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Acid-promoted synthesis and photophysical properties of substituted acridine derivatives†

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A simple and efficient synthetic protocol for the preparation of acridinium esters and amides through the cyclization and esterification or amidation of isatins with alcohols or amines as nucleophiles in the presence of CF_3SO_3H is established. A series of polycyclic acridine derivatives bearing large π-conjugated systems were obtained in high yields, including some key intermediates for the synthesis of biologically active molecules. The photophysical properties of these synthesized acridines were investigated, demonstrating that the sulfur heterocyclic acridine **9w** was obtained in a high quantum yield.

Introduction

Acridine derivatives exhibit many biological activities, exemplified by compounds **1–6** in Fig. 1, and have therefore been attracting the attention of organic chemists.[1,2] Due to their importance in human health care and many other applications, significant effort has been devoted to developing efficient synthetic methodologies for the preparation of acridine derivatives over the past few decades.[3] Most methods for the synthesis of acridines involve several types of ring closure reactions, including the reaction of arynes with a number of partners, such as 2-aminoaryl ketones and hydrazones.[4] The cross-coupling reactions of aromatic amines or azide compounds with suitable partners have provided various substituted acridines under catalysis by Pd or Rh.[5] The intramolecular electrophilic cyclization of diphenylamine-2-carbonyls or 2,6-diaryl-3,5-dialkynylpyridines has also led to the formation of acridines.[6] A thermal rearrangement reaction of indazolium salts afforded 9-amino-substituted acridines.[7] Although there are some reports on the synthesis of acridine-9-carboxylic acids by the treatment of isatin with a base, both substrate scope and functional group tolerance are very limited.[8] Here, we report an efficient, one-step synthetic method to synthesize various 9-ester or amide substituted acridines from commercially available isatins in the presence of an acid promoter. Furthermore, to explore their potential applications in materials science, the photophysical properties of these synthesized acridines were investigated.

Results and discussion

We first examined the reaction of 1-phenylisatin **7a** in the presence of 2.0 equivalents of $BF_3{\cdot}Et_2O$ in MeOH at 100 °C for 36 h. To our delight, the methyl acridine-9-carboxylate **9a** was obtained in 10% yield (Table 1, entry 1), and its structure was unambiguously confirmed by X-ray diffraction analysis.[9] We then investigated the solvent effect on the reaction and found that 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was the best solvent (Table 1, entries 2–5). When the amount of $BF_3{\cdot}Et_2O$ was increased to 5.0 equivalents, the yield of product **9a** increased from 40% to 54% (Table 1, entries 5 and 6). Next, we tested some other Lewis acids in the reaction. All three Lewis acids ($Al(OTf)_3$, *p*-$TsOH{\cdot}H_2O$ and CF_3SO_3H) promoted the reaction. The reaction in the presence of 7.0 equivalents of *p*-$TsOH{\cdot}H_2O$ or 2.0 equivalents of CF_3SO_3H afforded the acri-

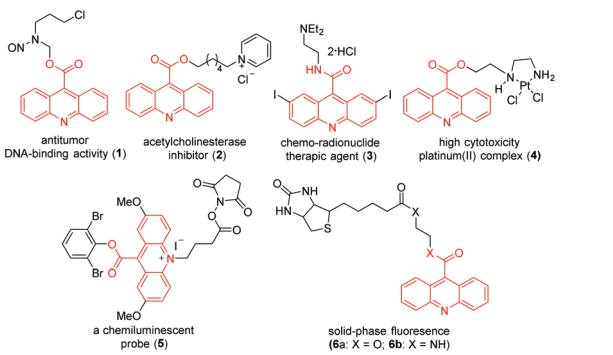

Fig. 1 Biologically active compounds with acridinium ester and amide derivatives.

