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# Novel 2-Pyridone Synthesis via Nucleophilic Addition of Malonic Esters to Alkynyl Imines

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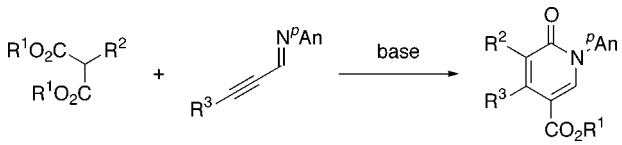
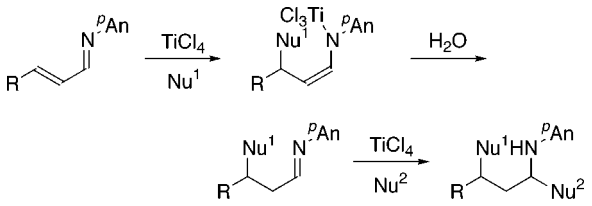
## ABSTRACT




**A novel 2-pyridone synthesis via nucleophilic addition of malonic esters to alkynyl imines has been developed. The reaction of dialkylalkyl sodiomalonates with alkynyl imines provided 2-pyridones in good to excellent yields.**

Nucleophilic addition to imines is one of the most important carbon−carbon bond formation reactions for the synthesis of nitrogen-containing compounds. For example, Lewis acid catalyzed imino aldol reactions of silyl enol ethers with aldimines are a useful method for the preparation of $\beta$-amino esters, which are readily converted into $\beta$-lactams and amino acids.[1] $\alpha,\beta$-Unsaturated aldimines are also employed as electrophiles in not only imino aldol reactions[2] but also Michael reactions.[3] We have already reported a double nucleophilic addition reaction to $\alpha,\beta$-unsaturated aldimines promoted by titanium tetrahalide or aluminum chloride.[4] In these reactions, ketene silyl acetals underwent 1,4- and subsequently 1,2-addition to $\alpha,\beta$-unsaturated aldimines to give doubly alkylated products in good yields (Scheme 1).

**Scheme 1**




During these investigations, we were interested in the addition to alkynyl imines and have now found a new approach to 2-pyridone possessing a 5-alkoxycarbonyl group via nucleophilic addition of malonic esters to alkynyl imines.

The initial examination was carried out using the addition of ketene silyl acetal as nucleophile to alkynyl imines[5] in order to obtain a doubly alkylated product possessing a double bond. However, the reaction of alkynyl imine **1a** with ketene silyl acetal **2** in the presence of $TiCl_4$ proceeded to give only 1,2-additon adduct **3** in a quantitative yield (Scheme 2, eq 1).

To facilitate the conjugate addition, dimethyl malonate anion, which is a stabilized carbon nucleophile and frequently employed in conjugate addition reactions, was used as a nucleophile.[6] The reaction of dimethyl sodiomalonate prepared from dimethyl malonate with sodium hydride in THF under reflux for 7 h gave 2-pyridone **4** in 54% yield (Scheme 2, eq 2). 2-Pyridone **4** is formed most probably via the mechanism shown in Scheme 3. Metalloallenamine **5** is generated via 1,4-addtion reaction of dimethyl sodiomalonate

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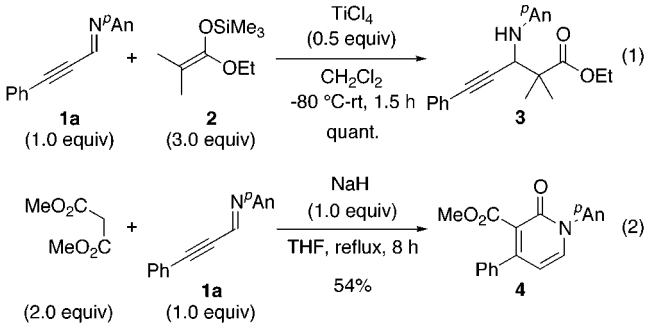
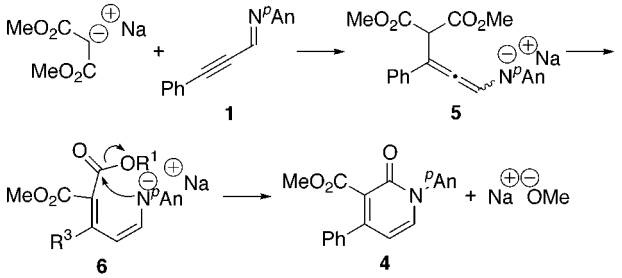
**Scheme 2**




**Scheme 3**



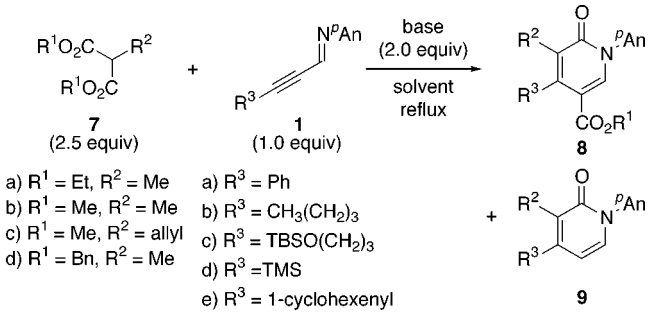

**5** to alkynyl imine **1a**. The metalloallenamine **5** in turn isomerizes into metalloenamine **6**, and the cyclization gives 2-pyridone **4**.

