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Active methylene compounds (AMCs) controlled facile synthesis of acridine and phenanthridine from morita Baylis–Hillman acetate†

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We carried out simple and facile syntheses of acridines and phenanthridines from MBH acetates of 2-chloro-quinoline-3-carbaldehydes with active methylene compounds (AMCs). Formation of products was found to be dependent on the functional group of the AMC. For example, ethylcyanoacetate and malononitrile favoured the formation of acridines and cyanoacetamide, and ethyl nitroacetate and malonic esters favoured formation of angularly-fused phenanthridines. The reactions leading to the formation of phenanthridines proceeded through single bond rotation of S_N2' intermediate which was attributed to electronic/steric repulsion between the functional groups of AMCs and the nitrogen of quinoline.

Introduction

Acridines and phenanthridines constitute an important class of linearly and angularly benzo-fused quinolines.¹ Derivatives of these quinolines have garnered great interest from synthetic chemists due to their significant biological activities,² such as their anti-tumor, antimalarial, antituberculosis, antibacterial, antiprotozoal, antileukemic, anticancer, and anti-HIV activities, and due to their ability to intercalate between base pairs of double-stranded DNA and hence alter the cellular machinery.³ Some derivatives are used as pigments and dyes in industry⁴ and are also used as biological fluorescent probes to monitor polymerization processes.⁵ In addition, conjugated derivatives showing electronic and photophysical properties are used as organic semiconductor materials.⁶

Owing to the great medicinal and industrial importance of acridine derivatives, several methods for synthesizing them have been reported in the past few decades, with these methods including dehydrogenation,⁷ metal-catalyzed coupling,⁸ C–H functionalization,⁹ and inter-¹⁰ and intramolecular¹¹ cyclization. Similarly, radical reactions,¹² metal-catalyzed coupling reactions,¹³ cycloaddition reactions¹⁴ and other synthetic methods,¹⁵ mostly involving *ortho*-functionalized biaryl derivatives as substrates, have been reported for the synthesis of phenanthridine derivatives. However, these reactions constructed the aza ring of the acridine and phenanthridine moieties. Substrates, in particular quinoline derivatives, affording either acridines or phenanthridines *via* benzannulation have, in contrast, been less explored.¹⁶ However, these methods have

certain limitations such as requiring a high temperature, a strongly basic or acidic medium, expensive reagents, starting materials that are difficult to obtain, and moderate yields. Therefore, developing simple routes from easily accessible precursors, under relatively mild reaction conditions, is highly desirable for the synthesis of acridines and phenanthridines.

In recent years, Morita Baylis Hillman (MBH) reaction, a three-component, atom-economical, carbon–carbon bond-forming reactions of aldehydes, activated alkenes and catalysts led to the formation of MBH adduct which is an attractive precursors for various organic synthetic transformations¹⁷ with various functionalities.

Recently, we prepared MBH acetates of 2-chloro-quinoline-3-carbaldehydes,¹⁸ which afforded the synthesis of benzo[*b*][1,8] naphthyridines.¹⁸ⁱ We have also reported a new route for the synthesis of dihydroacridines^{18d} (instead of the synthesis of acridine) by reacting these MBH acetates with acetylacetone/ acetoacetic esters (Fig. 1, eqn (1)).

These unusual results have inspired us to systematically investigate using other active methylene compounds (AMCs)

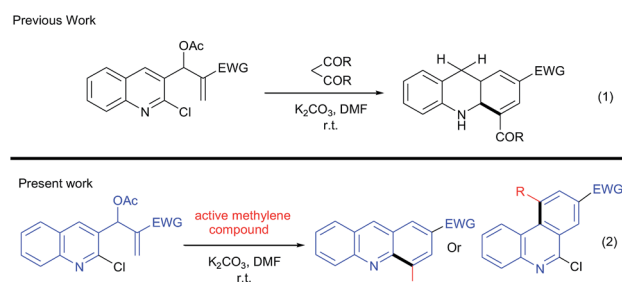


Fig. 1 Previous work and present work.

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such as ethylcyanoacetate, malononitrile, cyanoacetamide, ethylnitroacetate, dimethyl/diethylmalonate. We herein report the reaction of AMCs with MBH acetates of 2-chloro-quinoline-3-carbaldehydes, which provided facile routes to acridines and phenanthridines, respectively.

Results and discussion

Initially we focused our studies on the reaction of the ethylcyanoacetate reagent (1.5 equiv.) with MBH acetate **1a** (0.5 mmol) and K_2CO_3 (1.5 equiv.) under our previously reported conditions^{18d} in DMF at room temperature. The reaction was completed in 30 min and afforded the single product **2a** in 78% yield. The structure of **2a** was determined to be 4-cyanoacridine-2-carboxylic acid methyl ester on the basis of its spectral and analytical data. This result suggested the decarboxylation of the ester followed by dehydrogenation to be faster than the elimination of the cyano group and decarboxylation could be attributed due to the formation of carboxylate anion (**I**) (Scheme 1).

