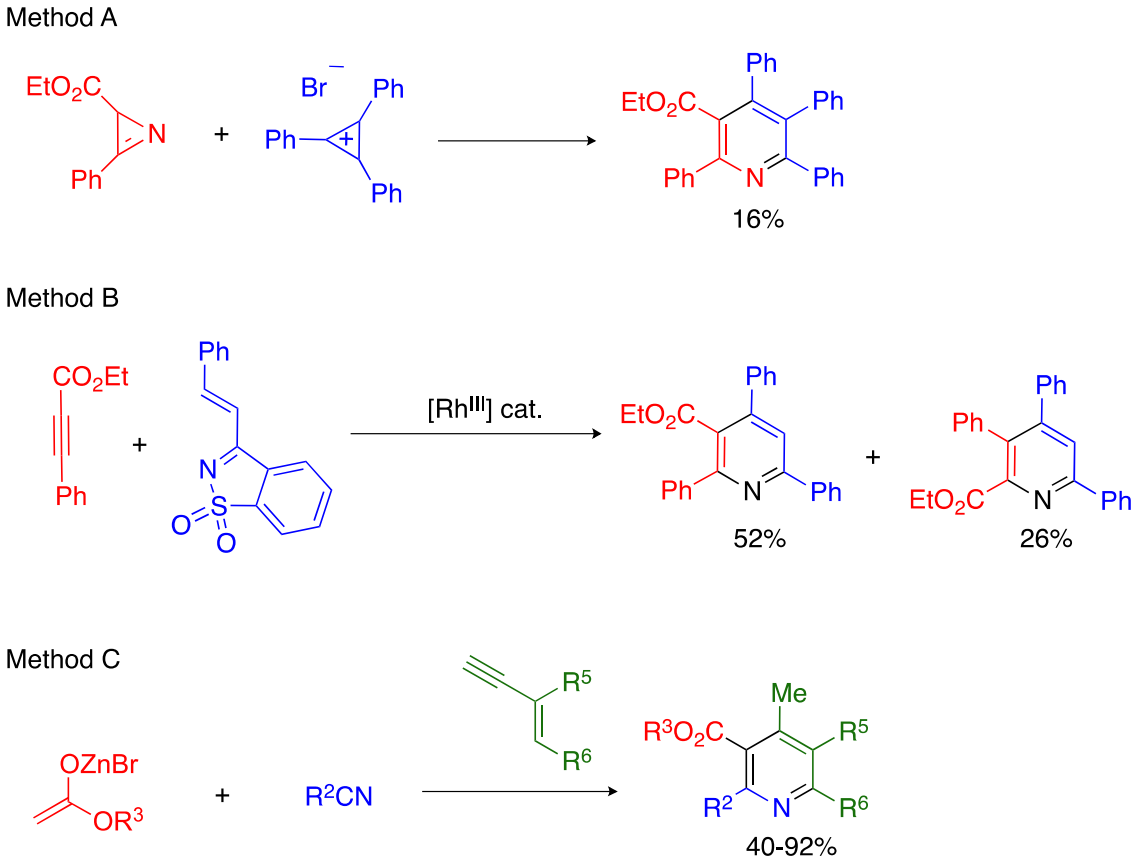
Chapter 5. Synthesis of Polysubstituted Nicotinate

1. Introduction

Nicotinate is one of the fundamental frameworks in natural products,[1] medicines,[2] and agrochemicals.[3] Because of their useful biological activities, numerous synthetic methods have been developed to prepare versatile nicotinates. The most commonly used method is the Hantzsch reaction—the multi-component condensation of an aldehyde with two 1,3-dicarbonyl compounds and an ammonium salt—which affords the production of symmetrical pyridine-3,5-dicarboxylates after subsequent oxidation.[4] As an alternate approach, enamino esters are often employed as fundamental motifs, which condense with a C3 unit such as an α,β-unsaturated carbonyl compound to produce nicotinates. It is necessary to use reactive α,β-unsaturated aldehydes (enals)[5] or α,β-unsaturated ketones (enones) activated with an electron-withdrawing group at the α-position[6] or on the carbonyl group,[7] which prevents the modification of the nicotinates at the 4-, 5-, and 6-positions with a simple alkyl or aryl group. Recently, two excellent methods were reported, in which enamino esters were prepared from β-keto esters and ammonium acetate in situ. Condensation of enamino esters with chalcones proceeded efficiently in the presence of CAN to produce 4,6-diarylnicotinates.[8] Zhang *et al.* synthesized 4,6-diaryl-5-fluoronicotinates using α-fluoro-β-keto esters and enones.[9] These are effective synthetic methods. However, nicotinates possessing three successive alkyl/aryl groups at the 4-, 5-, and 6-positions are not available.

Although many approaches have shown impressive advances in the synthesis of nicotinates in the past decades,[10] only a few synthetic methods for polysubstituted nicotinates are found in literature (Scheme 1).[11–13] Battiste *et al*. obtained a small amount of tetraphenylnicotinate by the [3+3] cycloaddition of phenylazirinecarboxylate with a triphenylcyclopropenyl cation (Method A).[11] Dong *et al*. synthesized triphenylnicotinate with a better yield by a hetero Diels-Alder reaction using an azadiene derived from saccharin with phenylpropiolate, forming a mixture of regioisomers (Method B).[12] Compared to these methods, Lee's three-component reaction, using zinc α-alkoxyenolate, benzonitrile, and enyne exhibits a wide scope of substrates; however, this method suffers from poor availability of enynes.[13] Hence, the substituent at the 4-position of nicotinate is limited to

the methyl group.



Scheme 1. Synthetic procedure for polysubstituted nicotinates.

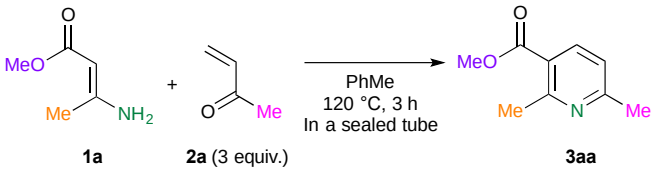
The development of a facile synthetic method for the production of polyalkylated or polyarylated nicotinates is still a challenging problem, prompting us to revisit the conventional method—the condensation of enamino esters with enones— because this method has a great potential to be a general synthetic method for polysubstituted nicotinates simply by changing the substrates. As a result of our study, we found that the use of $FeCl_3$ was effective and succeeded in synthesizing high quality, fully alkylated/arylated nicotinates.

2. Results and Discussions

2-1. Optimization of conditions of 1a with 2a.

Enamino esters **1** were efficiently prepared by heating a commercially available keto esters and ammonium acetate in ethanol. When β-amino-α,β-unsaturated ester **1a** was heated with 5 equiv. of methyl vinyl ketone **2a** in a sealed tube at 90 °C for 3 h, methyl 2,6-dimethylnicotinate **3aa** was obtained in 38% yield without any detectable by-product derived from **1a**. As a result of screening of the reaction conditions such as solvent, temperature, and molar ratio of the reagent, the yield of **3aa** was increased to 87% when the reaction was heated with 3 equiv. **2a** at 120 °C for 3 h in toluene (Table 1). By-products such as polymers of **2a** were easily removed by short column chromatography on silica gel to afford **3aa** in 82% isolated yield. When three-component reactions of methyl acetoacetate with **2a** and ammonium acetate were conducted under the same conditions, a low yield of **3aa** was obtained (39%). Hence, it was confirmed to be better to prepare the enamino ester **1a** beforehand.

Table 1. Optimization of conditions of **1a** with **2a.**



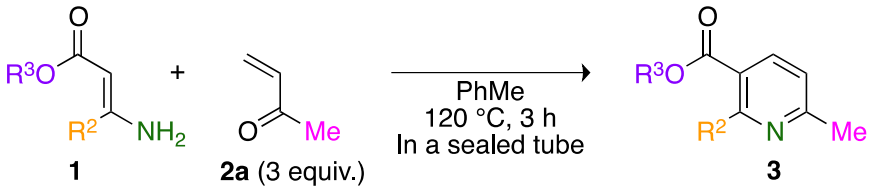
Entry	Solv.	Temp./°C	**2a**/equiv.	**3aa**/%[a]
1	MeOH	90	5	38
2	DMF	90	5	56
3	MeCN	90	5	53
4	EtOAc	90	5	54
5	THF	90	5	52
6	$CHCl_3$	90	5	58
7	Hexane	90	5	63
8	PhMe	90	5	72
9	PhMe	120	5	88
10	PhMe	120	3	87
11	PhMe	120	2	64

[a] NMR Yield.

2-2. Synthesis of nicotinates modified at the 2- and 6-position and ester function.

Having optimized the reaction conditions, the scope of the substrate was expanded (Table 2). First, modification of the 2-position was studied. Enone **2a** was reacted with several enamino esters **1b**–**1e** to produce 2-alkylated/2-arylated nicotinates **3ba–3ea**, respectively (entries 2–5). It was also possible to modify the corresponding nicotinates **3fa**–**3ma** in high yields (entries 6–13). This reaction was applicable to substrates possessing bulky *tert*-butoxy and β-phenethyloxy groups (entries 10 and 11). Furthermore, allyl and propargyl groups were tolerated during the reaction leading to esters **3la** and **3ma**, respectively (entries 12 and 13).

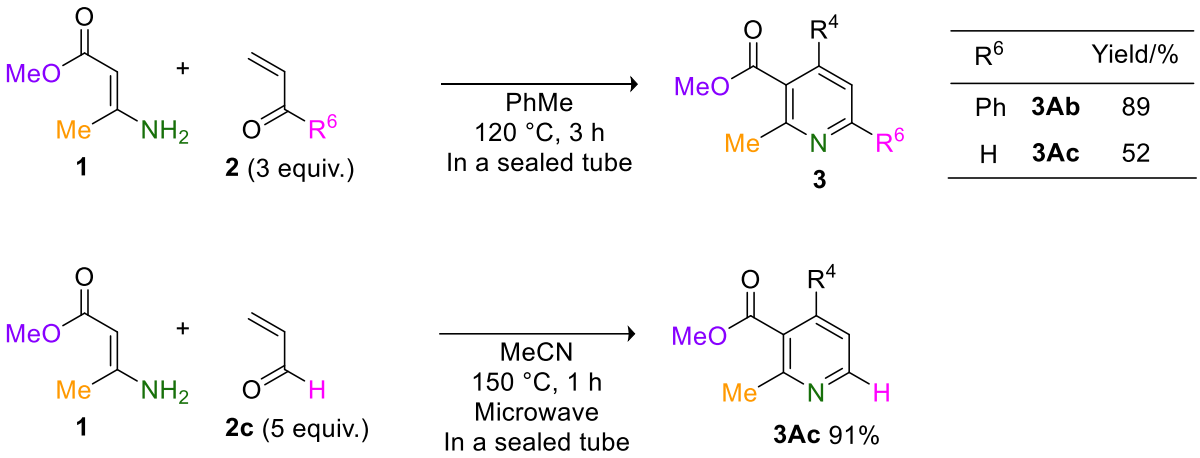
Table 2. Synthesis of nicotinates modified at the 2-position and the ester function.



Entry	Enamino ester **1**			Product **3**	
	R^2	R^3			Yield/%[a]
1	Me	Me	**1a**	**3aa**	87 (82)
2	Pr	Et	**1b**	**3ba**	82 (80)
3	*tert*-Bu	Me	**1c**	**3ca**	44 (42)
4	Ph	Et	**1d**	**3da**	88 (85)
5	4-$MeOC_6H_4$	Et	**1e**	**3ea**	90 (86)
6	Me	Et	**1f**	**3fa**	93 (85)
7	Me	Bu	**1g**	**3ga**	95 (92)
8	Me	*i*-Pr	**1h**	**3ha**	82 (81)
9	Me	*i*-Bu	**1i**	**3ia**	83 (79)
10	Me	*tert*-Bu	**1j**	**3ja**	75 (72)
11	Me	$PhCH_2CH_2$	**1k**	**3ka**	87 (82)
12	Me	Allyl	**1l**	**3la**	78 (76)
13	Me	Propargyl	**1m**	**3ma**	69 (65)

[a] NMR yield, and isolated yield in the parentheses.