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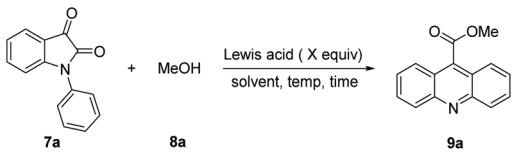
Table 1 Optimization of the reaction conditions[a]



7a 8a 9a

Entry	Solvent	Lewis acid (equiv.)	*T* (°C)	Time (h)	Yield of **9a** (%)
1	MeOH	$BF_3{\cdot}Et_2O$/2.0	100	36	10
2	TCE	$BF_3{\cdot}Et_2O$/2.0	100	36	13
3	MeCN	$BF_3{\cdot}Et_2O$/2.0	100	36	5
4	Toluene	$BF_3{\cdot}Et_2O$/2.0	100	36	16
5	HFIP	$BF_3{\cdot}Et_2O$/2.0	100	36	40
6	HFIP	$BF_3{\cdot}Et_2O$/5.0	100	36	54
7	HFIP	$Al(OTf)_3$/5.0	100	36	65
8	HFIP	*p*-TsOH·H_2O/5.0	100	24	81
9	HFIP	*p*-TsOH·H_2O/7.0	100	36	94
10	HFIP	CF_3SO_3H/5.0	100	24	85
11	HFIP	CF_3SO_3H/2.0	100	12	84
12	HFIP	CF_3SO_3H/1.0	100	24	62
13	HFIP	CF_3SO_3H/2.0	80	36	51
14	HFIP	None	100	36	0

[a] Reaction conditions: **7a** (0.1 mmol) and MeOH (10.0 equiv.) in solvent (1.0 mL). Isolated yield.

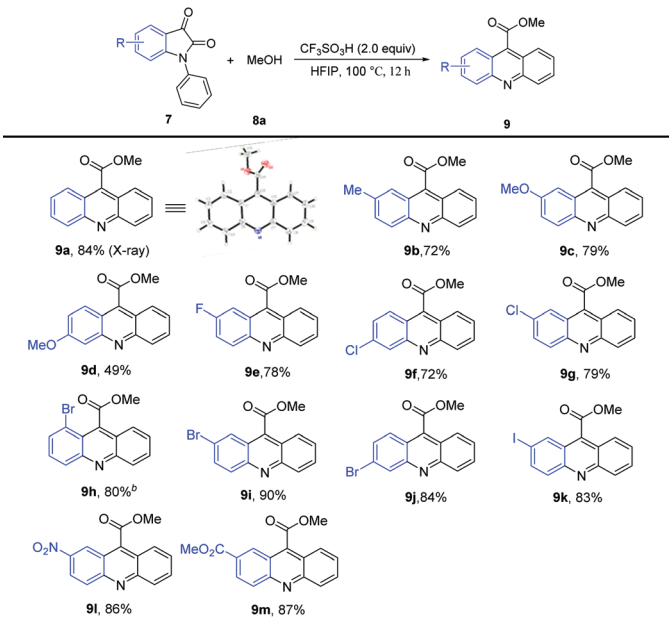
dine **9a** in 94% and 84% yields, respectively (Table 1, entries 9 and 11).[10] The yield of product **9a** decreased with lower temperature (Table 1, entry 13). The reaction did not occur in the absence of an acid (Table 1, entry 14). Considering the different efficiencies of *p*-TsOH·H_2O and CF_3SO_3H, 2.0 equivalents of CF_3SO_3H at 100 °C for 12 h were chosen as the optimal conditions.

With the optimized conditions in hand, we investigated the substrate scope of the reaction. Various electron-withdrawing or electron-donating groups were introduced into the benzene ring of the isatin scaffold (Table 2). The products **9b–9d** bearing Me or OMe groups were obtained in 49–79% yields. A series of halogen substituted products **9e–9k** were readily prepared in good to excellent yields, which provided a good basis for the synthesis of more complex acridine esters by transition-metal catalyzed cross-coupling reactions. The reaction of the isatin compounds **7l** and **7m** with NO_2 and CO_2Me groups substituted at the 5-position afforded the products **9l** and **9m** in 86% and 87% yields, respectively.

N-Aryl substituted isatins **7n–7w** were synthesized *via* copper-mediated cross coupling of isatin with various arylboron reagents. The reaction of the starting materials **7n–7w** under the standard conditions proceeded well to afford the acridines **9n–9w** bearing a large π-conjugated system in good yields up to 87%. Interestingly, we used two routes to prepare the acridine product **9g** in 79% and 53% yields, respectively (Table 3).

