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Communication

Nitrogen Heterocycles

Cascade S_N2'–S_NAr, Elimination, and 1,5-Hydride Shift Reactions by Acetylacetone/Acetoacetic Esters: Synthesis of 9,10-Dihydroacridines

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Abstract: A reaction involving the use of acetylacetone/methyl acetoacetate and Morita–Baylis–Hillman acetates for the efficient, one-pot, metal-free synthesis of 9,10-dihydroacridines at room temperature was developed. The cascade of reactions involved sequential S_N2'–S_NAr reactions, elimination, and reduction through ketene generation and hydride transfer. Evidence for hydride shift via a ketene intermediate was also discussed.

Introduction

The importance of active methylene compounds with two electron-withdrawing groups (EWGs) on the carbon atom is well known. They are highly versatile reagents in synthetic organic chemistry because of their easy conversion into the corresponding enolates.[1] They have been employed in a variety of reactions such as condensation, alkylation, cyclization halogenation, acylation, and Michael addition.[2] Recently, their cascade reaction with Morita–Baylis–Hillman (MBH)[3–5] acetates through successive S_N2'–S_NAr and eliminative aromatization was reported for the synthesis of naphthalene and quinoline derivatives (Figure 1).[6] We also reported the synthesis of acridine[6b] by using malononitrile.

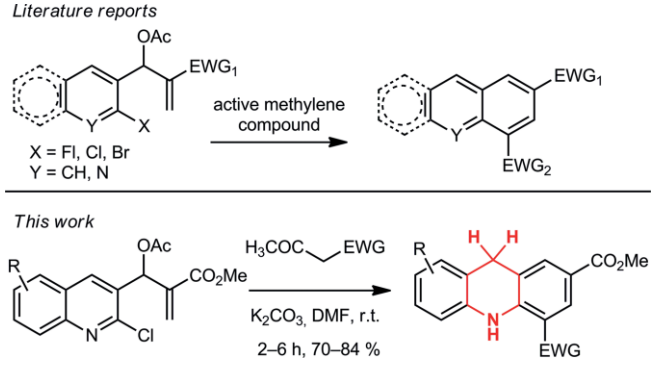
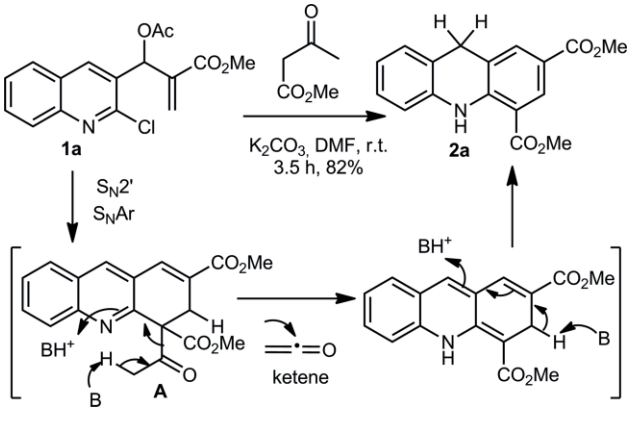


Figure 1. Literature reports and present work.

These reactions involve a variety of active methylene compounds such as ethyl cyanoacetate, dimethyl malonate, malononitrile, and nitroalkanes. However, the use of active methylene compounds containing an acetyl group remains elusive.[6a,6d] It can be speculated that cascade reactions of these reagents with MBH acetates should also lead to fused aromatic derivatives. Our expedition[7] for the application of acetyl acetone with MBH acetate lead to the discovery of a method for the metal-free synthesis of 9,10-dihydroacridines[8] from 2-chloroquinolinyl-3-carbaldehyde[7d] derived MBH acetates.[9] The sequence involves a cascade of reactions involving S_N2'–S_NAr reactions, elimination, and 1,5-hydride shift.