Other enones were subjected to this reaction (Scheme 2). Phenyl vinyl ketone **2b** was also used as a substrate for this reaction to furnish 6-phenylnicotinate **3ab** under the same conditions in excellent yield. On the other hand, when the highly reactive acrolein **2c** was used, the yield of **3ac** decreased considerably because of the competitive polymerization of **2c**. This problem was addressed by changing the solvent to acetonitrile, increasing the amount of **2c** to 5 equiv., and heating at 150 °C under microwave irradiation; **3ac** was isolated in 91% yield. This proceeded more efficiently than the reported method.[14]



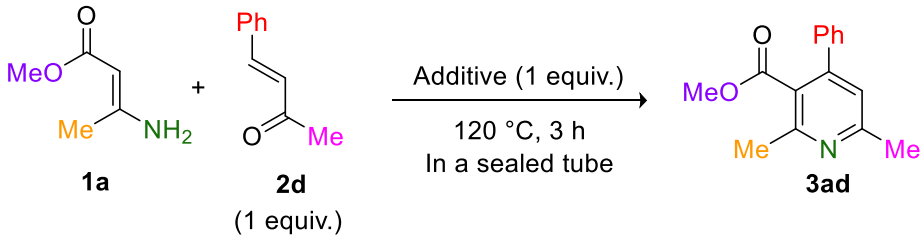
R^6		Yield/%
Ph	**3Ab**	89
H	**3Ac**	52

Scheme 2. Synthesis of 4-unsubstituted nicotinates.

2-3. Optimization of conditions of 1a with 2d.

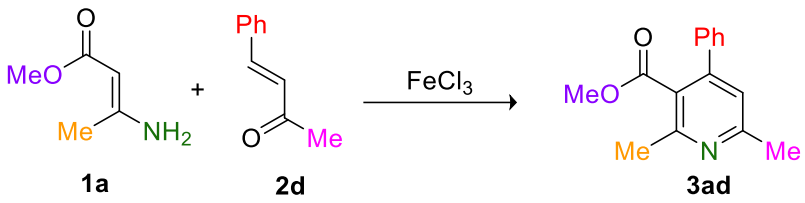
Although the reaction of **2a** occurred efficiently, no reaction proceeded in the case of the β-phenylated enone **2d**, even when the reaction mixture was heated at 150 °C for 1 d. Reaction conditions were studied to perform the reaction between **1a** and enone **2d**. Adding a Lewis acid like $AlCl_3$, $BF_3{\cdot}OEt_2$, $FeCl_3$, $InCl_3$, $SnCl_2{\cdot}2H_2O$, or $ZnCl_2$ proved effective. Among these Lewis acids, $FeCl_3$ was determined to be the most suitable from the environmental and economical viewpoints (Table 3). As a result of surveying the reaction conditions (Table 4), when the enone **2d** was heated with excess amounts of **1a** at 150 °C under microwave irradiation for 1 h in acetonitrile, 4-phenylnicotinate **3ad** was successfully obtained in 87% yield. The same reaction proceeded even under an argon atmosphere to produce **3ad** in 48% yield, which indicates that $FeCl_3$ serves as the activator of the substrate and also as the oxidant[15] of the dihydropyridine intermediate. Thus, oxygen in the air is considered to assist the oxidation of the reduced iron species (Scheme 3).

Table 3. Study on the additives in the reaction of **1a** with **2d.**



Entry	Additive	Yield/%
1	*p*-TsOH · H_2O	0
2	NEt_3	0
3	$BF_3 \cdot Et_2O$	20
4	$Cu(OAc)_2$	0
5	$Mn(OAc)_3 \cdot 2H_2O$	0
6	$Mg(OAc)_2 \cdot 4H_2O$	0
7	$CoSO_4 \cdot 7H_2O$	0
8	$AlCl_3$	23
9	$NiCl_2$	0
10	$SbCl_3$	0
11	$CuCl_2 \cdot 2H_2O$	0
12	$SnCl_2 \cdot 2H_2O$	26
13	$InCl_3$	30
14	$ZnCl_2$	34
15	$FeCl_3$	34
16	$FeCl_2 \cdot 4H_2O$	20
17	$FeCl_3 \cdot 6H_2O$	0
18	$Fe(OTs\text{-}p)_3 \cdot 6H_2O$	0
19	$Fe(NO_3)_3 \cdot 9H_2O$	0

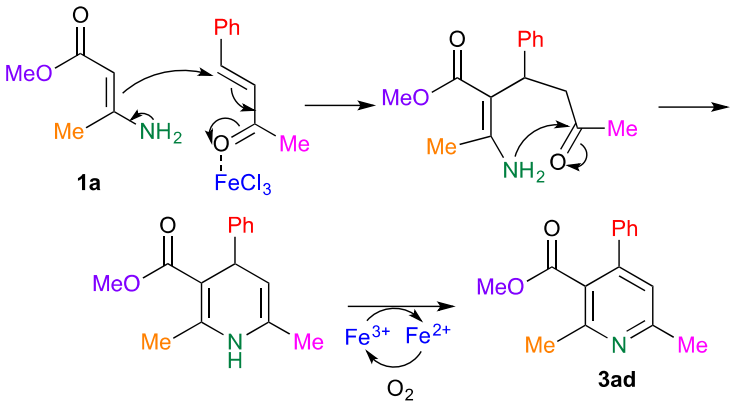
Table 4. Optimization of reaction conditions for synthesizing **3ad**.



1a **2d** **3ad**

Entry	Solv.	Molar ratio			Temp./°C	Time/h	Yield/%[a]
		1a	**2d**	$FeCl_3$			
1	PhMe	1	1	1	90	3	40
2	$CHCl_3$	1	1	1	90	3	45
3	EtOAc	1	1	1	90	3	31
4	THF	1	1	1	90	3	29
5	MeCN	1	1	1	90	3	48
6	MeOH	1	1	1	90	3	46
7	H_2O	1	1	1	90	3	0
8	MeCN	1	1	2	90	3	16
9	MeCN	1	2	1	90	18	54
10	MeCN	2	1	1	90	3	73
11	MeCN	1	1	1	90	24	63
12	MeCN	1	1	1	120	3	63
13[b]	MeCN	1	1	1	150	1	58
13	MeCN	2	1	1	150	1	72
14[b]	MeCN	2	1	1	150	1	87
15[b]	MeCN	2	1	0.2	150	1	74

[a] NMR yield, [b] Microwave heating was used.

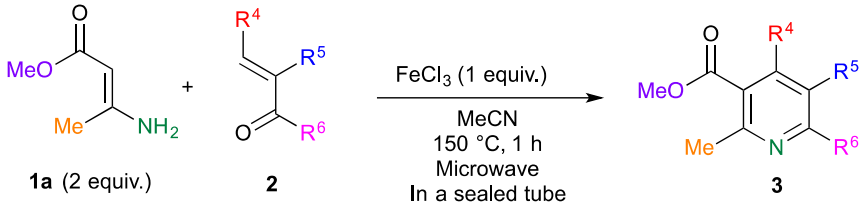


Scheme 3. A plausible mechanism for forming nicotinate **3ad.**

2-4. Synthesis of polysubstituted nicotinates.

Other enones **2e–s** were subjected to this reaction under the optimized conditions (in Table 5, both NMR yields and isolated yields (in the parentheses) are shown). Modifications at the 4- and 6-positions were easily achieved by modifying enones **2e–j** to produce 2,4-dialkyl-6-aryl- and 2-alkyl-4,6-diarylnicotinates **3ae**–**3aj** in high yields. The functionalized bipyridyls **3ak–3am** could be prepared using the pyridyl ketone **2k–m**.[16] 2,4-Disubstituted nicotinates **3an** and **3ao**, and the 2,5,6-trisubstituted derivative **3ap** were also available by this protocol when using β-substituted enals **2n** and **2o** and β-substituted enone **2p**. Further, fully substituted nicotinates **3aq**–**as** could be synthesized by the treatment of **1a** with the trisubstituted enones **2q**–**s**.

Table 5. Reactions of **1A** with other enones.

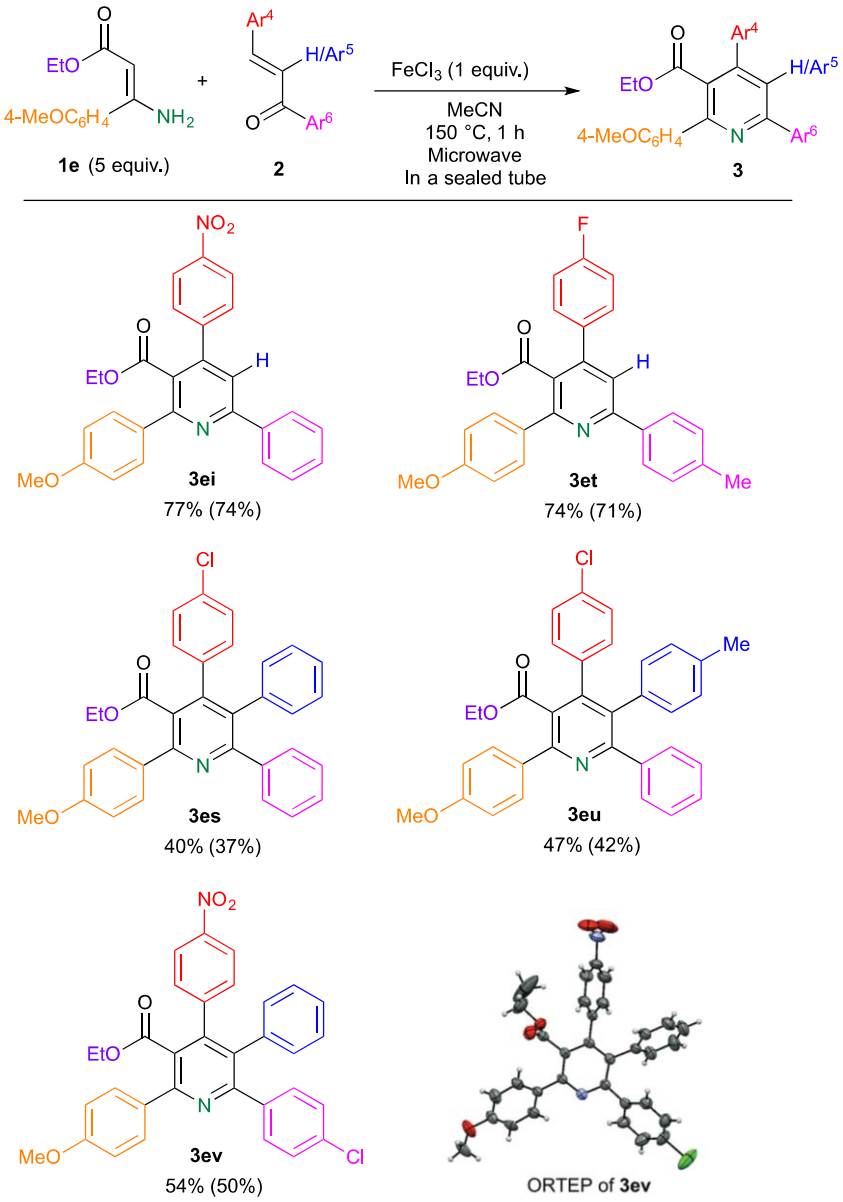


Entry	Enone **2**				Product	Yield/%[a]
	R^4	R^5	R^6			
1	Ph	H	Me	**2d**	**3ad**	87 (79)
2	4-$MeOC_6H_4$	H	Me	**2e**	**3ae**	82 (65)
3	4-MeC_6H_4	H	Me	**2f**	**3af**	93 (83)
4	4-ClC_6H_4	H	Me	**2g**	**3ag**	82 (72)
5	Ph	H	Ph	**2h**	**3ah**	77 (70)
6	4-$NO_2C_6H_4$	H	Ph	**2i**	**3ai**	66 (57)
7	Pr	H	Ph	**2j**	**3aj**	92 (72)
8	4-MeC_6H_4	H	2-Pyridyl	**2k**	**3ak**	94 (72)
9	3-$MeOC_6H_4$	H	2-Pyridyl	**2l**	**3al**	59 (57)
10	DMP[b]	H	2-Pyridyl	**2m**	**3am**	64 (52)
11	Me	H	H	**2n**	**3an**	86 (81)
12	Ph	H	H	**2o**	**3ao**	46 (39)
13	H	Me	Me	**2p**	**3ap**	87 (83)
14	Me	Me	Me	**2q**	**3aq**	91 (82)
15	Ph	-$(CH_2)_4$-		**2r**	**3ar**	82 (78)
16[c]	4-ClC_6H_4	Ph	Ph	**2s**	**3as**	41 (39)

[a] NMR yield (isolated yield), [b] 3,5-Dimethoxyphenyl, [c] 5 equiv. of **1a** were used.