To expand the utility of this reaction, the scope of nucleophiles including alcohols and alkylamines was explored (Table 4). The reaction of **7a** with primary alcohols **8b** and **8c** proceeded smoothly to afford the corresponding products **9ab** and **9ac** in good yields. Probably due to the lower nucleophilicity of isopropanol, product **9ad** was obtained in moderate yield (Table 4, entries 1–3). Compound **7a** reacted with chloroalcohol **8g** under the standard conditions to afford acridine-9-ester **9ag**, which was the key precursor for the preparation of bioactive molecule **2** (Scheme 1). Furthermore, glycol **8h**, with two hydroxyl groups, worked well to provide product **9ah**,

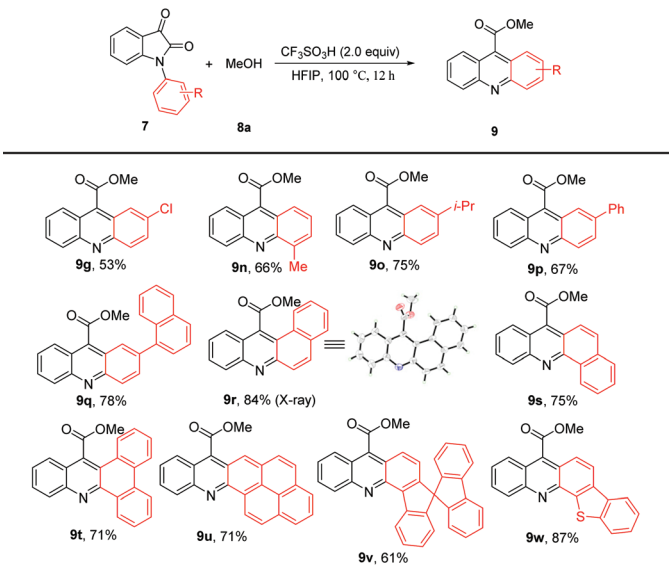
Table 2 Substrate scope[a]



7 8a 9

[a] Reaction conditions: **7** (0.10 mmol), **8a** (1.00 mmol), CF_3SO_3H (0.20 mmol), and HFIP (1.0 mL), 100 °C, 12 h. Isolated yield. [b] The reaction time was 48 h.

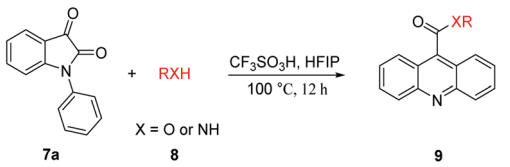
Table 3 Substrate scope[a]

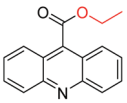
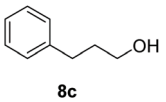
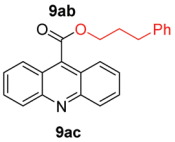
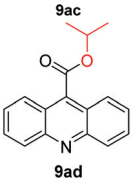
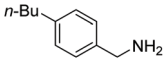
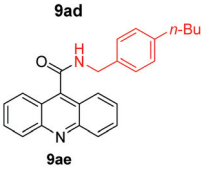
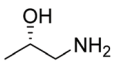
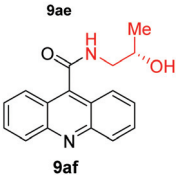


7 8a 9

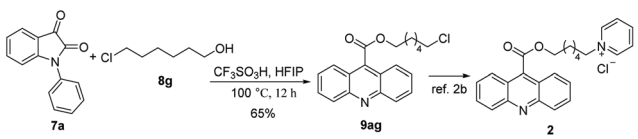
[a] Reaction conditions: **7** (0.10 mmol), **8a** (1.00 mmol), CF_3SO_3H (0.20 mmol), and HFIP (1.0 mL), 100 °C, 12 h. Isolated yield.

