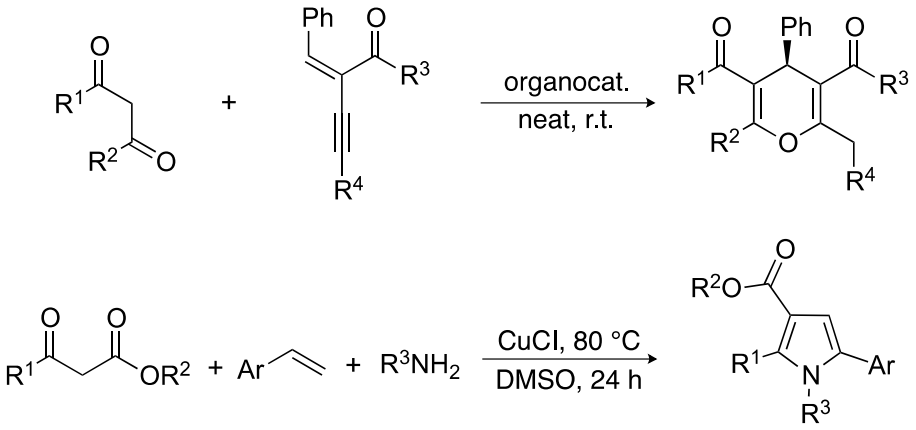
論 文 内 容 の 要 旨

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 multicomponent reactions to afford polyfunctionalized compounds. Indeed, a number of synthetic methods for heterocyclic compounds using 1,3-dicarbonyl compounds have been developed from old time, which affords pyridines, indoles, quinolones, pyrrole, oxazoles, dihydropyridine, pyrazoles, pyrimidinones and so on. While 1,3-dicarbonyl compounds have been energetically investigated for a long time, novel reactivity is often discovered even now. For example, Yue *et al.* used 1,3-dicarbonyl compounds in asymmetric formal [3+ 3] cycloaddition leading to 4*H*-pyrans under mild conditions. Liu *et al.* also synthesized functionalized pyrroles through cross-coupling-cyclization-oxdation by multicomponent reaction using 1,3-dicarbonyl compounds.



Scheme 1. Recent reported using 1,3-dicarbonyl compounds.

Although numerous reports dealing with 1,3-dicarbonyl compounds have been reported, majority of them describe 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. Indeed, nucleophilic substitution at the amide moiety of β-keto amides is also reported. 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.

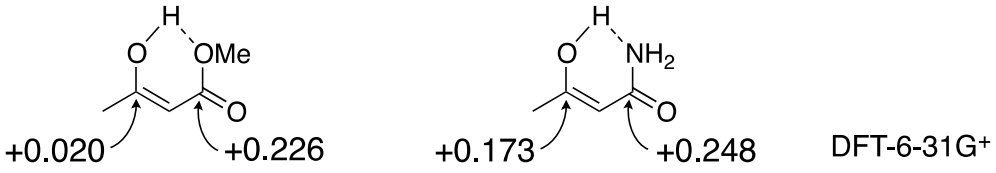


Figure 2. Estimated electrophilicities of carbonyl groups using DFT calculation.

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. The insights obtained here will afford valuable information and synthetic tools for many researchers studying synthetic chemistry.

2. Results and Discussions

2-1. Dimerization of acetoacetamide leading to 4,6-dimethyl-2-pyridone-5-carboxamide