These successful results prompted us to challenge the synthesis of 2,4,6- or 2,4,5,6-polyarylated nicotinates (Scheme 4). Despite congestion at the reaction site, the enamino ester **1e** underwent similar condensation as the diaryl/triarylenones **2i** and **2s**–**v** to produce the corresponding nicotinates **3ei**–**3ev**. It is noteworthy that different aryl groups could be introduced to the desired positions facilitating the elaborate

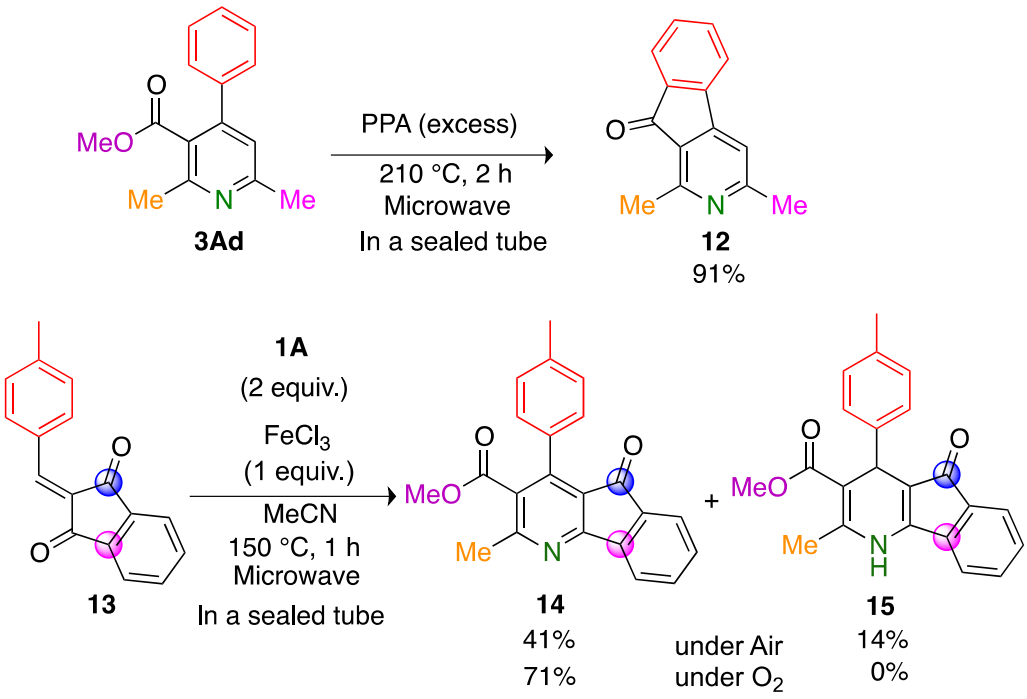
synthesis of nicotinates and their derivatives. The structure of **3ev** was unambiguously confirmed by single crystal X-ray analysis (the ORTEP view is shown in Scheme 4).



Scheme 4. Synthesis of polyarylated nicotinates.

The present method facilitates the efficient synthesis of high quality polysubstituted nicotinates **3**, among which the 4-phenylated nicotinates serve as the precursors to 2-azafluorenones. The azafluorenone framework is often found in natural products,[17] and its derivatives are useful as bioactive compounds[18] and optical materials.[19] However, the poor diversity of available azafluorenones prevents the

development of novel functional materials. Our synthetic method has great potential in synthesizing various kinds of azafluorenones. To confirm this, 4-phenylnicotinate **3ad** was treated with excess amounts of polyphosphoric acid (PPA) at 210 °C according to the literature,[20] which underwent intramolecular Friedel-Crafts acylation to produce 2-azafluorenone **12** in 91% yield (Scheme 5). The direct synthesis of 4-azafluorenone **14** was also possible by the reaction of enamino ester **1a** with 2-benzylidene-1,3-indandione **13**. In this reaction, the dihydropyridine derivative **15** was also isolated, which is considered to be an intermediate for **14**. It was possible to increase the yield of 4-azafluorenone **14** to 70% by conducting the reaction in an oxygen atmosphere.



Scheme 3. Synthesis of azafluorenone derivatives.

3. Conclusion

In conclusion, we developed a novel and facile method for the synthesis of polyalkylated/arylated nicotinates **3** using the condensation of enamino esters **1** with enones **2**, which enables the introduction of a desired substituent into the nicotinate framework with simple experimental manipulations. Further, a 4-arylated nicotinate was efficiently transformed to an azafluorenone derivative. Hence, this method is a new synthetic tool to facilitate the molecular design and synthesis of polysubstituted nicotinates and azafluorenones.

4. Experimental section and characterization of compounds

4-1. General information

Unless otherwise noted, all reagents were commercially supplied and were used without further purification. α,β-Unsaturated ketones **2b**,[21] **2e–2g**,[22] **2h–2i**,[23] **2j**,[24] **2k-2m**,[25] **2s-2u**,[26] **13**,[27] and enamino esters **1b-1d**[28] were synthesized in from 72% to quantitative yields according to the method in the literature, respectively. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ using tetramethylsilane as an internal standard. ^{1}H NMR spectroscopic data are reported as follows: chemical shift (δ, ppm), chemical shift mutiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, integration, coupling constant (Hz). ^{13}C NMR spectroscopic data are reported in terms of chemical shift (δ, ppm), and assignment was performed by DEPT experiment. Infrared spectra were recorded with a Shimadzu IR Affinity-1 spectrometer, and data are reported in frequency of absorption (wave numbers). Highresolution mass spectra were obtained with a AB SCIEX TripleTOF 4600 mass spectrometer. Melting points were recorded with a Stanford Research Systems MPA100 melting point apparatus. Microwave irradiation was used by Anton Paar Monowave 300.

4-2. Spectral data of enamino esters 1

Methyl 3-amino-2-butenoate (1a):[29] White solid, mp 75–76 °C, R_f = 0.33 (silica gel, hexane/EtOAc = 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (s, 3H), 3.63 (s, 3H), 4.52 (s, 1H),

4.1–5.3 (br, 1H), 7.5–8.5 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5 (CH_3), 50.2 (CH_3), 84.0 (CH), 159.9 (C), 170.7 (C); IR (ATR/cm^{-1}): 3458, 1667, 1557.

Ethyl 3-amino-2-hexenoate (1b):[30] Yellow oil, R_f = 0.32 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.55 (tq, *J* = 7.2, 7.2 Hz, 2H), 2.09 (t, *J* = 7.2 Hz, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 4.2–5.7 (br, 1H), 4.53 (s, 1H), 7.3-8.4 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 14.7 (CH_3), 21.3 (CH_2), 38.5 (CH_2), 58.7 (CH_2), 83.7 (CH), 163.7 (C), 170.6 (C); IR (ATR/cm^{-1}): 3333, 1667, 1557.

Methyl 3-amino-4,4-dimethyl-2-pentenoate (1c):[31] (1551.2 mg, 71% yield); Pale yellow oil, R_f = 0.55 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 9H), 3.64 (s, 3H), 4.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.9 (CH_3), 35.9 (C), 50.2 (CH_3), 80.0 (CH), 171.4 (C), 172.0 (C); IR (ATR/cm^{-1}): 3331, 1668, 1557.

Ethyl 3-amino-4-phenyl-2-butenoate (1d):[30] Yellow oil, R_f = 0.38 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.2 Hz, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.96 (s, 1H), 7.40−7.43 (m, 3H), 7.53 (dd, *J* = 6.0, 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7 (CH_3), 59.0 (CH_2), 84.8 (CH), 126.2 (CH), 128.9 (CH), 130.3 (CH), 137.8 (C), 160.6 (C), 170.5 (C); IR (ATR/cm^{-1}): 3326, 1661, 1557.

Ethyl 3-amino-4-(4-methoxyphenyl)-2-butenoate (1e):[30] Yellow oil, R_f = 0.21 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.2 Hz, 3H), 3.83 (s, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.93 (s, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8 (CH_3), 55.5 (CH_3), 59.0 (CH_2), 84.0 (CH), 114.3 (CH), 127.7 (CH), 130.1 (C), 160.3 (C), 161.4 (C), 170.7 (C); IR (ATR/cm^{-1}): 3323, 1645, 1557.

Ethyl 3-amino-2-butenoate (1f):[29] Colorless oil, R_f = 0.39 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.2 Hz, 3H), 1.90 (s, 3H), 4.11 (q, *J* = 7.2 Hz, 2H), 4.4–5.4 (br, 1H), 4.53 (s, 1H), 7.5–8.5 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7 (CH_3), 22.5 (CH_3), 58.7 (CH_2), 84.5 (CH), 159.7 (C), 170.4 (C); IR (ATR/cm^{-1}): 3335, 1659, 1557.

Butyl 3-amino-2-butenoate (1g):[32] Colorless oil, R_f = 0.31 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.2 Hz, 3H), 1.39 (tq, *J* = 7.2, 7.2 Hz, 2H), 1.61 (tt,

J = 7.2, 7.2 Hz, 2H), 1.89 (s, 3H), 4.05 (t, *J* = 7.2 Hz, 2H), 4.3–5.2 (br, 1H), 4.53 (s, 1H), 7.4–8.5 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 19.4 (CH_2), 22.5 (CH_3), 31.3 (CH_2), 62.7 (CH_2), 84.5 (CH), 159.6 (C), 170.5 (C); IR (ATR/cm^{-1}): 3439, 1667, 1566.

2-Propyl 3-amino-2-butenoate (1h):[29] Colorless oil, R_f = 0.31 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6.4 Hz, 6H), 1.89 (s, 3H), 3.9-4.9 (br, 1H), 4.50 (s, 1H), 5.01 (septet, *J* = 6.4 Hz, 1H), 7.4–8.6 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3 (CH_3), 22.5 (CH_3), 65.5 (CH), 85.0 (CH), 159.5 (C), 170.0 (C); IR (ATR/cm^{-1}): 3439, 1667, 1566.

2-Methyl-1-propyl 3-amino-2-butenoate (1i):[33] Colorless oil, R_f = 0.32 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, *J* = 6.8 Hz, 6H), 1.90 (s, 3H), 1.91 (septet t, *J* = 6.8, 6.8 Hz, 1H), 3.84 (d, *J* = 6.8 Hz, 2H), 4.2–5.0 (br, 1H), 4.55 (s, 1H), 7.4–8.3 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4 (CH_3), 22.5 (CH_3), 28.1 (CH), 69.1 (CH_2), 84.5 (CH), 159.6 (C), 170.5 (C); IR (ATR/cm^{-1}): 3330, 1667, 1557.

2-Methyl-2-propyl 3-amino-2-butenoate (1j):[29] Colorless oil, R_f = 0.39 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.86 (s, 3H), 4.2–5.1 (br, 1H), 4.46 (s, 1H), 7.3–8.3 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5 (CH_3), 28.8 (CH_3), 78.3 (C), 86.2 (CH), 158.8 (C), 170.4 (C); IR (ATR/cm^{-1}): 3308, 1659, 1557, 1148.

