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One-pot, three-component reaction of dimedone, amines, and isatin in the presence of tris(hydrogensulfato) boron: synthesis of pyrroloacridine derivatives

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Abstract A one-pot, three-component reaction of dimedone, anilines. and isatin has been described leading to the synthesis of 2-arylpyrroloacridin-1(2H)-ones in the presence of tris(hydrogensulfato) boron [$B(HSO_4)_3$] at reflux in ethanol. However, in the cases of aliphatic amines, tetrahydroxanthene has been obtained from the reaction of isatin and dimedone.

Keywords Pyrroloacridine · Dimedone · Anilines · Isatin · $B(HSO_4)_3$

Introduction

Heterocyclic compounds are a remarkably important class of compounds, making up more than half of all known organic compounds. Heterocycles are present in a wide variety of drugs, most vitamins, many natural products, biomolecules, and biologically active compounds [1]. Thus, efforts to synthesize these compounds are in demand by organic chemists.

Pyrroloacridone derivatives are of interest owing to their various pharmacological and biological activities [2–4]. Acridine- and acridone-based compounds comprise an important class of DNA-intercalating anticancer drugs [5]. A number of acridine derivatives have exhibited interesting antitumor properties, including acridone-4-carboxamide [6], and the bis-functionalized acridone/acridine-4-carboxamides [7].

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Thus, a variety of synthetic approaches are desirable to synthesize acridines from dimedone, aldehydes, and aniline derivatives, or ammonium acetate via the Hantzch reaction in the presence of various catalysts [8–13]. In this context, we planned to employ isatin instead of an aldehyde. However, recently, Kefayati's group reported the reaction of dimedone, anilines, and isatinin the ionic liquid [HMIm]HSO_4 at 80 °C. This reaction afforded 2-arylpyrrolo[2,3,4-kl]acridin-1(2H)-ones [14]. Also, these compounds were constructed by refluxing a mixture of isatins and enaminones in toluene in the presence of an L-proline catalyst [15].

The $B(HSO_4)_3$ catalyst was prepared by the addition of chlorosulfonic acid to boric acid at room temperature according to our reported method [16]. This catalyst is safe and easy to handle and has been successfully applied for the synthesis of biscoumarins [16], dihydroquinazolinones [17], and arylidenebisamide derivatives [18].

Experimental

The $B(HSO_4)_3$ catalyst was prepared by addition of chlorosulfonic acid to boric acid at room temperature according to our reported method [14].

General procedure for the synthesis of pyrroloacridine derivatives

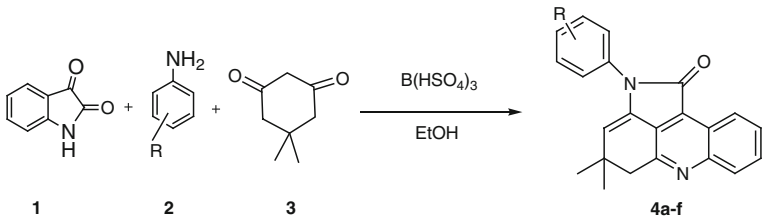
A solution of dimedone (2 mmol), aniline (1 mmol), isatin (1 mmol), and $B(HSO_4)_3$ (0.10 g) in 5.0 mL ethanol (96 %) was stirred at reflux conditions for the appropriate times (Table 1). Upon completion of the reaction, monitored by TLC, the reaction mixture was allowed to cool to room temperature. The solid was filtered off and washed with water (2 × 10 mL) and purified by recrystalization from ethanol. The structures of all products **4a–f** were confirmed by IR, ^{1}HNMR, ^{13}CNMR, and elemental analysis.

Compound (**4a**): IR (KBr): 3,035, 2,960, 1,698, 1,647, 1,460, 1,344, 1,095, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 1.34 (s, 6H, $2CH_3$), 3.23 (s, 2H, CH_2), 5.64 (s, 1H, CH), 7.43 (t, *J* 6.4 Hz, 1H), 7.51–7.56 (m, 4H), 7.68 (t, *J* 6.8 Hz, 1H), 7.78 (t, *J* 7.6 Hz, 1H), 8.19 (d, *J* 8.0 Hz, 1H), 8.76 (d, *J* 8.0 Hz, 1H); ^{13}CMNR (100 MHz, $CDCl_3$): 32.0, 38.2, 45.3, 119.5, 122.5, 123.8, 125.4, 126.1, 127.5, 127.6, 128.6, 128.9, 130.5, 130.6, 134,5, 135.9, 150.9, 155.7, 167.7.