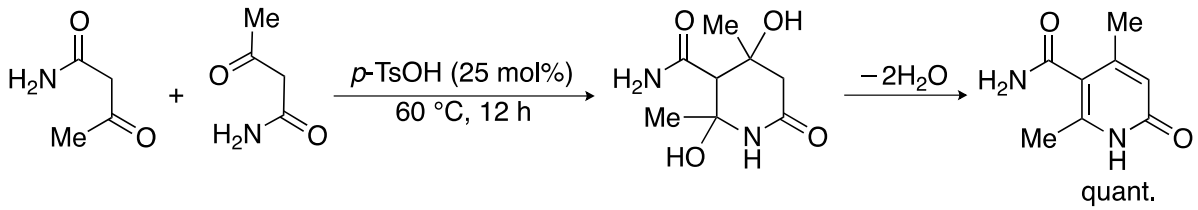
When I used commercially available acetoacetamide, I noticed that the structural change occurred in the bottle, which is stored for long time. This product was easily purified by washing with chloroform, and decided this compound to be a 4,6-dimethyl-2-pyridone-5-carboxamide. Surprisingly, dimerization of acetoacetamide proceeded in the bottle without any additive and

any special reaction conditions.

2-Pyridone-5-carboxamide scaffolds are widely used bioactive compounds and their synthetic intermediates. While multi-step reactions were necessary to construct pyridonecarboxamide framework, one-step synthesis of this structure was achieved by the dimerization of acetoacetamide derivatives. It is attractive because acetoacetamides are easily prepared upon treatment of diketene with amines. 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. To the contrary, the dimerization of the *N*-unsubstituted acetoacetamide has not been successfully achieved in a similar way. From this viewpoint, I tried to efficiently synthesize 2-pyridone-5-carboxyamide by dimerization of acetoacetamide under mild conditions.

I 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 was stood in air at room temperature for six months, intermediate were observed in the ^{1}H NMR spectrum of the resultant mixture. Finally, the signals of the pyridone appeared after standing for one year. 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. After investigated the optimized conditions, *p*-TsOH promoted the dimerization reaction, and pyridone was successfully obtained in quantitative yield by heating 60 °C for 12 h.

Finally, I investigated how the dimerization of acetoacetamide proceeds in the bottle. When the isolated pyridone was added to a reaction mixture, the rate of the dimerization became faster. Therefore, it was also found that the pyridone serves as a self-catalyst in this dimerization to proceed in the reaction efficiently.



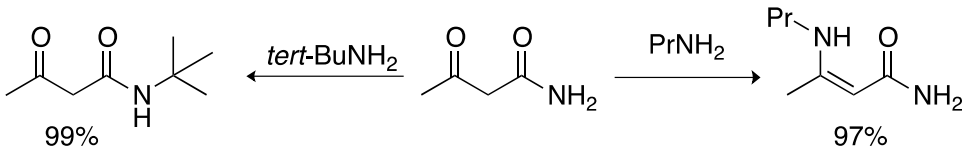
Scheme 2. Dimerization of acetoacetamide

2-2. Chemoselective amination of β-keto amides

Despite the promising high reactivity of β-keto amides, there has been no systematic study focusing on their reactivity towards nucleophiles to the best of our knowledge. Therefore, I studied the reactions of β-keto amides with various amines.

When acetoacetamide was heated with propylamine at 60 °C for 3 h, β-propylaminoacrylamide was obtained in 93%. Other amines such as isobutylamine, *sec*-butylamine and benzylamine also underwent similar amination to afford corresponding β-aminoacrylamides, respectively. This amination was not affected by *N*-substituent at β-position. On the other hand, bulky amine caused no reaction, and acetoacetamide was recovered quantitatively. When higher temperature was employed, different type reaction proceeded. Namely, the reaction occurs at the amide moiety instead of ketone moiety. Other bulky amines such as diisobutylamine and *tert*-butylamine also afforded *N*-modified acetoacetamide, respectively.

I have demonstrated that b-keto amide has high reactivity comparable to that of b-keto esters. Both carbonyl groups reacted readily with various amines to afford either β-aminobutenamide or *N*-substituted acetoacetamide. 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.