2-Phenylethyl 3-amino-2-butenoate (1k):[34] Colorless oil, R_f = 0.24 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (s, 3H), 2.96 (t, *J* = 7.2 Hz, 2H), 4.29 (t, *J* = 7.2 Hz, 2H), 4.3–5.0 (br, 1H), 4.54 (s, 1H), 7.2–7.4 (m, 5H), 7.5–8.6 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5 (CH_3), 35.7 (CH_2), 63.4 (CH_2), 84.3 (CH), 126.5 (CH), 128.5 (C), 129.1 (CH), 138.6 (C), 159.9 (C), 170.2 (C); IR (ATR/cm^{-1}): 3443, 1667, 1557.

3-Propenyl 3-amino-2-butenoate (1l):[29] Colorless oil, R_f = 0.29 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (s, 3H), 4.2–4.9 (br, 1H), 4.5–4.6 (m, 3H), 5.19 (ddt, *J* = 10.4, 1.6, 1.6 Hz, 1H), 5.30 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 1H), 5.95 (ddt, *J* = 17.2, 10.4, 1.6 Hz, 1H), 7.6–8.2 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5 (CH_3), 63.6 (CH_2), 84.1 (CH), 117.2 (CH_2), 133.6 (CH), 160.1 (C), 169.9 (C); IR (ATR/cm^{-1}): 3424, 1667, 1566.

3-Propynyl 3-amino-2-butenoate (1m):[32] Colorless oil, R_f = 0.22 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (s, 3H), 2.42 (t, *J* = 6.4 Hz, 1H), 4.2–5.5 (br, 1H), 4.56 (s, 1H), 4.66 (d, *J* = 6.4 Hz, 2H), 7.5–8.5 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5 (CH_3), 50.4 (CH_2), 74.0 (C), 79.2 (CH), 83.3 (CH), 161.0 (C), 169.1 (C); IR (ATR/cm^{-1}): 3474, 2126, 1667, 1557.

4-3. Synthesis of nicotinates 3 without using $FeCl_3$

To a solution of methyl 3-amino-2-butenoate (**1a**) (23.0 mg, 0.20 mmol) in toluene (0.5 mL), methyl vinyl ketone **2a** (48.7 μL, 0.60 mmol) was added, and the resultant solution was heated at 120 °C for 3 h in a sealed tube. After evaporation of the solvent under reduced pressure, the residue was treated by short silica gel column chromatography (hexane/EtOAc = 8/2) to give methyl 2,6-dimethylpyridine-3-carboxylate (**3a**) (26.9 mg, 0.16 mmol, 82%) as a pale yellow oil. Other nicotinates **3a**–**c** were also synthesized in a similar way.

Methyl 2,6-dimethylpyridine-3-carboxylate (3aa):[35] (26.9 mg, 82% yield). Pale yellow oil, R_f = 0.37 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 3H), 2.80 (s, 3H), 3.89 (s, 3H), 7.04 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8 (CH_3), 24.9 (CH_3), 52.2 (CH_3), 120.6 (CH), 122.5 (C), 138.9 (CH), 159.7 (C), 161.5 (C), 167.3 (C); IR (ATR/cm^{-1}): 2951, 1722, 1275.

Ethyl 6-methyl-2-propylpyridine-3-carboxylate (3ba):[36] (32.9 mg, 80% yield); Yellow oil, R_f = 0.44 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.6 Hz, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.71 (tq, *J* = 7.6, 7.6 Hz, 2H), 2.55 (s, 3H), 3.09 (t, *J* = 7.6 Hz, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4 (CH_3), 14.4 (CH_3), 23.8 (CH_2), 24.9 (CH_3), 39.3 (CH_2), 61.2 (CH_2), 120.5 (CH), 122.9 (C), 138.9 (CH), 161.3 (C), 163.2 (C), 167.1 (C); IR (ATR/cm^{-1}): 1722, 1251.

Ethyl 6-methyl-2-(2-methyl-1-propyl) pyridine-3-carboxylate (3ca): (17.2 mg, 42% yield). Yellow oil, R_f = 0.63 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.53 (s, 3H), 3.89 (s, 3H), 6.96 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ 24.8 (CH_3), 30.2 (CH_3), 39.3 (C), 52.5 (CH_3), 119.3 (CH), 125.0 (C), 136.9 (CH), 158.4 (C), 164.7 (C), 171.4 (C); IR (ATR/cm^{-1}): 1733, 1280, 1241, 1070; HRMS (ESI/TOF): *m/z calcd*. for $C_{12}H_{17}NO_2$ $[M + H]^+$ 208.1332, found 208.1323.

Ethyl 2-phenyl-6-methylpyridine-3-carboxylate (3da):[37] (40.7 mg, 85% yield). Yellow oil, R_f = 0.42 (silica gel, hexane/EtOAc = 8/2). ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, *J* = 7.2 Hz, 3H), 2.65 (s, 3H), 4.12 (q, *J* = 7.2 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.4–7.5 (m, 3H), 7.5–7.6 (m, 2H), 8.02 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.8 (CH_3), 25.0 (CH_3), 61.4 (CH_2), 121.3 (CH), 124.6 (C), 128.2 (CH), 128.5 (CH), 128.7 (CH), 138.4 (CH), 140.8 (C), 158.9 (C), 160.9 (C), 168.3 (C); IR (ATR/cm^{-1}): 1722, 1563, 1280.

Ethyl 2-(4-methoxyphenyl)-6-methylpyridine-3-carboxylate (3ea): (46.3 mg, 86% yield). Yellow oil, R_f = 0.24 (silica gel, hexane/EtOAc = 8/2). ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (t, *J* = 7.2 Hz, 3H), 2.63 (s, 3H), 3.84 (s, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.97 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 24.9 (CH_3), 55.5 (CH_3), 61.4 (CH_2), 113.7 (CH), 120.8 (CH), 124.3 (C), 130.2 (CH), 133.2 (C), 138.3 (CH), 158.3 (C), 160.2 (C), 160.8 (C), 168.6 (C); IR (ATR/cm^{-1}): 1714, 1516, 1250, HRMS (ESI/TOF): *m/z calcd*. for $C_{16}H_{17}NO_3$ $[M + H]^+$ 272.1281, found 272.1269.

Ethyl 2,6-dimethylpyridine-3-carboxylate (3fa):[37] (30.2 mg, 85% yield). Pale yellow oil, R_f = 0.38 (silica gel, hexane/EtOAc = 8/2). ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.2 Hz, 3H), 2.56 (s, 3H), 2.80 (s, 3H), 4.32 (q, *J* = 7.2 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4 (CH_3), 24.8 (CH_3), 25.0 (CH_3), 61.2 (CH_2), 120.5 (CH), 122.9 (C), 138.9 (CH), 159.5 (C), 161.3 (C), 166.9 (C); IR (ATR/cm^{-1}): 2357, 1722, 1273.

Butyl 2,6-dimethylpyridine-3-carboxylate (3ga): (37.9 mg, 92% yield). Pale yellow oil, R_f = 0.26 (silica gel, hexane/EtOAc = 9/1). ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.6 Hz, 3H), 1.47 (tq, *J* = 7.6, 7.6 Hz, 2H), 1.74 (tt, *J* = 7.6, 7.6 Hz, 2H), 2.56 (s, 3H), 2.80 (s, 3H), 4.30 (t, *J* = 7.6 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 19.5 (CH_2), 24.8 (CH_3), 25.0 (CH_3), 30.9 (CH_2), 65.1 (CH_2),

120.6 (CH), 123.0 (C), 138.9 (CH), 159.5 (C), 161.3 (C), 167.0 (C); IR (ATR/cm^{-1}): 2963, 2359, 1722, 1275; HRMS (ESI/TOF): *m/z calcd.* for $C_{12}H_{17}NO_2$ $[M + H]^+$ 208.1332, found 208.1331.

2-Propyl 2,6-dimethylpyridine-3-carboxylate (3ha): (35.9 mg, 81% yield). Yellow oil, R_f = 0.46 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, *J* = 6.0 Hz, 6H), 2.54 (s, 3H), 2.78 (s, 3H), 5.22 (septet, *J* = 6.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1 (CH_3), 24.8 (CH_3), 24.9 (CH_3), 68.7 (CH), 120.5 (CH), 123.4 (C), 138.8 (CH), 159.3 (C), 161.1 (C), 166.5 (C); IR (ATR/cm^{-1}): 2976, 2359, 1715, 1273; HRMS (ESI/TOF): *m/z calcd.* for $C_{11}H_{15}NO_2$ $[M + H]^+$ 194.1175, found 194.1173.

2-Methyl-1-propyl 2,6-dimethylpyridine-3-carboxylate (3ia): (29.4 mg, 79% yield). Yellow oil, R_f = 0.33 (silica gel, hexane/EtOAc = 9/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, *J* = 6.8 Hz, 6H), 2.07 (triple septet, *J* = 6.8, 6.8 Hz, 1H), 2.56 (s, 3H), 2.81 (s, 3H), 4.09 (d, *J* = 6.8 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4 (CH_3), 24.8 (CH_3), 25.1 (CH_3), 28.0 (CH), 71.4 (CH_2), 120.6 (CH), 123.0 (C), 138.9 (CH), 159.6 (C), 161.4 (C), 167.0 (C); IR (ATR/cm^{-1}): 2961, 2357, 1721, 1257; HRMS (ESI/TOF): *m/z calcd.* for $C_{12}H_{17}NO_2$ $[M + H]^+$ 208.1332, found 208.1334.

2-Methyl-2-propyl 2,6-dimethylpyridine-3-carboxylate (3ja):[37] (29.8 mg, 72% yield). Pale yellow oil, R_f = 0.37 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 9H), 2.55 (s, 3H), 2.77 (s, 3H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8 (CH_3), 25.0 (CH_3), 28.4 (CH_3), 81.8 (C), 120.5 (CH), 124.6 (C), 138.8 (CH), 158.9 (C), 160.8 (C), 166.4 (C); IR (ATR/cm^{-1}): 2978, 1721, 1254.

2-Phenylethyl 2,6-dimethylpyridine-3-carboxylate (3ka): (41.6 mg, 82% yield). Yellow oil, R_f = 0.18 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 3H), 2.74 (s, 3H), 3.06 (t, *J* = 6.8 Hz, 2H), 4.52 (t, *J* = 6.8 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 1H), 7.2–7.4 (m, 5H), 8.00 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8 (CH_3), 24.9 (CH_3), 35.3 (CH_2), 65.6 (CH_2), 120.5 (CH), 122.7 (C), 126.8 (CH), 128.7 (CH), 129.0 (CH), 137.9

(C), 138.9 (CH), 159.6 (C), 161.4 (C), 166.7 (C); IR (ATR/cm^{-1}): 2968, 2359, 1726, 1271; HRMS (ESI/TOF): *m/z calcd.* for $C_{16}H_{18}NO_2$ $[M + H]^+$ 256.1332, found 256.1331.

3-Propenyl 2,6-dimethylpyridine-3-carboxylate (3la): (28.9 mg, 76% yield). Pale yellow oil, R_f = 0.36 (silica gel, hexane/EtOAc = 8/2). ^1H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 3H), 2.81 (s, 3H), 4.80 (ddd, *J* = 6.4, 1.2, 1.2 Hz, 2H), 5.29 (ddt, *J* = 10.4, 1.2, 1.2 Hz, 1H), 5.29 (ddt, *J* = 17.2, 1.2, 1.2 Hz, 1H), 6.03 (ddt, *J* = 17.2, 10.4, 6.4 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8 (CH_3), 25.0 (CH_3), 65.8 (CH_2), 118.7 (CH_2), 120.6 (CH), 122.6 (C), 132.2 (CH), 138.9 (CH), 159.8 (C), 161.6 (C), 166.5 (C); IR (ATR/cm^{-1}): 2355, 1728, 1269; HRMS (ESI/TOF): *m/z calcd.* for $C_{11}H_{13}NO_2$ $[M + H]^+$ 192.1019, found 192.1019.