Results and Discussion

We began our studies with MBH acetate **1a** by using our previously reported conditions (Scheme 1).[6b] Initially, reaction of **1a** (0.5 mmol) with methyl acetoacetate (1.5 equiv.) was performed by using K_2CO_3 (1.5 equiv.) in DMF (2 mL) at room temperature (Scheme 1). The reaction was complete in 3.5 h, and product **2a** was isolated in 82 % yield.



Scheme 1. Initial reaction and plausible mechanism.

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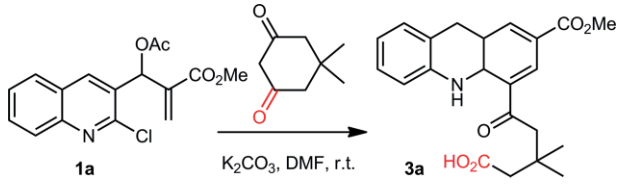
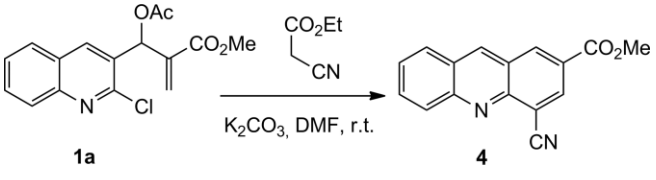
However, from the single-crystal X-ray data of **2k** (see below), **2a** was characterized as 2,4-bis(methoxycarbonyl)-9,10-dihydroacridine, which is an important synthetic template.[10] The result was quite interesting, as it involved annulation along with metal-free hydrogenation of the central ring. The formation of this unusual product can be explained by S_N2' and S_NAr reactions of acetate and chloride, respectively, which would result in annulated precursor **A**. Subsequently, **A** undergoes base-mediated double 1,5-hydride shift along with expulsion of ketene to give required product **2a** (Scheme 1). Ketene formation is the key to obtaining reduced product **2a**. To confirm the existence of the ketene, we next turned our attention to isolate a ketene-derived product. Towards this end, dimedone, a cyclic 1,3-diketone, was selected as an active methylene compound so as to retain the ketene in the molecular framework (Scheme 2). Thus, treating **1a** with dimedone under identical conditions led to the formation of **3a** in 71 % yield (Scheme 3). The formation of the alkyl chain with a carboxylic end group can be attributed to hydrolysis of the ketene generated during the reaction.



Scheme 2. Isolation of the ketene-hydrolyzed acid.



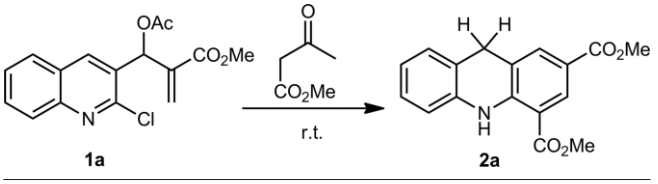
Scheme 3. Use of cyanoethyl acetate as an active methylene reagent.

The reaction conditions were then explored with other bases such as Cs_2CO_3, Na_2CO_3, KOH, and *t*BuOK (Table 1, entries 2–5) and different solvents such as DMSO, CH_3CN, and THF (Table 1, entries 6–8). However, the best yield was obtained by using potassium carbonate (1.5 equiv.) in DMF (Table 1, entry 1).

Next, the scope of the cascade transformation was explored on different precursors (Table 2). Initially, the reaction was explored with methyl acetoacetate. The reactions proceeded smoothly and afforded corresponding dihydroacridines **2a**–**j** in yields ranging from 70 to 82 %.