Compound (**4b**): IR (KBr): 3,064, 2,957, 1,699, 1,649, 1,494, 1,346, 1,090, 830, 775 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): 1.34 (s, 6H, $2CH_3$), 3.23 (s, 2H, CH_2), 5.62 (s, 1H), 7.47 (d, *J* 8.4 Hz, 2H), 7.53 (d, *J* 8.4 Hz, 2H), 7.69 (t, *J* 7.2 Hz, 1H), 7.77 (t, *J* 7.8 Hz, 1H), 7.19 (d, *J* 8.4 Hz, 1H), 8.72 (d, *J* 8.4 Hz, 1H).

Compound (**4d**): IR (KBr): 3,045, 2,961, 1,703, 1,648, 1,491, 1,344, 1,116, 1,076, 821, 773 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): 1.34 (s, 6H, $2CH_3$), 3.23 (s, 2H, CH_2), 5.63 (s, 1H), 7.41 (d, *J* 8.4 Hz, 2H), 7.67–7.69 (m, 3H), 7.78 (t, *J* 7.2 Hz, 1H), 8.18 (d, *J* 8.4 Hz, 1H), 8.71 (d, *J* 8.0 Hz, 1H).

Compound (**5**) IR (KBr): 3,332, 3,090, 2,960, 1,724, 1,693, 1,599, 1,377, 1,233, 1,129, 905 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): 1.08 (s, 6H, $2CH_3$), 1.13 (s, 6H,



Scheme 1 Synthesis of pyrroloacridine derivatives

Table 1 Optimizing the reaction conditions for the synthesis of **4a**

Entry	Catalyst (g)	Conditions	Time (min)	Yield (%)
1	–	Ethanol, r.t.	120	0
2	–	Ethanol, reflux	120	Trace
3	$B(HSO_4)_3$, (0.05)	Ethanol, reflux	30	50
4	$B(HSO_4)_3$, (0.10)	Ethanol, reflux	5	96
5	$B(HSO_4)_3$, (0.10)	Ethanol, r.t.	120	0
6	$B(HSO_4)_3$, (0.10)	Solvent-free, 100 °C	30	70

$2CH_3$), 2.06–2.48 (m, 8H), 3.5 (s, 1H), 6.83 (d, *J* 6.8 Hz, 1H), 6.91–6.96 (m, 2H),7.20 (t, *J* 6.8 Hz, 1H).

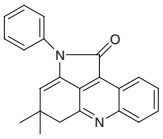
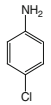
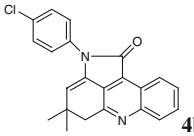
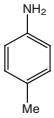
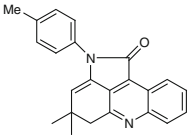
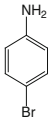
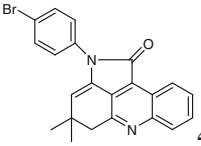
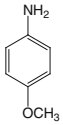
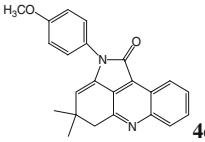
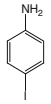
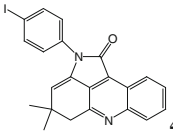
Results and discussion

Our efforts to develop an efficient methodology for the synthesis of pyrroloacridine derivatives focused initially on the three-component cyclocondensation of dimedone with aniline and isatin as a model reaction (Scheme 1). Thus, a catalytic amount of $B(HSO_4)_3$ was added to a mixture of dimedone, aniline, and isatin in different solvents and under solvent-free conditions, and the reaction conditions were optimized by conducting the reaction at different temperatures and employing different loadings of the catalyst (Table 1). Pleasingly, we discovered that the reaction was efficiently catalyzed by $B(HSO_4)_3$ at reflux conditions using ethanol as a solvent, providing a high yield of product **4a** (Table 1, Entry 4). A low yield of the product was only obtained in the absence of the catalyst, indicating that the catalyst was necessary to the reaction. The best result was obtained when the reaction was conducted at reflux in ethanol in the presence of 0.10 g of the $B(HSO_4)_3$ catalyst.

The scope of this methodology was further extended by the reaction of various anilines in this procedure. Different pyrroloacridine derivatives **4a**–**f** were prepared in short reaction times with good yields in the presence of $B(HSO_4)_3$(0.10 g). The results are summarized in Table 2.