3-Propynyl 2,6-dimethylpyridine-3-carboxylate (3ma): (24.4 mg, 65% yield). Pale yellow oil, R_f = 0.29 (silica gel, hexane/EtOAc = 8/2). ^1H NMR (400 MHz, $CDCl_3$) δ 2.51 (t, *J* = 2.4 Hz, 1H), 2.57 (s, 3H), 2.82 (s, 3H), 4.90 (d, *J* = 2.4 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9 (CH_3), 25.0 (CH_3), 52.6 (CH_2), 75.2 (CH), 77.7 (C), 120.6 (CH), 121.8 (C), 139.1 (CH), 160.1 (C), 162.0 (C), 165.9 (C); IR (ATR/cm^{-1}): 3391, 2127, 1730; HRMS (ESI/TOF): *m/z calcd.* for $C_{11}H_{11}NO_2$ $[M + H]^+$ 190.0863, found 190.0862.

Methyl 2-methyl-6-phenylpyridine-3-carboxylate (3ab):[38] (40.2 mg, 89% yield). Yellow oil, R_f = 0.32 (silica gel, hexane/EtOAc = 95/5). ^1H NMR (400 MHz, $CDCl_3$) δ 2.92 (s, 3H), 3.94 (s, 3H), 7.4–7.5 (m, 3H), 7.63 (d, *J* = 8.4 Hz, 1H), 8.0–8.1 (m, 2H), 8.26 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4 (CH_3), 52.3 (CH_3), 117.5 (CH), 123.5 (C), 127.5 (CH), 129.0 (CH), 129.8 (CH), 138.6 (C), 139.5 (CH), 159.3 (C), 160.2 (C), 167.2 (C); IR (ATR/cm^{-1}): 2951, 2355, 1728, 1267.

Methyl 2-methypyridine-3-carboxylate (3ac):[35] (27.5 mg, 91% yield). Yellow oil, R_f = 0.29 (silica gel, hexane/EtOAc = 8/2). ^1H NMR (400 MHz, $CDCl_3$) δ 2.83 (s, 3H), 3.91 (s, 3H), 7.19 (dd, *J* = 7.6, 4.8 Hz, 1H), 8.17 (dd, *J* = 7.6, 1.6 Hz, 1H), 8.60 (dd, *J* = 4.8, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9 (CH_3), 52.3 (CH_3), 121.0 (CH), 125.5 (C), 138.5 (CH), 152.0 (CH), 160.0 (C), 167.1 (C); IR (ATR/cm^{-1}): 2949, 1726, 1277.

4-4. Synthesis of nicotinates 3 and 14 using $FeCl_3$

To a solution of methyl 3-amino-2-butenoate (**1a**) (46.0 mg, 0.40 mmol) in acetonitrile (0.5 mL), were added 4-phenyl-3-buten-2-one (**2d**) (29.2 mg, 0.20 mmol) and iron(III) chloride (32.4 mg, 0.20 mmol), and the resultant solution was heated at 150 °C for 1 h under microwave irradiation. After evaporation of the solvent under reduced pressure, the residue was washed with water (15 mL×3), and then extracted with chloroform (15 mL×3). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by short silica gel column chromatography (hexane/EtOAc = 8/2) to afford methyl 2,6-dimethyl-4-phenylnicotinate (**3ad**) (35.5 mg, 0.16 mmol, 79%) as a yellow oil. Other nicotinates **3ae**–**3av**, and **14** were also synthesized in a similar way.

Methyl 2,6-dimethyl-6-phenylpyridine-3-carboxylate (3ad): (35.5 mg, 79% yield). Yellow oil, R_f = 0.36 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 3H), 2.60 (s, 3H), 3.61 (s, 3H), 7.02 (s, 1H), 7.3–7.4 (m, 2H), 7.4–7.5 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0 (CH_3), 24.6 (CH_3), 52.3 (CH_3), 121.2 (CH), 125.7 (C), 127.9 (CH), 128.6 (CH), 128.7 (CH), 138.9 (C), 148.6 (C), 155.3 (C), 159.0 (C), 169.8 (C); IR (ATR/cm^{-1}): 2953, 1728, 1267; HRMS (ESI/TOF): *m/z calcd.* for $C_{15}H_{15}NO_2$ $[M + H]^+$ 242.1176, found 242.1172.

Methyl 2,6-dimethyl-4-(4-methoxyphenyl)pyridine-3-carboxylate (3ae): (35.1 mg, 65% yield). Yellow solid, mp 103–104 °C, R_f = 0.20 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (s, 3H), 2.58 (s, 3H), 3.66 (s, 3H), 3.85 (s, 3H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.00 (s, 1H), 7.30 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0 (CH_3), 24.6 (CH_3), 52.3 (CH_3), 55.5 (CH_3), 114.3 (CH), 121.1 (CH), 125.6 (C), 129.2 (CH), 131.1 (C), 148.0 (C), 155.2 (C), 158.8 (C), 160.1 (C), 170.1 (C); IR (ATR/cm^{-1}): 2938, 1726, 1250; HRMS (ESI/TOF): *m/z calcd.* for $C_{16}H_{17}NO_3$ $[M + H]^+$ 272.1281, found 272.1294.

Methyl 2,6-dimethyl-4-(4-methylphenyl)pyridine-3-carboxylate (3af): (42.3 mg, 83% yield). Yellow oil, R_f = 0.28 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.57 (s, 3H), 2.58 (s, 3H), 3.65 (s, 3H), 7.01 (s, 1H), 7.2–7.3 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4 (CH_3), 23.0 (CH_3), 24.6 (CH_3), 52.3 (CH_3), 121.2 (CH), 125.6 (C),

127.8 (CH), 129.5 (CH), 135.9 (C), 138.6 (C), 148.5 (C), 155.2 (C), 158.9 (C), 170.0 (C); IR (ATR/cm^{-1}): 2945, 1726, 1267; HRMS (ESI/TOF): *m/z calcd.* for $C_{16}H_{17}NO_2$ $[M + H]^+$ 256.1332, found 256.1342.

Methyl 4-(4-chlorophenyl)-2,6-dimethylpyridine-3-carboxylate (3ag):[39] (39.3 mg, 72% yield). Yellow oil, R_f = 0.26 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 3H), 2.59 (s, 3H), 3.65 (s, 3H), 6.98 (s, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1 (CH_3), 24.6 (CH_3), 52.4 (CH_3), 121.0 (CH), 125.5 (C), 129.0 (CH), 129.3 (CH), 134.9 (C), 137.3 (C), 147.3 (C), 155.6 (C), 159.2 (C), 169.5 (C); IR (ATR/cm^{-1}): 2951, 1726, 1261.

Methyl 4,6-diphenyl-2-methylpyridine-3-carboxylate (3ah):[40] (42.4 mg, 70% yield). White solid, mp 82–83 °C, R_f = 0.60 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (s, 3H), 3.65 (s, 3H), 7.4–7.5 (m, 8H), 7.58 (s, 1H), 8.04 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4 (CH_3), 52.3 (CH_3), 118.7 (CH), 126.7 (C), 127.4 (CH), 128.0 (CH), 128.7 (CH), 128.8 (CH), 128.9 (CH), 129.5 (CH), 138.9 (C), 139.0 (C), 149.1 (C), 156.0 (C), 157.7 (C), 169.7 (C); IR (ATR/cm^{-1}): 1726, 1271.

Methyl 2-methyl-4-(4-nitrophenyl)-6-phenylpyridine-3-carboxylate (3ai): (39.7 mg, 57% yield). Yellow solid, mp 141–142 °C, R_f = 0.41 (silica gel, hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (s, 3H), 3.67 (s, 3H), 7.4–7.5 (m, 3H), 7.55 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 2H), 8.05 (dd, *J* = 2.0, 8.4 Hz, 2H), 8.32 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5 (CH_3), 52.5 (CH_3), 118.1 (CH), 124.0 (CH), 126.1 (C), 127.4 (CH), 129.0 (CH), 129.1 (CH), 129.9 (CH), 138.4 (C), 145.6 (C), 148.1 (C), 156.7 (C), 158.1 (C), 168.9 (C); IR (ATR/cm^{-1}): 2951, 1728, 1518, 1271; HRMS (ESI/TOF): *m/z calcd.* for $C_{20}H_{16}N_2O_4$ $[M + H]^+$ 349.1183, found 349.1187.

Methyl 2-methyl-6-phenyl-4-propylpyridine-3-carboxylate (3aj): (38.4 mg, 72% yield). Yellow oil, R_f = 0.61 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.2 Hz, 3H), 1.68 (tq, *J* = 7.2, 7.2 Hz, 2H), 2.61 (s, 3H), 2.64 (t, *J* = 7.2 Hz, 2H), 3.95 (s, 3H), 7.41 (s, 1H), 7.4–7.5 (m, 3H), 7.98 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 23.5 (CH_3), 23.8 (CH_2), 35.7 (CH_2), 52.3 (CH_3), 118.6 (CH), 127.3 (CH), 127.6

(C), 128.9 (CH), 129.3 (CH), 139.3 (C), 150.0 (C), 155.5 (C), 157.5 (C), 169.8 (C); IR (ATR/cm^{-1}): 2955, 1726, 1269; HRMS (ESI/TOF): *m/z calcd.* for $C_{17}H_{19}NO_2$ $[M + H]^+$ 270.1489, found 270.1490.

Methyl 2-methyl-4-(4-methylphenyl)-6-(2-pyridinyl)pyridine-3-carboxylate (3ak): (226.8 mg, 72% yield). Brown oil, R_f = 0.23 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.69 (s, 3H), 3.68 (s, 3H), 7.23 (br d, *J* = 8.0 Hz, 2H), 7.31 (ddd, *J* = 7.6, 4.8, 0.8 Hz, 1H), 7.35 (br d, *J* = 8.0 Hz, 2H), 7.82 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 8.28 (s, 1H), 8.47 (ddd, *J* = 7.6, 0.8, 0.8 Hz, 1H), 8.67 (ddd, *J* = 4.8, 1.6, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 (CH_3), 23.1 (CH_3), 52.2 (CH_3), 118.9 (CH), 121.6 (CH), 123.9 (CH), 127.8 (CH), 127.9 (C), 129.3 (C), 135.7 (C), 136.9 (CH), 138.4 (C), 148.9 (C), 149.2 (CH), 155.2 (C), 155.6 (C), 155.9 (C), 169.7 (C); IR (ATR/cm^{-1}): 1730, 1557, 1267; HRMS (ESI/TOF): *m/z calcd.* for $C_{20}H_{18}N_2O_2$ $[M + H]^+$ 319.1441, found 319.1441.

Methyl 2-methyl-4-(3-methoxyphenyl)-6-(2-pyridinyl)pyrinine-3-carboxylate (3al): (37.6 mg, 57% yield). Yellow oil, R_f = 0.19 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 3H), 3.68 (s, 3H), 3.83 (s, 3H), 6.9−7.0 (m, 3H), 7.3−7.4 (m, 2H), 7.82 (dd, *J* = 7.6, 7.6 Hz, 1H), 8.30 (s, 1H), 8.48 (d, *J* = 7.6 Hz, 1H), 8.67 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1 (CH_3), 52.2 (CH_3), 55.3 (CH_3), 113.2 (CH), 114.4 (CH), 118.8 (CH), 120.3 (CH), 121.6 (CH), 124.0 (CH), 127.9 (C), 129.6 (CH), 136.8 (CH), 140.0 (C), 148.9 (C), 149.2 (CH), 155.3 (C), 155.5 (C), 155.9 (C), 159.7 (C), 169.5 (C); IR (ATR/cm^{-1}): 1729, 1549, 1271; HRMS (ESI/TOF): *m/z calcd.* for $C_{20}H_{18}N_2O_3$ $[M + H]^+$ 335.1390, found 335.1375.