Different acrylates (e.g., Me, Et, *t*Bu) in the molecular framework were applicable to this reaction (see products **2a**–**c**), although lengthening or branching of the alkyl chain led to a slight reduction in the yield (see products **2b** and **2c**). The reaction was also applicable to ethyl acetoacetate, which gave product **2d**. Variation of the backbone of the quinoline did not lead to any major variation in the yield, although the reaction went to completion more quickly with substrates having electron-donating groups (see products **2e**–**h**) than with substrates having electron-withdrawing groups (see products **2i** and **2j**). Next, the reaction was investigated by using acetyl acetone as the active methylene reagent, and it delivered products **2k**–**r**. A similar trend was observed with electron-donating groups (see products **2n**–**p**) and electron-withdrawing groups (see products **2q** and **2r**). The applicability of the reaction was further extended by using dimedone and 1,3-cyclohexanedione, which afforded **3a** and **3b**, respectively. We were also able to obtain the crystal structure of **2k**, which further confirmed the structure (Figure 2).[11]

Table 1. Screening of reaction conditions.[a]



Entry	Base	Solvent	Time [h]	Yield[b] [%]
1	K_2CO_3	DMF	3.5	82
2	Cs_2CO_3	DMF	3.5	76
3	Na_2CO_3	DMF	5	60
4	KOH	DMF	2	72
5	*t*BuOK	DMF	2.5	64
6	K_2CO_3	DMSO	3.5	78
7	K_2CO_3	MeCN	4	60
8	K_2CO_3	THF	4.5	57

[a] All reactions were performed with **1a** (0.5 mmol) by using the active methylene compound (1.5 equiv.) and base (1.5 equiv.) in the appropriate solvent (2 mL). [b] Yield of isolated product.

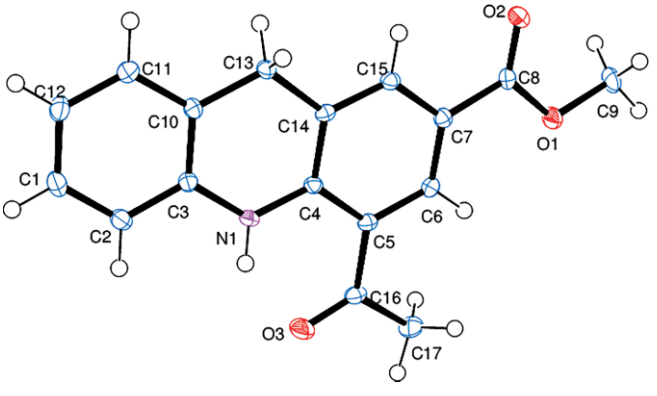
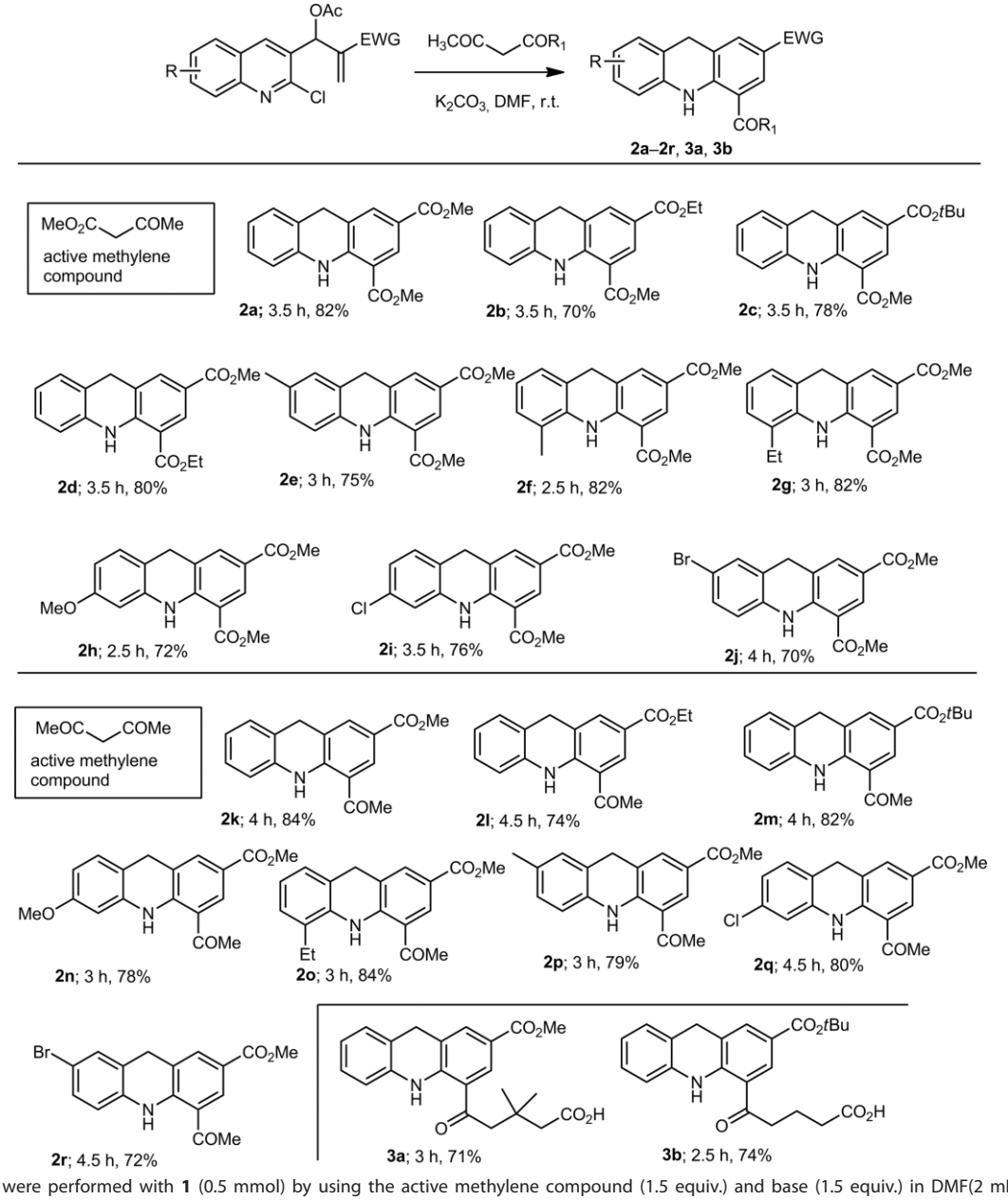