The scope of ethylcyanoacetate was further investigated with other MBH acetates. All reactions proceeded smoothly to afford acridines **2a–i** in good to excellent yields. The results are listed in Table 1. Lengthening or branching of ester alkyl in the MBH acetate lowered the yields (**2b** & **2c**). Replacing the ester with a cyano group in the MBH acetate resulted in product **2d**, but with a decreased yield of 68%. Similar reactions were further investigated with MBH acetates of substituted quinolines. The results are given in Table 1 (**2e–j**). MBH acetates with electron-donating groups (EDGs) were more reactive than those with electron-withdrawing groups (EWGs), and hence afforded the product in higher yields (**2e–j**).

The malononitrile reagent was also examined with **1a** under similar conditions and afforded the same product **2a**, in 5 min with 92% yield, as described above. Next, we reacted the cyanoacetamide reagent with **1a** for the purpose of synthesizing an acridine derivative. When **1a** was treated with cyanoacetamide (1.5 equiv.) and K_2CO_3 (1.5 equiv.) under similar conditions as described above, the reaction took a longer time (2.5 h) to complete, and the isolated product **3a** was obtained, instead of acridine **2a**, in 62% yield. The structure of **3a** was determined to be 6-chloro-10-cyano-phenanthridine-8-carboxylic acid methyl ester from its spectral and analytical data. The formation of **3a** suggested that S_N2' product (**II**) underwent rotation about the single bond connecting two sp^2 carbons to form conformation (**III**) followed by cyclization, deamidation and dehydrogenation to form product **3a** (Scheme 2). The loss of the amide group may have been due to isocyanic acid ($H-N=C=O$)^{18d} (Scheme 2).

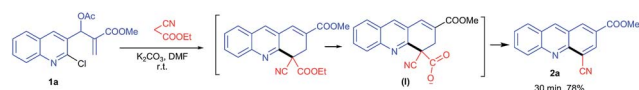
The dependence of the synthesis of planar/angular tricyclic benzo-fused quinolines such as dihydroacridines, acridines and

Table 1 Substrate scope^a

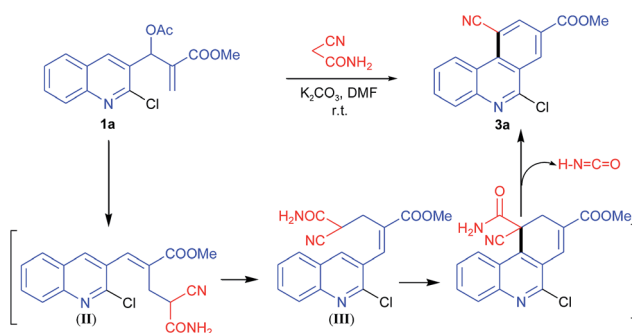
Using EtOOC-CH2-CN	 2a (30 min, 78%)	 2b (60 min, 72%)
	 2c (90 min, 72%)	 2d (30 min, 68%)
	 2e (45 min, 75%)	 2f (30 min, 80%)
	 2g (30 min, 82%)	 2h (50 min, 74%)
	 2i (30 min, 75%)	 2j (30 min, 82%)
	 2k (90 min, 70%)	 2l (120 min, 64%)

^a All reactions were performed with **1** (0.5 mmol) by using ethylcyanoacetate (1.5 equiv.) and K_2CO_3 (1.5 equiv.) in DMF (2 mL). The reaction time and yields of isolated products are given.

phenanthridines on the functional group of the AMC inspired us to test the reactions of additional AMCs with MBH acetate. We tested the reaction with ethylnitroacetate and found that MBH acetate provided phenanthridine template as did cyanoacetamide. When MBH acetate **1a** was treated with ethylnitroacetate (1.5 equiv.) and K_2CO_3 under reaction conditions similar to those described above, the reaction completed in 5 h and a single product was isolated in 59% yield and characterized as angularly fused phenanthridine derivative **3g**. The

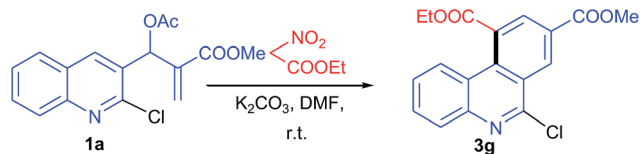


Scheme 1 Use of ethylcyanoacetate.



Scheme 2 Use of cyanoacetamide.