Scheme 3. Chemoselective Amination of β-keto amides

2-3. Synthesis of pyrrolinones

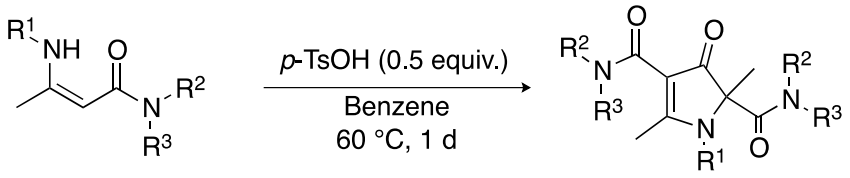
Pyrroline-4-ones are one of the attractive frameworks because these scaffolds are widely found in optical materials and biologically active compounds such as HIV-1 protease inhibitors,

antimalarials, and antimicrobials. Despite the highly valuable and versatile applications, only a few synthetic methods have been reported for pyrrolinones. 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.

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 and Cu(II)-catalyzed oxidative tandem cyclization. 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.

After investigation of optimized the reaction conditions, the addition of *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 in the best yield. When ≤ 0.5 equiv of *p*-TsOH was used, the starting material was recovered. In contrast, acetoacetamide, hydrolized product of enamide, was obtained when more than 0.5 equiv of *p*-TsOH in the reactions.

When enamide 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, indicating that the oxygen present in air serves as the oxidant to furnish pyrrolinone. Moreover, the reaction delivered pyrrolinone in a good yield even in the presence of an excess amount of a radical scavenger indicating that this reaction possibly proceeds with the ionic mechanism. Finally we achieved to subject the plausible mechanism in this dimerization of enamide.



Scheme 4: Synthesis of pyrrolinones.

2-4. Synthesis of nicotinates

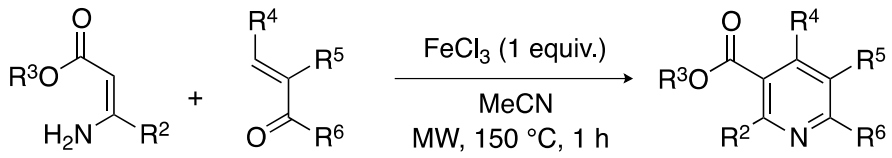
The nicotinate framework is one of the fundamental frameworks in natural products, medicines, and agrochemicals. Because of their useful biological activities, numerous synthetic methods for preparing versatile nicotinates have been developed. The most commonly used method is the Hantzsch reaction–the multi-component condensation of an aldehyde with two 1,3-dicarbonyl compounds and an ammonium salt–which affords symmetrical pyridine-3,5-dicarboxylates after subsequent oxidation. As an alternative approach, the Bohlmann-Rahtz method is employed for synthesizing trisubstituted nicotinates, involving conjugate addition of an enamino ester to an ynone followed by a thermal cyclodehydration. Although many approaches have shown impressive advances in the synthesis of nicotinates in the past decades, only a few synthetic methods for polysubstituted nicotinates were found in the literature; however, these methods suffers from some drawbacks. From these circumstances, the development of a facile synthetic method for polyalkylated or polyarylated nicotinates is still one of the challenging problems.

β-Aminated α,β-unsaturated esters (enamino esters)–one of the push-pull alkenes–was appointed as a new synthetic reagent for polyfunctionalized compounds, and conducted the hetero Diels-Alder reaction with α,β-unsaturated ketones (enones) as a general synthetic method for polyalkylated or polyarylated nicotinates.

The reaction of enamino esters and methyl vinyl ketone efficiently afforded the desired nicotinate upon heating the mixture at 120 °C. In this method, modification of the ester functionality was easily achieved. In addition, it was also found that various enones underwent the reaction efficiently to afford corresponding nicotinate in good yield. However, no reaction

proceeded in the case of the β-phenylated enone even when the reaction mixture was heated at 150 °C for 1 day. Therefore, reaction conditions were surveyed in order to perform the reaction between enamino ester and enone. As a result, it was found that adding a $FeCl_3$ was the effective to afford nicotinate in good yield. After the optimized investigation, when β-phenylenone was heated with excess amounts of enamino ester at 150 °C under microwave irradiation for 1 h, 4-phenylnicotinate was successfully obtained in excellent yield.