Table 4 Substrate scope[a]



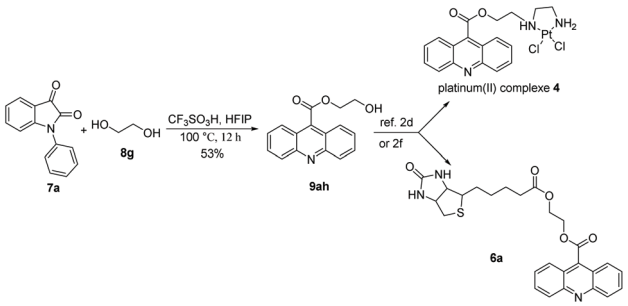
Entry	8	9	Yield (%)
1	 **8b**	 **9ab**	63
2	 **8c**	 **9ac**	70
3	 **8d**	 **9ad**	39[b]
4	 **8e**	 **9ae**	66[c]
5	 **8f**	 **9af**	57

[a] Reaction conditions: **7a** (0.10 mmol), **8** (1.00 mmol), CF_3SO_3H (0.20 mmol), and HFIP (1.0 mL), 100 °C, 12 h. Isolated yield. [b] The reaction time was 24 h. [c] In the case of **9ae**, **7a** (0.10 mmol), **8e** (1.00 mmol), $TsOH{\cdot}H_2O$ (0.70 mmol), and HFIP (1.0 mL), 100 °C, 24 h.

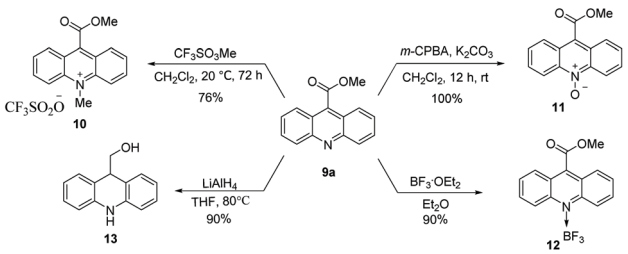


Scheme 1 Formal synthesis of a competitive inhibitor of acetylcholinesterase.

bearing a free hydroxyl group at its terminal end. Compound **9ah** could be used to prepare biologically active platinum(II) complex **4** and **6a** (Scheme 2). A primary alkylamine was also suitable as a nucleophile for this reaction. For example, the reaction of **7a** with benzylamine **8e** and aminoalcohol **8f** in the presence of CF_3SO_3H produced **9ae** and **9af** in 66% and 57% yields, respectively (Table 4, entries 4 and 5). To further illustrate the applications of this type of acridine compound, four other derivative reactions starting from **9a** were conducted (Scheme 3). An *N*-methylation reaction was achieved to provide



Scheme 2 Formal synthesis of platinum(II) complexes **4** and **6a**.



Scheme 3 Transformations of acridinium ester **9a**.

10 in 76% yield.[11] Compound **9a** was totally oxidized to **11** in quantitative yield.[12] The reaction of **9a** with Lewis acid $BF_3{\cdot}Et_2O$ led to **12** in 90% yield.[13] In addition, **9a** was reduced to **13** in excellent yield.

In recent years, acridine derivatives emerge as one of the important fluorescent probes for metal ions and anions.[14] Although the biotinylated fluorophore (2-biotinyloxyethyl)acridine-9-carboxylate (**6a**) and its analogue (2-biotinylamidoethyl) acridine-9-carboxamide (**6b**) were synthesized as fluorescent materials and labels in bioanalytical applications, little has been studied on their fluorescence properties based on acridine skeletons.[2f,g] Thus, the photophysical properties of compounds **9a–9ah**, **10** and **11** were investigated by UV/Vis absorption and fluorescence spectroscopic techniques. The typical absorption and emission spectral data of these compounds were recorded in dichloromethane, as shown in Table 5, and the fluorescence spectra of **9c**, **9d**, **9q**, **9s**, **9u–9w** and **10** are shown in Fig. 2. In the absorption spectra, the acridinium ester and amide derivatives show an absorption band at 355–460 nm, where the position of the absorption depends on the substitution pattern on the benzene ring. The absorption bands of the acridine-9-carboxylic acid derivatives increase with the increase of the extended π-conjugated system. The emission wavelength and fluorescence quantum yield of all acridine-9-carboxylic acid derivatives were tested to explain the substituent effects. Most substituent groups at different positions of the acridine ring lead to a certain redshift of emission wavelengths. Alkyl, halogen, nitro and other substituent groups have little influence on the emission wavelength and fluorescence quantum yield. With the further enhancement of the π-conjugate system and rigid plane, an obvious redshift of

Table 5 Photophysical properties of acridinium ester and amide derivatives[a]