The reaction of diethylmethyl sodiomalonate possessing a single acidic proton was next examined to prevent isomerization of the double bond. We found that the reaction of diethylmethyl sodiomalonate (**7a**) with imine **1a** in THF under reflux for 7 h afforded 2-pyridone **8** ($R^1$ = Et, $R^2$ = Me, $R^3$ = Ph) having a 5-ethoxycarbonyl group in 55% yield along with the recovered **1a** in 13% yield (Scheme 4). In this paper, we describe the novel synthesis of 2-pyridone possessing a 5-alkoxycarbonyl group via nucleophilic addition of malonic esters to alkynyl imines.

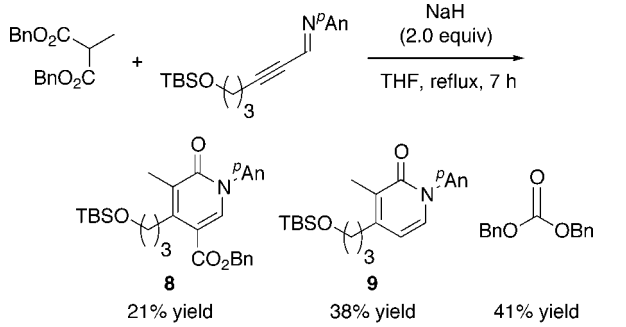
The amounts of a base and a malonic ester were investigated using the reaction of dimethylmethyl malonate (**7b**) with imine **1a**. When amounts of both **7b** and NaH were increased, the reaction gave 2-pyridone **8** ($R^1$ = Me, $R^2$ = Me, $R^3$ = Ph) in 58% yield accompanied by the decarboxylated 2-pyridone **9** ($R^1$ = Me, $R^2$ = Me, $R^3$ = Ph) in 15% yield (Table 1, entry 1). Several examples are shown in Table 1.[7] When sodium methoxide (NaOMe) was used as a base, 2-pyridone **8** ($R^1$ = Me, $R^2$ = Me, $R^3$ = Ph) and its decarboxylated derivative **9** ($R^2$ = Me, $R^3$ = Ph) were obtained in 47% and 42% yields, respectively (entry 2). When 1,4-dioxane as a reaction solvent was used instead of THF, the yield of **8** increased (entries 3, 5, and 10), and especially the reaction of **7b** with **1a** gave **8** as the sole product in 91% yield (entry 3). Even increasing the steric bulk of the nucleophile as with dimethyl allylmalonate (**7c**), 2-pyridones **8** were obtained in moderate yields (entries 6, 7, 12, and 16). However, the reaction of **7c** with **1a** using NaOMe in 1,4-dioxane gave 2-pyridone **8** ($R^1$ = Me, $R^2$ = (*E*)-CH=CHCH$_3$, $R^3$ = Ph) a double bond of which isomerized internally (entry 7). The reaction of alkynyl imine **1d** possessing a TMS group gave the desilylated 2-pyridone **9** ($R^2$ = Me, $R^3$ = H) in 82% yield.

The alkynyl imine **1e** having a double bond still gave good yields (entries 14−16). We next examined the reaction of **1c** with dibenzylmethyl malonate (**7d**) to clarify the reaction mechanism. The reaction in THF under reflux for 7 h gave 2-pyridone **8** ($R^1$ = Bn, $R^2$ = Me, $R^3$ =TBSO(CH$_2$)$_3$, 21%), its decarboxylated derivative **9** ($R^2$ = Me, $R^3$ = TBSO(CH$_2$)$_3$, 38%), and dibenzyl carbonate (41%) (Scheme 5).

**Scheme 4**




**Scheme 5**




From this result, we propose a plausible reaction mechanism as shown in Scheme 6. Metalloallenamine **10** would be generated via a 1,4-addtion reaction of dialkyl alkyl sodiomalonate **7** to alkynyl imine **1** and undergoes an intramolecular cyclization to give cyclobutenone **11** and sodium alkoxide. The cyclobutenone **11** would be transformed into the metalloenamine **12** via a ring-opening reaction by a nuecleophilic addition of sodium alkoxide, and the subsequent cyclization gives 2-pyridone **8** (path a).

(7) **Typical Experimental Procedure. Reaction of Alkynyl Imines with Malonic Esters.** To 60% NaH or sodium methoxide (0.400 mmol) was added a solution of malonic ester **7** (0.500 mmol) in THF or 1,4-dioxane (2.0 mL) and a solution of alkynyl imine **1** (0.200 mmol) in THF or 1,4-dioxane (2.0 mL) at room temperature. The reaction mixture was stirred under reflux for several hours (see Table 1) and then cooled to room temperature. Brine (10 mL) was added to quench the reaction. The mixture was extracted with dichloromethane (15 mL × 3). The combined organic layers were dried over sodium sulfate. The solvents were evaporated in vacuo, and then the residue was purified by preparative TLC on silica gel to give 2-pyridone **8** and 2-pyridone **9**, respectively.