Methyl 2-methyl-4-(3,5-dimethoxyphenyl)-6-(2-pyridinyl) pyridine-3-carboxylate (3am): (186.6 mg, 52% yield). Yellow oil, R_f = 0.15 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (s, 3H), 3.70 (s, 3H), 3.79 (s, 6H), 6.50 (t, *J* = 2.0 Hz, 1H), 6.61 (d, *J* = 2.0 Hz, 2H), 7.28 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.78 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 8.31 (s, 1H), 8.46 (ddd, *J* = 7.6, 1.2, 0.8 Hz, 1H), 8.65 (ddd, *J* = 4.8, 1.6, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0 (CH_3), 52.2 (CH_3), 55.3 (CH_3), 100.8 (CH), 105.9 (CH), 118.6 (CH), 121.5 (CH), 123.9 (CH), 127.8 (C), 136.8 (CH), 140.6 (C), 148.8 (CH), 149.1

(C), 155.1 (C), 155.4 (C), 155.9 (C), 160.8 (C), 169.5 (C); IR(ATR/cm^{-1}): 1730, 1580, 1268; HRMS (ESI/TOF): *m/z calcd*. for $C_{21}H_{20}N_2O_4$ $[M + H]^+$ 365.1496, found 365.1484.

Methyl 2,4-dimethylpyridine-3-carboxylate (3an): (26.5 mg, 81% yield). Yellow oil, R_f = 0.21 (silica gel, hexane/EtOAc = 8/2). ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.54 (s, 3H), 3.94 (s, 3H), 6.99 (d, *J* = 4.8 Hz, 1H), 8.38 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6 (CH_3), 23.1 (CH_3), 52.4 (CH_3), 122.8 (CH), 129.5 (C), 145.0 (C), 149.7 (CH), 155.4 (C), 169.3 (C); IR (ATR/cm^{-1}): 1732, 1287; HRMS (ESI/TOF): *m/z calcd.* for $C_9H_{11}NO_2$ $[M + H]^+$ 166.0863, found 166.0865.

Methyl 2-methyl-4-phenylpyridine-3-carboxylate (3ao): (17.7 mg, 39% yield). Yellow oil, R_f = 0.26 (silica gel, hexane/EtOAc = 8/2). ^1H NMR (400 MHz, $CDCl_3$) δ 2.63 (s, 3H), 3.64 (s, 3H), 7.17 (d, *J* = 5.2 Hz, 1H), 7.3–7.4 (m, 2H), 7.4–7.5 (m, 3H), 8.57 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0 (CH_3), 52.4 (CH_3), 121.8 (CH), 127.9 (CH), 128.5 (C), 128.8 (CH), 129.0 (CH), 138.5 (C), 148.2 (C), 149.8 (CH), 155.8 (C), 169.4 (C); IR (ATR/cm^{-1}): 2955, 1728, 1267; HRMS (ESI/TOF): *m/z calcd.* for $C_{14}H_{13}NO_2$ $[M + H]^+$ 228.1019, found 228.1027.

Methyl 2,5,6-trimethylpyridine-3-carboxylate (3ap): (29.7 mg, 83% yield). Pale yellow oil, R_f = 0.38 (silica gel, hexane/EtOAc = 8/2). ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.50 (s, 3H), 2.76 (s, 3H), 3.89 (s, 3H), 7.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6 (CH_3), 22.8 (CH_3), 24.4 (CH_3), 52.1 (CH_3), 122.8 (C), 128.7 (C), 139.5 (CH), 156.7 (C), 160.3 (C), 167.5 (C); IR (ATR/cm^{-1}): 2951, 1728, 1281. HRMS (ESI/TOF): *m/z calcd.* for $C_{10}H_{13}NO_2$ $[M + H]^+$ 180.1019, found 180.1020.

Methyl 2,4,5,6-tetramethylpyridine-3-carboxylate (3aq):[41] (31.3 mg, 82% yield). White solid, mp 55–56 °C, R_f = 0.21 (silica gel, hexane/EtOAc = 8/2). ^1H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.20 (s, 3H), 2.44 (s, 3H), 2.50 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8 (CH_3), 17.1 (CH_3), 22.7 (CH_3), 23.5 (CH_3), 52.3 (CH_3), 127.5 (C), 127.9 (C), 142.5 (C), 150.8 (C), 156.9 (C), 170.3 (C); IR (ATR/cm^{-1}): 2947, 1726, 1267.

Methyl 2-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (3ar): (43.8 mg, 78% yield). Orange solid, mp 68–69 °C, R_f = 0.28 (s ilica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70 (tt, *J* = 6.0, 6.8 Hz, 2H), 1.86 (tt, *J* = 6.0, 6.8 Hz, 2H), 2.40 (t, *J* = 6.0 Hz, 2H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.53 (s, 3H), 3.46 (s, 3H), 7.1–7.2 (m, 2H), 7.3–7.4 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7 (CH_3), 22.9 (CH_2), 23.0 (CH_2), 27.1 (CH_2), 33.3 (CH_2), 52.0 (CH_3), 127.1 (C), 127.6 (C), 128.0 (CH), 128.3 (CH), 128.6 (CH), 137.3 (C), 147.8 (C), 151.5 (C), 158.2 (C), 169.3 (C); IR (ATR/cm^{-1}): 2938, 1730, 1271; HRMS (ESI/TOF): *m/z calcd.* for $C_{18}H_{19}NO_2$ $[M + H]^+$ 282.1489, found 282.1484.

Methyl-4-(4-chlorophenyl)-5,6-diphenyl-2-methylpyridiney-3-carboxylate (3as): (20.2 mg, 24% yield). White solid, mp 133–134 °C, R_f = 0.55 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (s, 3H), 3.59 (s, 3H), 6.7–6.8 (m, 2H), 6.9–7.0 (m, 2H), 7.0–7.1 (m, 3H), 7.1–7.2 (m, 5H), 7.2–7.3 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1 (CH_3), 52.4 (CH_3), 126.9 (CH), 127.9 (CH), 127.9 (CH), 128.1 (CH), 128.4 (C), 130.0 (CH), 130.6 (CH), 131.3 (CH), 132.5 (C), 133.8 (C), 135.9 (C), 137.0 (C), 140.3 (C), 146.7 (C), 153.8 (C), 158.5 (C), 169.1 (C), one signal of a tertiary carbon was not observed presumably due to overlapping with another signal; IR (ATR/cm^{-1}): 3055, 1730, 1549, 1227; HRMS (ESI/TOF): *m/z calcd.* for $C_{26}H_{20}ClNO_2$ $[M + H]^+$ 414.1255, found 414.1254.

Ethyl 2-(4-methoxyphenyl)-4-(4-nitrophenyl)-6-phenylpyridine-3-carboxylate (3ei): (67.4 mg, 74% yield); White solid, mp 67−68 °C, R_f = 0.30 (silica gel, hexane/EtOAc = 8/2), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.2 Hz, 3H), 3.87 (s, 3H), 4.01 (q, *J* = 7.2 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.4−7.5 (m, 3H), 7.63 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 8.12 (dd, *J* = 8.8, 1.6 Hz, 2H), 8.32 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (CH_3), 55.4 (CH_3), 61.7 (CH_2), 113.9 (CH), 118.1 (CH), 123.7 (CH), 125.9 (C), 127.2 (CH), 128.9 (CH), 129.3 (CH), 129.8 (CH), 130.0 (CH), 132.2 (C), 138.1(C), 145.2 (C), 147.3 (C), 148.0 (C), 156.6 (C), 157.5 (C), 160.5 (C), 168.4 (C); IR(ATR/cm^{-1}):1723, 1516, 1349, 1251; HRMS (ESI/TOF): *m/z calcd*. for $C_{27}H_{22}N_2O_5$ $[M + H]^+$ 455.1602, found 455.1607.

Ethyl 4-(4-fluorophenyl)-2-(4-methoxyphenyl)-6-(4-methylphenyl)pyridine-3-carboxylate (3et): (62.7 mg, 71% yield); Pale yellow oil, R_f = 0.40 (silica gel, hexane/EtOAc = 8/2), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.2 Hz, 3H), 2.40 (s, 3H), 3.85 (s, 3H), 4.00 (q, *J* = 7.2 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 7.14 (dd, *J* = 8.8, 8.8 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.4−7.5 (m, 2H), 7.60 (s, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 8.02 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (CH_3), 21.3 (CH_3), 55.3 (CH_3), 61.4 (CH_2), 113.8 (CH), 115.5 (CH, *J* = 21.6 Hz), 118.4 (CH), 126.2 (C), 127.1 (CH), 129.5 (CH), 130.0 (CH, *J* = 8.2 Hz), 130.0 (CH), 132.6 (C), 134.8 (C, *J* = 3.5 Hz), 135.7 (C), 139.7 (C), 148.4 (C), 156.1 (C), 157.1 (C), 160.3 (C), 163.0 (C, *J* = 248 Hz), 168.9 (C); IR(ATR/cm^{-1}): 1723, 1506, 1252, HRMS (ESI/TOF): *m/z calcd*. for $C_{28}H_{24}FNO_3$ $[M + H]^+$ 442.1813; found 442.1810.

Ethyl 4-(4-chlorophenyl)-2-(4-methoxyphenyl)-5,6-diphenylpyridine-3-carboxylate (3es): (38.5 mg, 37% yield); White solid, mp 235−237 °C. R_f = 0.48 (silica gel, hexane/EtOAc = 8/2), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.2 Hz, 3H), 3.85 (s, 3H), 3.93 (q, *J* =7.2 Hz, 2H), 6.85 (dd, *J* = 1.6, 8.0 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 7.0−7.1 (m, 5H), 7.1−7.2 (m, 5H), 7.34 (dd, *J* = 1.6, 8.0 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 55.5 (CH_3), 61.6 (CH_2), 114.0 (CH), 127.0 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 130.2 (CH), 130.2 (CH), 130.9 (CH), 131.3 (CH), 132.3 (C), 133.0 (C), 133.8 (C), 135.7 (C), 137.2 (C), 140.3 (C), 147.4 (C), 154.2 (C), 158.3 (C), 160.5 (C), 168.6 (C) one quaternary carbon is lacked because of overlapping; IR(ATR/cm^{-1}): 1729, 1514, 1251; HRMS (ESI/TOF): *m/z calcd*. for $C_{33}H_{26}ClNO_3$ $[M + H]^+$ 520.1674, found 520.1661.

Ethyl 4-(4-chlorophenyl)-2-(4-methoxyphenyl)-5-(4-methylphenyl)-6-phenylpyridine-3-carboxylate (3eu): (44.8 mg, 42% yield); White solid, mp 229−230 °C. R_f = 0.43 (silica gel, hexane/EtOAc = 8/2), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.2 Hz, 3H), 2.21 (s, 3H), 3.85 (s, 3H), 3.91 (q, t = 7.2 Hz, 2H), 6.71 (d, *J* = 7.6 Hz, 2H), 6.83 (d, *J* = 7.6 Hz, 2H), 6.95 (d, *J* = 7.6 Hz, 2H), 7.02 (d, *J* = 7.6 Hz, 2H), 7.1−7.2 (m, 5H), 7.3−7.4 (m, 2H), 7.73 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (CH_3), 21.1 (CH_3), 55.3 (CH_3), 61.4 (CH_2),

113.8 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.5 (CH), 130.0 (CH), 130.1 (CH), 130.8 (CH), 130.9 (CH), 132.2 (C), 132.8 (C), 133.5 (C), 133.8 (C), 135.7 (C), 136.4 (C), 140.3 (C), 147.3 (C), 153.8 (C), 158.2 (C), 160.3 (C), 168.5 (C) one quaternary carbon is lacked because of overlapping; IR(ATR/cm^{-1}): 1730, 1533, 1250; HRMS (ESI/TOF): *m/z calcd*. for $C_{34}H_{28}ClNO_3$ $[M + H]^+$ 534.1831, found 534.1833.

