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SYNTHESIS OF BICYCLIC COMPOUNDS CONTAINING A 2-PYRIDONE STRUCTURE BY ADDITION REACTIONS OF MALONIC ESTERS TO ALKYNYLPYRIDINES, PYRIMIDINE, AND THIAZOLES

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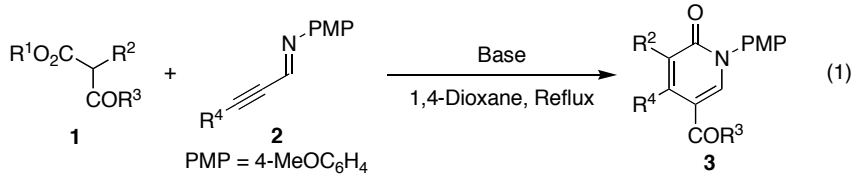
Abstract – *4H*-Quinolizin-4-ones, *6H*-pyrido[1,2-*a*]pyrimidin-6-ones, and *5H*-thiazolo[3,2-*a*]pyridin-5-ones were prepared by addition reactions of malonic esters to 2-alkynylpyridines, pyrimidine, and thiazoles.

Bicyclic compounds containing a 2-pyridone structure are key intermediates for the total synthesis of anagyrine,[1] lupinine,[1a] and ipalbidine.[2] There is also a biologically active compound having a 2-pyridone structure such as (-)-A58365A.[3-7] We have already reported 2-pyridone (**3**) synthesis *via* the nucleophilic addition of active methine compounds such as 2-substituted malonic esters or β-keto esters (**1**) to alkynyl imines (**2**) (Eq. (1)).[8,9]



On the basis of our 2-pyridone synthesis, we envisioned that the use of cyclic alkynyl imines (**5**) could produce bicyclic compounds (**6**) containing a 2-pyridone structure (Eq. (2)). First, we examined the use of 2-alkynylpyridine as a cyclic alkynyl imine equivalent.[10] The reaction of 2-phenylethynylpyridine (**8a**) with dimethyl methylmalonate (**7a**) (2.5 equiv.) using NaH (2.0 equiv.) as a base in 1,4-dioxane at reflux, which are standard reaction conditions for the synthesis of 2-pyridones (**3**) using malonic esters (**1**) with

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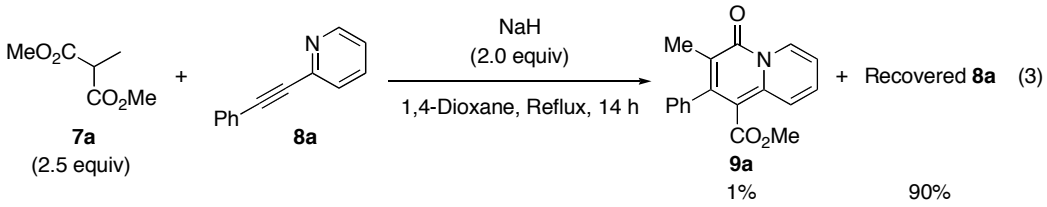
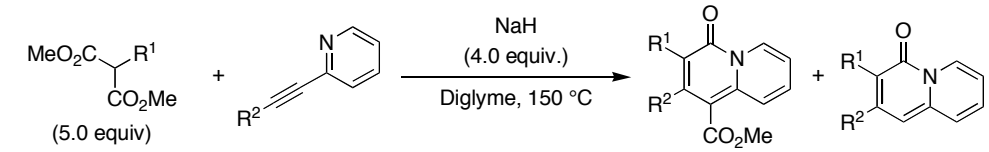
This paper is dedicated to Professor Barry M. Trost on the occasion of his 65th birthday.

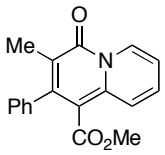
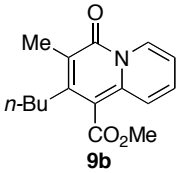
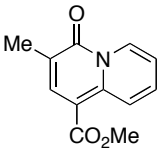
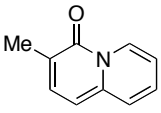
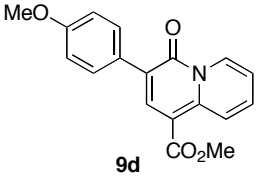
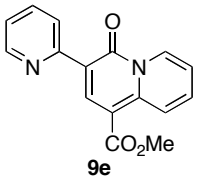
alkynyl imines (**2**),[8] was carried out. However, the desired *4H*-quinolizin-4-one (**9a**)[11] was obtained in only 1% yield along with the recovered **8a** in 90% yield (Eq. (3)).



To improve the yield, we investigated several reaction conditions such as solvents, bases, reaction temperatures, reaction times, and the amounts of malonic ester (**7a**) and bases. We found that the use of an excess of malonic ester (**7a**) (5.0 equiv.) with NaH (4.0 equiv.) in diglyme at 150 °C gave **9a** in 38% yield along with the recovered **8a** in 50% yield (Table1, Entry 1).