As shown in Table 2, anilines with halogen, methyl, and methoxy groups are easily converted to their corresponding products under the same reaction conditions.

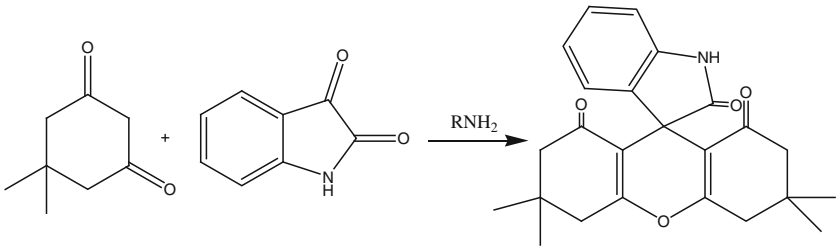
Table 2 One-pot synthesis of pyrroloacridone derivatives using $B(HSO_4)_3$ in ethanol

Entry	Amine	Product	Time (min)	Yield (%)	M.p. (°C)
1		 **4a**	5	96	193–194
2		 **4b**	7	92	191–192
3		 **4c**	5	90	218–219
4		 **4d**	8	90	191–192
5		 **4e**	5	86	189–190
6		 **4f**	5	86	183–184

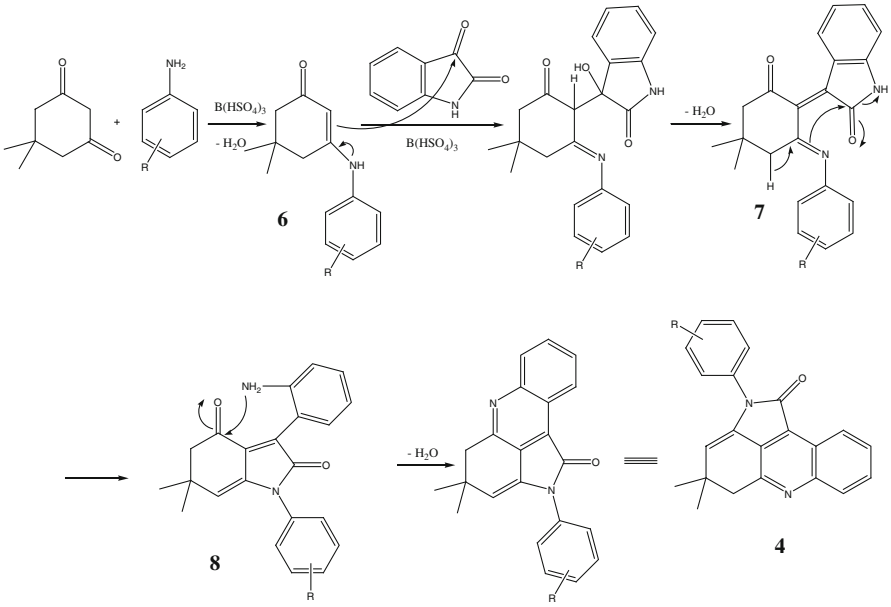
However, when the reaction was triggered on anilines with electron-withdrawing groups such as the nitro group, only a low yield of the product was obtained.

Furthermore, under the same conditions, it was observed that aliphatic amines, such as methyl amine, 2-phenyl ethyl amine, and 1,2-ethylene diamine, failed to react and tetrahydroxanthene **5** has been obtained from the reaction of isatin and dimedone (Scheme 2).

The formation of the compounds **4** was assumed to proceed via formation of a Michael adduct intermediate followed by cyclization according to Scheme 3. At first, enamine **6** was derived in turn from condensation of dimedone and aniline.



Scheme 2 The reaction of isatin and dimedone in the presence of aliphatic amines



Scheme 3 Proposed mechanism

Then, the reaction proceeds via formation of the intermediate **7**, which is formed in situ by reaction of isatin with the intermediate enamine **6**. A proton shift from intermediate **7** induces an intramolecular translactamization to give the intermediate **8**. This intermediate undergoes a cyclocondenzation reaction to afford the corresponding pyrroloacridine.

In conclusion, this article describes an efficient method for the synthesis of pyrroloacridine derivatives through a one-pot three-component reaction of dimedone, isatin, and anilines using $B(HSO_4)_3$ as catalyst under reflux in ethanol. Moreover, aliphatic amines failed to react and tetrahydroxanthene has been achieved from the reaction of isatin and dimedone. The present procedure offers several unique advantages like high catalytic activity, short reaction times, good yields, and simple workup.

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