Figure 2. ORTEP diagram of **2k**.

The use of cyanoethyl acetate as the active methylene reagent lacking the acetyl functional group was also investigated (Scheme 3). Treatment of **1a** under the optimized conditions led to the formation of acridine **4**.[6b] This further supported the crucial role of the acetyl functionality as the hydrogen source for the formation of the dihydro derivative.

Table 2. Substrate scope.[a]



[a] All reactions were performed with **1** (0.5 mmol) by using the active methylene compound (1.5 equiv.) and base (1.5 equiv.) in DMF(2 mL). The reaction times and yields of the isolated products are given.

Conclusion

In conclusion, we developed one-pot, mild reaction conditions for the synthesis of 9,10-dihydroacridines from MBH acetates by using active methylene compounds having an acetyl group. The reaction proceeded through successive S_N2'–S_NAr, elimination, and 1,5-hydride shift. The protocol avoids the use of metal hydride and is safe and convenient.

Experimental Section

General Procedure: Methyl acetoacetate (0.08 mL, 0.75 mmol) and potassium carbonate (0.103 g, 0.75 mmol) were added to a solution of MBH acetate **1a** (0.16 g, 0.5 mmol) in DMF (2.0 mL), and the mixture was was stirred at room temperature for 3.5 h. Upon completion of the reaction, ethyl acetate was added to the mixture. The organic phase was then washed with water (3×), dried, and concentrated. The residue was purified by column chromatography (hexane/ethyl acetate, 98:2) to obtain **2a** (0.121 g, 82 %) as a yellow solid.

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Keywords: Domino reactions · Hydride shift · Elimination · Fused-ring systems · Nitrogen heterocycles

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[11] CCDC 1489369 (for **2k**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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