Table 1. Synthesis of *4H*-Quinolizin-4-ones

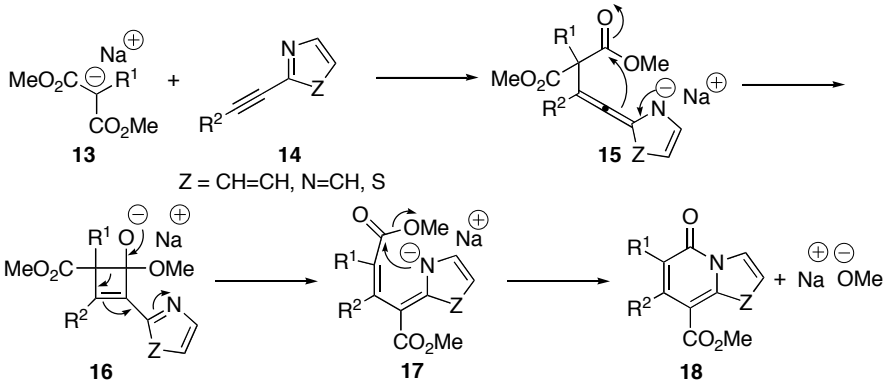


Entry	Malonic Ester, R^1	Alkyne, R^2	Time (h)	Product, yield (%)	
1	Me	Ph	22	 **9a**	38%
2	Me	^{n}Bu	23	 **9b**	36%
3	Me	H	20	 **9c**	10%
4[a]	Me	H	20		26%
5[a]	Me	Me_3Si	12		56%
3	Me	H	20	 **10**	76%
4[a]	Me	H	20		60%
5[a]	Me	Me_3Si	12		14%
6	4-$MeOC_6H_4$	H	8	 **9d**	77%
7	2-Pyridyl	H	8	 **9e**	43%

[a] The reactions were carried out using NaH (2.0 equiv.) and **7a** (2.0 equiv.) in 1,4-dioxane at reflux.

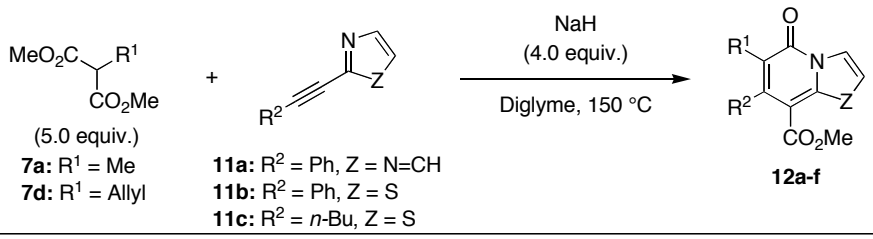
Several examples are shown in Table 1.[12] Not only aromatic but also aliphatic groups as a substituent in alkynylpyridines gave the corresponding *4H*-quinolizin-4-ones; *i. e.*, the adduct (**9b**) was obtained in 36% yield (Entry 2). The reaction of 2-ethynylpyridine (**8c**) in diglyme at 150 °C or 1,4-dioxane at reflux gave the decarboxylated *4H*-quinolizin-4-one (**10**) as a major product (Entries 3 and 4) probably due to the formation of dimethyl carbonate *via* the attack of sodium methoxide, which was generated as a byproduct in these reactions, to the methoxycarbonyl group of the desired *4H*-quinolizin-4-one (**9c**).[11n] On the other hand, when 2-trimethylsilylethynylpyridine (**8d**) was used in 1,4-dioxane at reflux, the desired *4H*-quinolizin-4-one (**9c**) possessing a methoxycarbonyl group was obtained as a major product in 56% yield probably because sodium methoxide preferentially reacted with the trimethylsilyl group of the initial product (Entry 5). The reaction of malonic esters having aromatic groups such as 4-methoxyphenyl and 2-pyridyl proceeded to give the *4H*-quinolizin-4-ones (**9d**) and (**9e**)[1b] in 77% and 43 % yields, respectively (Entries 6 and 7). We next examined the reaction of 2-alkynylpyrimidine (**11a**), 2-alkynylthiazoles (**11b**), and (**11c**) (Table 2). The reaction of 2-phenylethynylpyrimidine (**11a**) with dimethyl methylmalonate (**7a**) or dimethyl allylmalonate (**7d**) gave the desired *6H*-pyrido[1,2-*a*]pyrimidin-6-one[13] (**12a**) or (**12b**) in 48% and 30% yields, respectively (Entries 1 and 2). The reaction of 2-phenylethynylthiazole (**11b**) with dimethyl methylmalonate (**7a**) gave *5H*-thiazolo[3,2-*a*]pyridin-5-one (**12c**)[11a,11o,14] in 83% yield (Entry 3). Even increasing the steric bulk of the nucleophile as with dimethyl allylmalonate (**7d**), *5H*-thiazolo[3,2-*a*]pyridin-5-one (**12d**) was obtained in good yield (Entry 4). The reaction of 2-(1-hexynyl)thiazole (**11c**) also proceeded smoothly to give *5H*-thiazolo[3,2-*a*]pyridin-5-ones (**12e**) and (**12f**) in 75% and 53% yields, respectively (Entries 5 and 6).