Ethyl 6-(4-chlorophenyl)-2-(4-methoxyphenyl)-4-(4-nitrophenyl)-5-phenylpyridine-3-carboxylate (3ev): (56.5 mg, 50% yield); White solid, mp 211−212 °C, R_f = 0.40 (silica gel, hexane/EtOAc = 8/2), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3H), 3.86 (s, 3H), 3.90 (q, t = 7.2 Hz, 2H), 6.8−6.9 (m, 2H), 6.98 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.0−7.1 (m, 3H), 7.15 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.27 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.30 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.72 (dd, *J* = 6.8, 2.0 Hz, 2H), 8.04 (dd, *J* = 6.8, 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5 (CH_3), 55.3 (CH_3), 61.6 (CH_2), 113.9 (CH), 122.7 (CH), 127.1 (C), 127.4 (CH), 127.9 (CH), 128.2 (CH), 130.0 (CH), 130.4 (CH), 130.8 (CH), 131.4 (CH), 131.6 (C), 132.2 (C), 134.2 (C), 136.3 (C), 138.1 (C), 143.9 (C), 146.5 (C), 147.1 (C), 154.5 (C), 156.9 (C), 160.5(C), 168.0 (C); IR(ATR/cm^{-1}): 1728, 1516, 1348, HRMS (ESI/TOF): *m/z calcd*. for $C_{33}H_{25}ClN_2O_5$ $[M + H]^+$ 565.1525; found 565.1536.

Methyl 2-methyl-4-(4-methylphenyl)-5-oxo-indeno[1,2-*b*]pyridine-3-carboxylate (14):[42] (66.7 mg, 71% yield). Yellow solid, mp 179–181 °C, R_f = 0.28 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.63 (s, 3H), 3.57 (s, 3H), 7.24 (br s, 4H), 7.38 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 7.55 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 7.59 (br d, *J* = 7.6 Hz, 1H), 7.86 (br d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4 (CH_3), 23.5 (CH_3), 52.2 (CH_3), 121.1 (C), 122.1 (C), 123.8 (CH), 128.2 (CH), 128.7 (CH), 129.5 (C), 130.3 (C), 131.2 (CH), 134.4 (CH), 135.4 (C), 139.1 (C), 142.3 (C), 146.8 (C), 160.7 (C), 165.6 (C), 168.5 (C), 190.2 (C); IR (ATR/cm^{-1}): 2920, 1730, 1712, 1557, 1236.

Methyl 4,5-dihydro-2-methyl-4-(4-methylphenyl)-5-oxo-*1H*-Indeno[1,2-b]pyridine-3-carboxylate (15):[43] (45.7 mg, 14% yield). Red solid, mp 255–260 °C, R_f = 0.05 (silica gel,

hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.50 (s, 3H), 3.59 (s, 3H), 4.96 (s, 1H), 6.48 (br s, 1H), 7.01–7.04 (m, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.24–7.28 (m, 2H), 7.34–7.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9 (CH_3), 21.0 (CH_3), 36.7 (CH_3), 51.1 (CH), 107.9 (C), 111.1 (C), 116.6 (CH), 121.4 (CH), 127.6 (CH), 129.0 (CH), 130.0 (CH), 131.1 (CH), 133.9 (C), 135.8 (C), 136.1 (C), 142.7 (C), 143.3 (C), 152.5 (C), 167.8 (C), 192.0 (C); IR (ATR/cm^{-1}): 3269, 1697, 1634, 1504, 1173.

4-5. Synthesis of 4-azafluorenone 12

Azafluorenones **12** were synthesized according to the method in the literature.[44] An excess amount of polyphosphoric acid (PPA, 0.5mL) and nicotinate **3ad** (44.3 mg, 0.18 mmol) was heated 210 °C for 2 h under microwave irradiation. To the reaction mixture, saturated $NaHCO_3$ aqueous solutionwas added, and the reaction mixture was extracted with chloroform (10 mL × 3). The organic layer was washed with water, and was dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/EtOAc = 8/2) to afford 2-azafluorenone **12** (34.2 mg, 0.16 mmol, 91%) as a white solid.

1,3-Dimethyl-2-azafluorenone 12:[45] (34.2 mg, 91%). White solid, mp 155–157 °C, R_f = 0.13 (silica gel, hexane/EtOAc, 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (s, 3H), 2.79 (s, 3H), 7.20 (s, 1H), 7.43 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.54 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0 (CH_3), 25.7 (CH_3), 113.0 (CH), 121.5 (CH), 123.2 (C), 124.4 (CH), 131.3 (CH), 134.5 (C), 135.0 (CH), 141.5 (C), 153.1 (C), 157.4 (C), 164.9 (C), 193.6 (C); IR (ATR/cm^{-1}): 1703, 1593, 1186.

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Chapter 6. An NMR Study on a Pseudo-Intramolecular Transacylation of α-Aryl-β-keto Ester

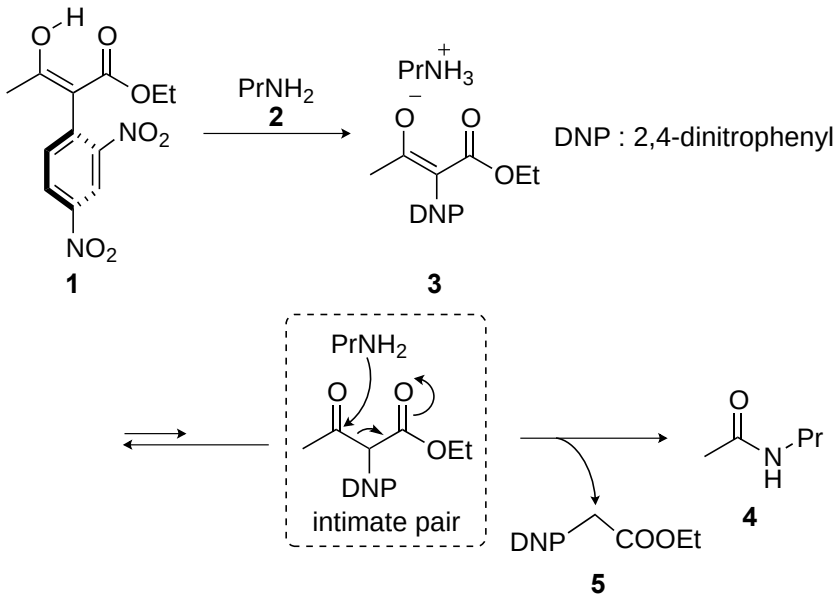
1. Introduction

The development of a highly efficient reaction which diminishes both resource waste and energy, is highly desirable from the viewpoint of green chemistry. In general, an intramolecular reaction proceeds more efficiently than an intermolecular reaction because of a higher collision frequency between reaction sites. In other words, an increase in the collision frequency of reactants results in the improvement of the reaction efficiency, even in an intermolecular process. Indeed, the use of reaction fields such as micelles and microcapsules, enables reactions to proceed easily by increasing the opportunity of reactants to encounter each other.[1] Such great success implies that efficient intermolecular reactions can be achieved if the collision frequency of the reactants can be increased, even in the absence of a reaction field.

Recently, we demonstrated a highly effective method called pseudo-intramolecular reactions.[2,3] The reactions proceed under mild conditions without any reaction fields, additives and troublesome manipulations. Using this method vicinally functionalized 1,4-dihydropyridines, 1,2-diazepines, and diazabicyclic compounds have been readily synthesized.[2]

The transacylation reaction is another example of the pseudo-intramolecular process (Scheme 1).[3a] The α-arylation of a β-keto ester increases the acidity of the hydrogen atom of the active methylene[4] because the aryl group stabilizes its enol form.[5] As a result, the ammonium salt **3** is easily formed upon treatment with the amine **2**. When a small amount of the amine is liberated under equilibrium, the nucleophilic amine and the electrophilic keto ester locate close to each other. This is referred to as an intimate pair. The spatial proximity of the reagents enables an efficient nucleophilic substitution reaction to proceed, transferring the acyl group from the keto ester **1** to the amine **2** under mild conditions. The steric congestion around the reaction site also prevents the approach of other molecules, which consequently depresses any side reactions.[3] Indeed, the efficient progress of the reaction could be easily monitored by 1H NMR spectroscopy. Just after the addition of an equimolar amount of the amine **2** to a solution of the α-aryl-β-keto ester **1** in $CDCl_3$, the formation of

the ammonium enolate **3** could be confirmed by the immediate disappearance of the signal assigned to the enol hydrogen atom. With the decrease in the signals for the salt, the signals for the transacylated products **4** and **5** increased, without any detectable formation of by-products, to achieve quantitative conversion.



Scheme 1. A mechanism for the pseudo-intramolecular transacylation reaction.

The above features of the pseudo-intramolecular process enable the chemoselective and regioselective acylation reaction to proceed without any modification of the substrate, such as the protection of another functionality. Furthermore, this reaction also enables us to facilely synthesize unsymmetrical malonic acid derivatives by using an α-arylated acetonedicarboxylate.[3] Hence, the present transacylation reaction is a promising method for synthesising polyfunctionalized compounds. However, for applying the method to more elaborate syntheses, it is necessary to obtain further insights into the concept of "the pseudo-intramolecular process". If the reaction proceeds in a pseudo-intramolecular process, the reaction order is considered to be close to first order because the reactants have already encountered each other in the intimate pair. From this viewpoint, we have studied the correlation between the reaction rate and the polarity of the reaction medium/the concentration of the substrates by monitoring the progress of the reaction using ^{1}H NMR spectroscopy. In addition, we have evaluated the reaction order on the basis of the results.

Solvation is one of the crucial factors affecting the reactivity of an intermolecular process, because two solvated substrates diminish the collision frequency.[6] As a result, the rate of an intermolecular process changes depending on the polarity of the reaction medium. On the other hand, for an intramolecular process reaction sites close to each other should be less influenced by the polarity of the solvent.[7] With the characteristics of intermolecular and intramolecular processes in mind, we hypothesized that the rate of the pseudo-intramolecular process should not be influenced by the polarity of the solvent even though it is actually an intermolecular process. In order to confirm this hypothesis, we monitored the transacylation reaction by ^{1}H NMR spectroscopy using six different deuterated solvents (acetonitrile-d_3, THF-d_8, benzene-d_6, chloroform-d, methanol-d_4, and acetone-d_6) (Fig. 1). The dielectric constants (ε_r) and dipole moments (μ) of these solvents are shown in Table 1.[8]

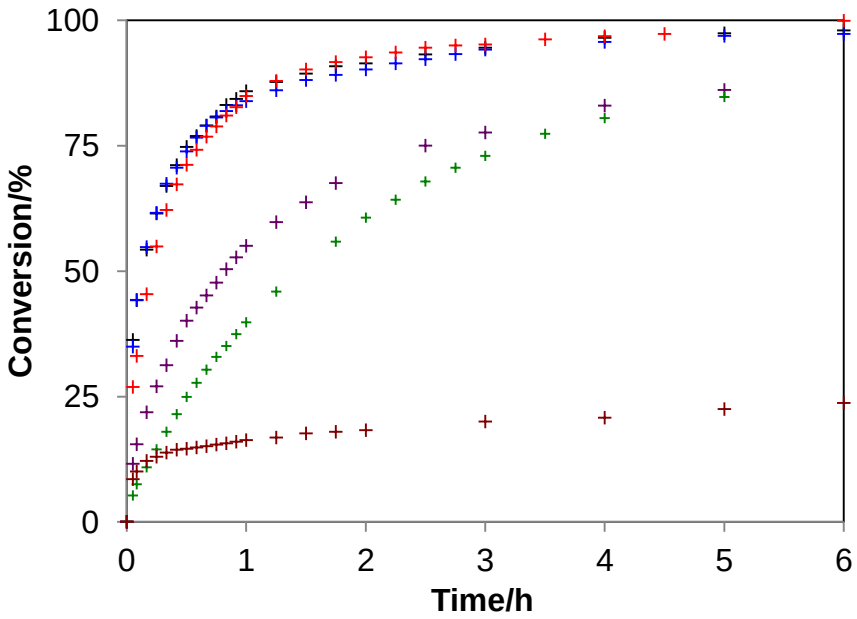


Figure 1. Time/conversion curves for 3 in different solvents. Acetonitrile (+), THF (+), benzene (+), chloroform (+), methanol (+), and acetone (+). The reaction conducted at 30 °C using a 0.06 M solution.