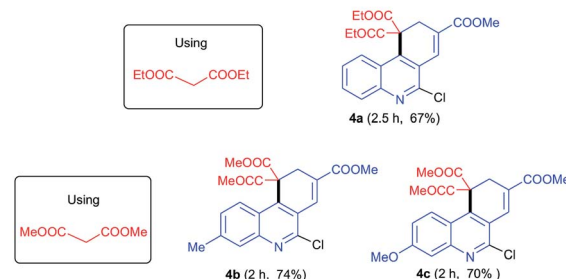
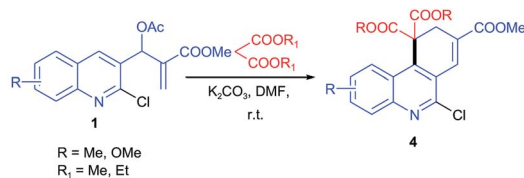


Scheme 3 Use of ethylnitroacetate.

corresponding linearly fused cyclized acridine was not isolated from the reaction mixture (Scheme 3). However, the aromatization step proceeded *via* elimination of the nitro group. Rotation about the carbon–carbon single bond of the S_N2' product (**II**) in nitrogen-containing functional groups of AMCs could be presumed to be due to electronic repulsion between the nitrogen functional group and the nitrogen of the quinoline, and to be a source of instability of S_N2' product (**II**).

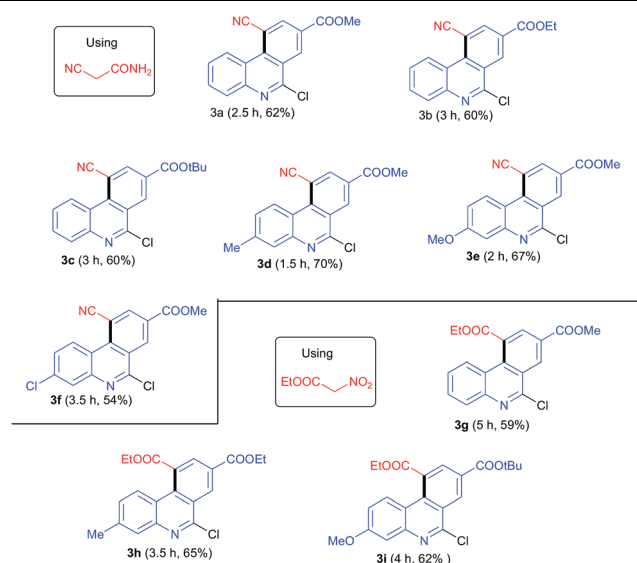
The scopes of both the cyanoacetamide and ethylnitroacetate reagents were further investigated with other MBH acetates under the optimized conditions. All reactions proceeded and afforded phenanthridine derivatives **3a–f** with cyanoacetamide in 54–70% yields and **3g–i** with ethylnitroacetate in 59–66% yields. Lengthening and branching of the ester group of MBH acetate gave products **3a–c** in nearly the same yields, specifically 60–62%. Similarly, MBH acetates bearing EDG were more reactive than those bearing EWG, and hence gave products **3d–e** and **3h–i** in better yields than **3f**. The results are summarized in Table 2.

Next, we explored the reaction of malonic ester reagents with MBH acetate **1a** for the purpose of synthesizing either acridines or 1,4-dihydroacridines. For this purpose, MBH acetate **1a** was employed with malonic esters under similar reaction



Scheme 4 Use of malonic esters. ^aAll reactions were performed with **1** (0.5 mmol) by using dimethylmalonate/diethylmalonate (1.5 equiv.) and K₂CO₃ (1.5 equiv.) in DMF (2 mL). The reaction time and yield of isolated product are given.

conditions. The reactions were completed in 2–3 h and afforded products **4** in 67–74% yields and the products **4** were determined to be 1,4-dihydro-phenanthridines. The reaction mixture was further heated at 70 °C for 24 hours for the purpose of effecting a complete aromatization of the product but failed to proceed and the dihydro product was recovered. The reagent applicability was further evaluated with other MBH acetates, and corresponding dihydro products **4a–c** were afforded in 67–74% yields (Scheme 4).

Table 2 Substrate scope^a

^a All reactions were performed with **1** (0.5 mmol) by using cyanoacetamide/nitroethylacetate (1.5 equiv.) and K₂CO₃ (1.5 equiv.) in DMF (2 mL). The reaction time and yield of isolated product are given.

Conclusions

In conclusion, we have developed an efficient method for synthesis of acridines and phenanthridines from reactions of MBH acetates of 2-chloro-quinoline-3-carbaldehydes with various AMCs in one pot at room temperature under aerobic conditions. Formation of products was found to be dependent on the functional group of the AMC. Our synthetic route is advantageous with respect to reaction conditions, and the availability of substrates from easily accessible starting materials.

Conflicts of interest

There are no conflicts to declare.

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