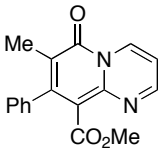
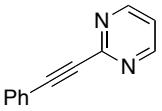
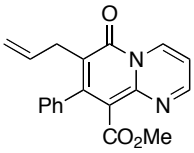
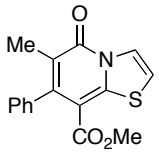
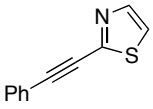
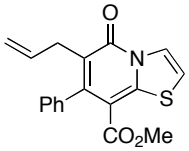
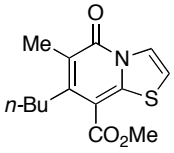
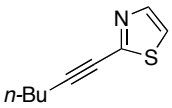
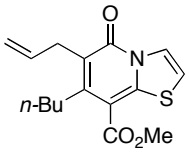
We proposed a plausible reaction mechanism as shown in Scheme 1. The metalloallenamine (**15**) would be generated *via* the addition reaction of malonic esters sodium salts (**13**) to alkynylpyridines, pyrimidine, or thiazoles (**14**) and would undergo an intramolecular cyclization to give the cyclobutenoxide intermediate (**16**). The intermediate (**16**) would be transformed into the metalloenamine (**17**) *via* a ring-opening, and the subsequent cyclization would give *4H*-quinolizin-4-ones, *6H*-pyrido[1,2-*a*]pyrimidin-6-ones, or *5H*-thiazolo[3,2-*a*]pyridin-5-ones (**18**).



Scheme 1. A Plausible Reaction Mechanism

Table 2. Synthesis of *6H*-Pyrido[1,2-*a*]pyrimidin-6-ones and *5H*-Thiazolo[3,2-*a*]pyridin-5-ones



Entry	Malonic Ester, R^1	Alkyne	Time (h)	Product, yield (%)
1	Me		22	 **12a** 48%
2	Allyl	 **11a**	22	 **12b** 30%
3	Me		22	 **12c** 83%
4	Allyl	 **11b**	20	 **12d** 61%
5	Me		8	 **12e** 75%
6	Allyl	 **11c**	18	 **12f** 53%

In summary, we have found a useful method for the synthesis of *4H*-quinolizin-4-ones, *6H*-pyrido[1,2-*a*]pyrimidin-6-ones, and *5H*-thiazolo[3,2-*a*]pyridin-5-ones by addition reactions of malonic esters to alkynylpyridines, pyrimidine, and thiazoles. The present method is an attractive alternative method among numerous precedents because alkynylarenes and substituted malonic esters can be easily prepared from haloarenes, malonic esters, or arylacetic acid esters. The synthetic application of the present method for the synthesis of bioactive compounds is currently underway.

ACKNOWLEDGMENTS

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12. **A typical experimental procedure of the reaction of malonic esters with alkynylarenes:** To 60% NaH (32.0 mg, 0.800 mmol) was added a solution of malonic ester (**7d**) (172.2 mg, 1.00 mmol) in diglyme (2.0 mL) and a solution of alkynylthiazole (**11b**) (37.0 mg, 0.200 mmol) in diglyme (2.0 mL) at room temperature. The reaction mixture was stirred at 150 °C for 20 h and then cooled to room temperature. Brine (10 mL) was added to quench the reaction. The mixture was extracted with dichloromethane (15 mL x 3) and 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 (*n*-Hex/EtOAc = 4/1, as an eluent) to give *5H*-thiazolo[3,2-*a*]pyridin-5-one (**12d**) (39.7 mg, 61%) as a white powder. mp: 128-130 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 4.3 Hz, 1H), 7.37-7.39 (m, 3H), 7.12-7.17 (m, 3H), 5.74-5.89 (m, 1H), 4.80-4.94 (m, 2H), 3.44 (s, 3H), 3.10 (d, *J* = 6.3 Hz, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 166.2, 158.7, 152.1, 150.3, 139.0, 135.4, 127.5, 127.4, 127.2, 124.4, 119.6, 115.5, 115.2, 102.8, 51.6, 32.1. IR (KBr): 3090, 3064, 3025, 2955, 1722, 1652, 1552, 1470, 1434, 1394, 1335, 1275, 1200, 1151, 1086, 1017, 919, 805, 765, 739, 702, 679 cm^{-1}. MS (ESI) m/z: 326 $(M+H)^+$.
13. For examples of the synthesis of *6H*-pyrido[1,2-*a*]pyrimidin-6-ones, see: (a) A. Copar, B. Stanovnik, and M. Tisler, *Bull. Soc. Chim. Belg.*, 1991, **100**, 533. (b) K. T. Potts and K. C. Hsia, *J. Org. Chem.*, 1973, **38**, 3485.
14. For examples of the synthesis of *5H*-thiazolo[3,2-*a*]pyridin-5-ones, see: (a) K. T. Potts and S. Kanemasa, *J. Org. Chem.*, 1979, **44**, 3808. (b) R. A. Coburn and R. A. Glennon, *J. Heterocycl. Chem.*, 1973, **10**, 487.