The progress of the transacylation reaction was monitored by ^{1}H NMR spectroscopy at intervals of several minutes (hours). Since no signals were observed other than those for the ammonium salt **3**, the transacylated product **4** and 2,4-dinitrophenylacetate **5**, the reaction rate can be discussed on the basis of the conversion of **3**. When acetone-d_6, methanol-d_4, and chloroform-*d* were used, the reactivities were different from each other. This is probably due to the interaction of the solvent with the amine **2**, which would arise from an electrophilic moiety[9,10] or a hydroxy group to form a hydrogen bond. Contrary to this, when benzene-d_6, THF-d_8, and acetonitrile-d_3 were used as the solvent, the transacylation reactions proceeded with the same reaction rate. It is noteworthy that the reaction rates in the latter three solvents were almost the same despite their extremely different polarities. This result strongly indicates that the transacylation reaction was not affected by the polarity of the solvent, as we hypothesized.

Next, the effect of the concentration of the reaction mixture was studied in a similar way by changing the concentration in the range from 0.24 to 0.015 M (Fig. 2 and Table 2). Although the reaction rate varied depending on the concentration, it became almost the same in highly diluted solutions. In the case of an intermolecular process, the reaction rate would become considerably slower with the dilution of the reaction mixture. Thus, the results support the fact that the reaction is a pseudo-intramolecular process.

In order to obtain further insight, the reaction orders n of the reactions carried out at different concentrations were calculated using eqn (1), where *k* is the rate constant, *A* is the concentration of the ammonium enolate **3**, and *t* is the reaction time.[11] The calculated value *n* of each reaction was between first and second order (Table 3). Since the quantitative formation of the ammonium salt **3** was confirmed just after the addition of the amine **2** to a solution of the keto ester **1**, the higher reaction order is caused by the intermolecular reaction between two intimate pairs, as shown in Fig. 3.

$$\frac{1}{n-1}\left(\frac{1}{[A]^{n-1}}-\frac{1}{[A]_0^{n-1}}\right)=kt \qquad (1)$$

These results imply that a first order reaction and a second order reaction proceed in the present system. Consequently, the pseudo-intramolecular process is concluded to be fundamentally a first order reaction.

Table 1. Rate constant k and relative rate constant k_{rel} with solvent parameters.

Solvent	ε_r	μ/D	k/mol^{-1}	k_{rel}
Acetonitrile	37.5	3.4	5.57×10^{-4}	1.0
THF	7.6	1.7	5.46×10^{-4}	0.99
Benzene	2.3	0	5.50×10^{-4}	1.0
Chloroform	4.8	1.2	1.77×10^{-4}	0.32
Methanol	32.6	1.7	1.18×10^{-4}	0.21
Acetone	20.7	2.7	5.60×10^{-6}	0.010

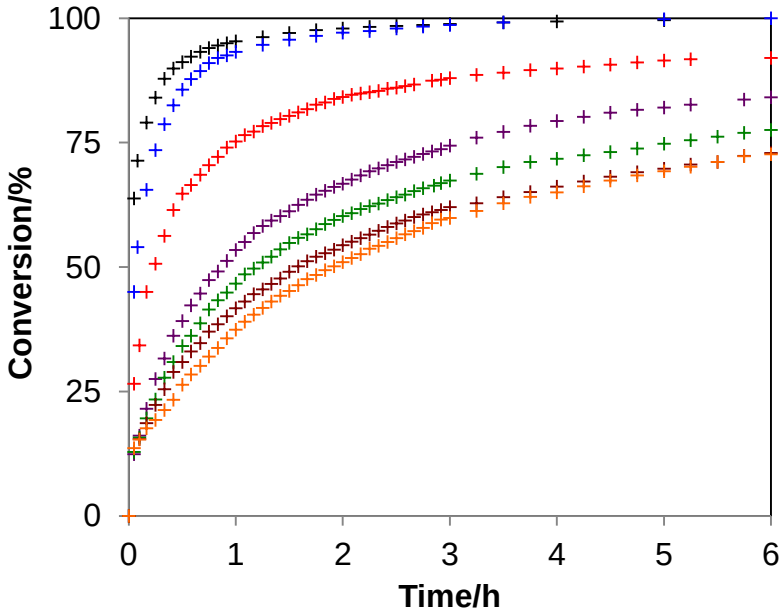


Figure 2. Time/conversion curves for 3 under various concentrations. 0.24 (+), 0.12 (+), 0.06 (+), 0.03 (+), 0.025 (+), 0.02 (+), and 0.015 (+) M. The reaction conducted at 30 °C using benzene-d_6 as a solvent.

Table 2. % conversions of **3** monitored at hourly intervals at hourly intervals at 30 °C using benzene-d_6, at differing concentrations of **3**.

Concentration/M	Conversion/%			
	1 h	2 h	3 h	4 h
0.24	96	98	99	100
0.12	94	98	99	100
0.06	76	85	88	90
0.03	54	67	75	80
0.025	47	61	68	72
0.02	42	55	62	67
0.015	38	51	60	65

Table 3. Reaction orders measured for reaction in benzene-d_6.

Concentration/M	Reaction order
0.24	1.8
0.12	1.6
0.06	1.6
0.03	1.6
0.015	1.4

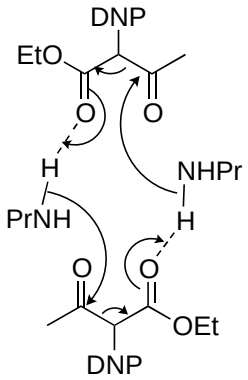


Figure 3. A plausible reaction between two intimate pairs.

3. Conclusion

In summary, the present transacylation reaction was monitored by ^{1}H NMR spectroscopy to give the following insights: (1) the reaction rate was not affected by the polarity of the solvent; (2) the reaction proceeded efficiently even in highly diluted solvents; and (3) the reaction order was lower than second order. These results reveal that the trans- acylation reaction proceeds like an intramolecular process rather than an intermolecular process. This information will be helpful for designing highly efficient and environmentally benign synthetic protocols for polyfunctionalized compounds.

4. Experimental section and characterization of compounds

4-1. General information

All the reagents and solvents were commercially available and used as received. The ^{1}H spectra were measured on a Bruker Ascend-400 at 400 MHz with TMS as an internal standard.

4-2. Synthesis of Ethyl 2-(2,4-dinitropheny)-3-hydroxy-2-butenoate (1)

To a solution of ethyl 3-oxobutanoate (1.30 g, 10 mmol) in THF (10 mL), sodium hydride (60 wt %, 0.80 g, 20 mmol) was gradually added, and the mixture was stirred at room temperature for 15 min. Then 1-chloro-2,4-dinitrobenzene (2.02 g, 10 mmol) was added, and the resultant reddish solution was stirred for 1 day. After addition of 3 M hydrochloric acid (10 mL), generated sodium chloride was filtered off, and the filtrate was concentrated. The extraction of the residue with hot hexane (30 mL × 3) followed by concentration afforded the keto ester **1** (2.70 g, 9.1 mmol, 91%). Further purification was performed with recrystallization from hexane.

Ethyl 2-(2,4-dinitropheny)-3-hydroxy-2-butenoate (1):[12] Yellow solid, mp 96–97 °C, R_f = 0.49 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.2 Hz, 3H), 1.92 (s, 3H), 4.05 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.23 (dq, *J* = 10.8, 7.2 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 8.84 (dd, *J* = 8.4, 2.4 Hz, 1H), 13.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 20.1 (CH_3), 61.6 (CH_2), 100.0 (C), 120.2 (CH), 126.8 (CH), 135.4 (CH), 136.8 (C), 147.3 (C), 149.9 (C), 170.1 (C), 174.4 (C); IR (ATR/cm^{-1}): 1640, 1530.

***N*-propylacetamide (4):**[3a] Brown oil, R_f = 0.70 (silica gel, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.2 Hz, 3H), 1.51 (tq, *J* = 7.2, 7.2 Hz, 2H), 1.96 (s, 3H), 3.19 (dt, *J* = 7.2, 7.2 Hz, 2H), 5.5–5.6 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (CH_3), 23.0 (CH_2), 23.4 (CH_3), 41.5 (CH_2), 170.2 (C); IR (ATR/cm^{-1}): 1633.

Ethyl (2,4-dinitrophenyl)acetate (5):[3a] Yellow oil, R_f = 0.32 (silica gel, hexane/EtOAc = 8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.2 Hz, 3H), 4.14 (s, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 8.44 (dd, *J* = 8.4, 2.4 Hz, 1H), 8.94 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3), 39.8 (CH_2), 62.0 (CH_2), 120.9 (CH), 127.5 (CH), 134.7 (CH), 136.6 (C), 147.6 (C), 149.2 (C), 168.7 (C); IR (ATR/cm^{-1}): 1732, 1531.

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[10] When equimolar amount of acetone was added to a solution of the propylamine **2** in benzene-d_6, small signals were observed in the lower field, which were assigned to the propylammonium group derived from the addition of **2** to the carbonyl group (see ESI). In acetone solution, larger amount of the adduct should be formed.

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Conclusion

In conclusion, I have demonstrated that β-keto amide has high reactivity comparable to that of other 1,3-dicarbonyl compounds. I disclosed that both carbonyl groups of β-keto amide reacted readily with various amines to afford either β-amino-α,β-unsaturatedamides or *N*-substituted β-keto amides. In addition, β-keto amides and their derivatives were found to serve as a building block for polyfunctionalized aza-heterocyclic compounds such as pyridone, pyrrolinones and nicotinates. The each product is expected to serve as a key synthetic intermediates for versatile frameworks using the polyfunctinalities to construct a compound library. These reactions require only simple experimental manipulations and proceeded without any special reagents and conditions, which facilitates the molecular design besides highly efficient and environmentally benign synthesis of polyfunctionalized compounds. Hence, these results obtained here will afford new synthetic tools for researchers.

LIST OF PUBLICATION

Journals

1. Tailor-made Synthesis of Fully Alkylated/Arylated Nicotinates by $FeCl_3$-Mediated Condensation of Enamino Esters with Enones
   Sho Hirai, Yurie Horikawa, Haruyasu Asahara, Nagatoshi Nishiwaki
   Chemical Communications, **2017**, *53*, 2390–2393.
2. Acid Promoted Dimerization of β-Amino-α,β-unsaturated Amides Affording Bis(functionalized) Pyrrolinones
   Sho Hirai, Haruyasu Asahara, and Nagatoshi Nishiwaki
   Tetrahedron Letters, **2016***, 57*, 5896–5898.
3. Chemoselective Amination of β-Keto Amides
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   Current Organic Chemistry, **2016**, *20*, 2911-2916.
4. Revisiting Dimerization of Acetoacetamide Leading to 4,6-Dimethyl-2-Pyridone-5-Carboxamide
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5. An NMR Study on a Pseudo-Intramolecular Transacylation Reaction of an α-Aryl-β-Keto Ester
   Sho Hirai, Haruyasu Asahara, Shotaro Hirao, Jun Sawayama, Ryuichi Sugimoto, Kazuhiko Saigo, and Nagatoshi Nishiwaki
   RSC Advances, **2014**, *4*, 4889–4892.

Conference

1. Highly Efficient Transacylation via the Pseudo-Intramolecular Process
   Nagatoshi Nishiwaki, Sho Hirai, Shotaro Hirao, Jun Sawayama, and Kazuhiko Saigo
   World Congress on Oleo Science & 29th ISF Congress
   Sasebo, Japan (Oct. **2012**) Poster Presentation
2. Acetoacetamide : A Useful Building Block for Functionalized Aza-Heterocyclic Compounds
   Sho Hirai, Haruyasu Asahara, and Nagatoshi Nishiwaki
   International Conference on Organic Chemistry
   Sunzhou, China (Jun. **2015**) Oral Presentation

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