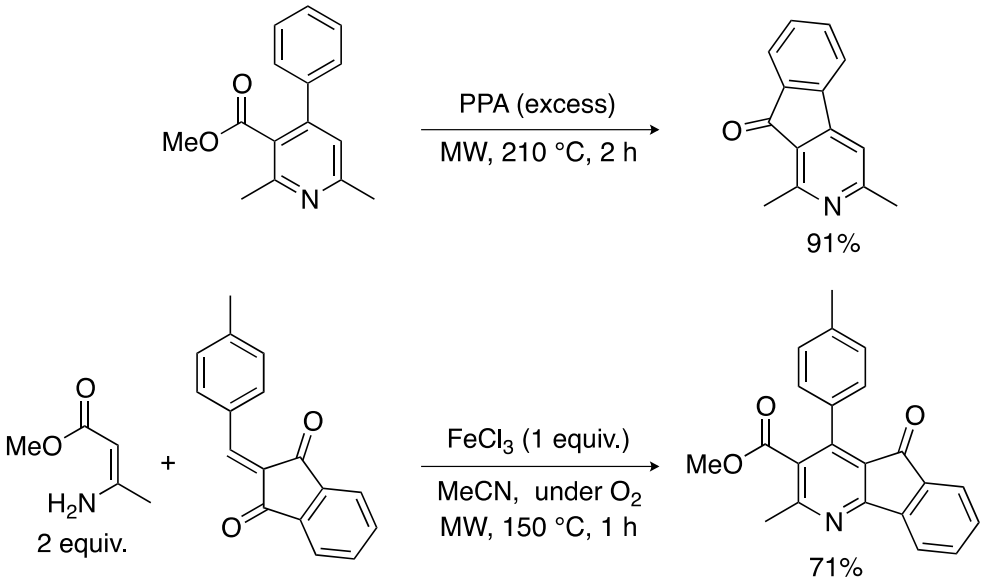
This reaction was applicable to other enones, and modifications at the 4- and 6-positions were easily achieved by simply changing enones to afford 4,6-dialkylated/arylated or diarylated nicotinates in high yields, respectively. The functionalized bipyridyl could be prepared using the pyridyl ketone. 2,4-Disubstituted nicotinates, and the 2,5,6-trisubstituted derivative were also available by this protocol. Furthermore, fully substituted nicotinates could be synthesized by treatment of enamino ester with trisubstituted enones.



Scheme 5. Synthesis of polysubstituted nicotinates.

The present method facilitates the efficient synth esis of versatile polysubstituted nicotinates, among which the 4-phenylated nicotinates are considered to serve as precursors of 2-azafluorenones. The azafluorenone framework is often found in natural products and its derivatives are highly useful as bioactive compounds and optical materials. However, the poor diversity of available azafluorenones prevents the development of novel functional materials. Our synthetic method has a great potential to synthesize various kinds of azafluorenones. In order to confirm this, 4-phenylnicotinate was treated with excess amounts of polyphosphoric acid (PPA) at 210 °C, which underwent intramolecular Friedel-Crafts acylation to afford 2-azafluorenone in 91% yield. Direct synthesis of 4-azafluorenone was also possible by the

reaction of enamno ester with 2-benzylidene-1,3-indandione, which afforded the corresponding 4-azafluorenone in 71% yield.



Scheme 6. Synthetic procedures for azafluorenones.

3. Conclusion

In conclusion, I have demonstrated that β-keto amide has high reactivity comparable to that of other 1,3-dicarbonyl compounds. I disclosed the reactivity that both carbonyl groups of β-keto amide reacted readily with various amines to afford either β-aminobutenamide or *N*-substituted acetoacetamide. In addition, β-keto amides and their derivatives were found to serve as a building brock for aza-heterocyclic compounds, which is useful for the construction of a new compound library. These reactions require only simple experimental manipulations and proceeded without any special reagents and conditions. Hence, these results obtained here will afford new synthetic tools for researchers, which facilitates the molecular design besides highly efficient and environmentally benign synthesis of polyfunctionalized compounds.