**Table 1.** Nucleophilic Addition of Malonic Esters to Imines[a]

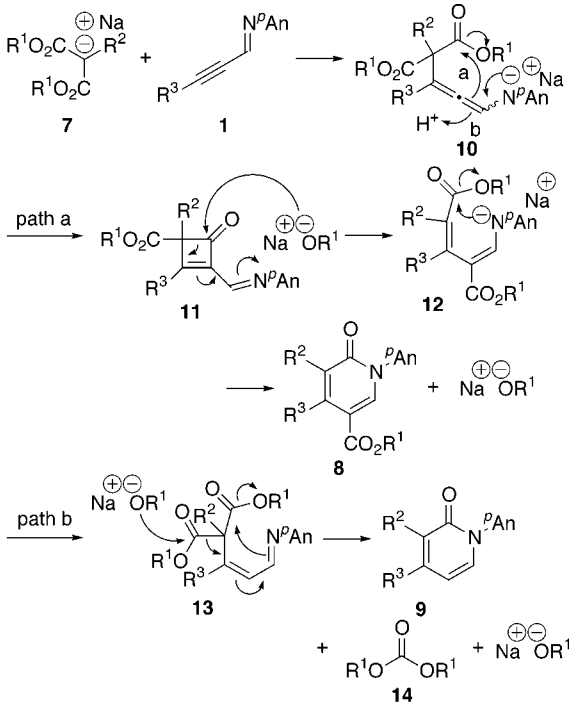
| entry | $R^1$ | $R^2$ | $R^3$ | base | solvent | time, h | yield,[b] % **8** | yield,[b] % **9** |
|---|---|---|---|---|---|---|---|---|
| 1 | Me | Me | Ph | NaH | THF | 7 | 58 | 15 |
| 2 | Me | Me | Ph | NaOMe | THF | 7 | 47 | 42 |
| 3 | Me | Me | Ph | NaOMe | 1,4-dioxane | 2 | 91 | |
| 4 | Et | Me | Ph | NaH | THF | 7 | 39 | 28 |
| 5 | Et | Me | Ph | NaOEt | 1,4-dioxane | 3 | 82 | |
| 6[c] | Me | allyl | Ph | NaH | THF | 23 | 59 | 19 |
| 7 | Me | allyl | Ph | NaOMe | 1,4-dioxane | 2 | 67[d] | 4 |
| 8 | Me | Me | $CH_3(CH_2)_3$ | NaH | 1,4-dioxane | 2 | 71 | 11 |
| 9 | Me | Me | $TBSO(CH_2)_3$ | NaH | THF | 3 | 26 | 39 |
| 10[c] | Me | Me | $TBSO(CH_2)_3$ | NaH | 1,4-dioxane | 2 | 57 | 1 |
| 11 | Et | Me | $TBSO(CH_2)_3$ | NaH | THF | 3 | 26 | 53 |
| 12[c] | Me | allyl | $TBSO(CH_2)_3$ | NaH | THF | 20 | 46 | 4 |
| 13 | Me | Me | TMS | NaH | THF | 0.5 | | 82[e] |
| 14 | Me | Me | 1-cyclohexeyl | NaH | 1,4-dioxane | 12 | 82 | |
| 15 | Me | Me | 1-cyclohexeyl | NaOMe | 1,4-dioxane | 4 | 72 | |
| 16 | Me | allyl | 1-cyclohexeyl | NaH | 1,4-dioxane | 8 | 63 | |

[a] For reaction conditions, see ref 7. [b] Isolated yields. [c] NaH (0.80 mmol, 4.0 equiv) and **7b** or **7c** (1.0 mmol, 5.0 equiv) were used. [d] 2-Pyridone **8** possessing a double bond that isomerized internally was obtained. [e] Desilylated 2-pyridone **9** was obtained.

The metalloallenamine **10** would undergo protonation to give α,β-unsaturated imine **13**. The decarboxylated 2-pyridone **9** and dialkyl carbonate **14** would be formed via a nucleophilic addition of sodium alkoxide to the ester group of **13** and the subsequent cyclization (path b).

In summary, we have found a novel method for 2-pyridone synthesis by 1,4-addition of malonic esters to alkynyl imines.

**Scheme 6**




The development of the synthetic methods of functionalized 2-pyridones is important as a result of the large number of biologically active compounds containing a 2-pyridone structure.[8] Numerous methods for the synthesis of 2-pyridones have been reported.[9,10] However, the present 2-pyridone synthesis is an attractive alternative method because alkynyl imines and substituted malonic esters are readily available from alkynals and malonic esters, respectively.[11] The synthetic application of 2-pyridones for the synthesis of bioactive compounds is now in progress.

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**Supporting Information Available:** Experimental procedures and product characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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