	Absorption		Fluorescence	
Compd	λ_{max} [b]/nm	ε [c]/cm^{-1} M^{-1}	λ_{FLmax} [c]/nm	Φ_{FL} [d,e]
9a	362	9797	446	0.013
9b	364	4850	453	0.037
9c	356	6801	483	0.254
9d	355	7377	475	0.131
9e	361	5167	444	0.025
9f	366	10 954	449	0.013
9g	367	8709	446	0.016
9h	364	4051	440	0.013
9i	368	6601	447	0.013
9j	366	5864	448	0.001
9k	371	13 832	444	0.050
9l	367	5188	476	0.007
9m	366	4919	455	0.014
9n	362	3088	468	0.038
9o	364	5359	455	0.039
9p	376	14 495	475	0.082
9q	370	6040	507	0.451[f]
9r	391	5219	450	0.033
9s	392	10 182	449	0.144
9t	380	11 735	457	0.041
9u	460	10 154	561	0.205[f]
9v	397	8500	470	0.245
9w	392	10 331	522	0.813[f]
9ab	362	5611	445	0.016
9ac	362	9853	444	0.018
9ad	362	15 626	445	0.026
9ae	361	9680	444	0.017
9af	361	9843	446	0.015
9ag	362	12 186	446	0.049
9ah	362	6897	446	0.002
10	367	11 668	520	0.600
11	446	18 885	457	0.031

[a] In CH_2Cl_2. [b] Longest wavelength absorption maximum is shown. [c] Excited at the wavelength of the absorption maximum. [d] Fluorescence quantum yield. [e] Determined with quinine sulfate as a standard. [f] Determined with Rh6G as a standard.

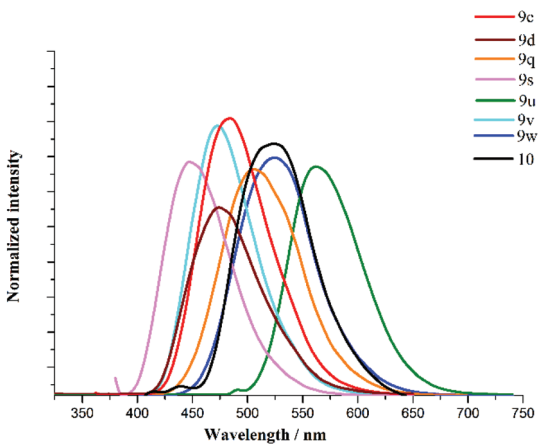
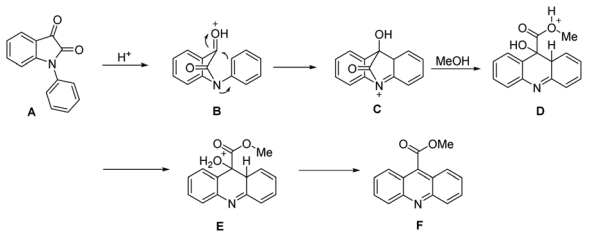


Fig. 2 Fluorescence spectra of **9c**, **9d**, **9q**, **9s**, **9u–9w** and **10** in CH_2Cl_2.

the emission band and a significant increase of quantum yield can be observed. The fluorescence spectra of **9c**, **9d**, **9q**, **9s**, **9u–9w** and **10** show emissions at 440–561 nm with quantum yields of 13–81%. Notably, sulfur heterocyclic acridine **9w** shows the highest quantum yield among these compounds.



Scheme 4 Plausible mechanism.

Based on these primary investigations and results from the literature,[6b] a mechanism can be proposed, as shown in Scheme 4. Intermediate **B** was formed by protonation of **A**, followed by an intramolecular nucleophilic attack of benzene on the ketone moiety at the 3-position of isatin to afford intermediate **C**. **C** could be converted to **D** by esterification with MeOH, followed by a proton transfer and dehydration reaction to give methyl acridine-9-carboxylate **F**.

Experimental

General procedure for the preparation of substituted isatin 7 [15]

A mixture of the substrate (1.0 equiv.), arylboronic acid (2–3 equiv.), anhydrous $Cu(OAc)_2$ (1–2 equiv.), and triethylamine or pyridine (2–3 equiv.) in dichloromethane (10–12 mL/0.5 g of substrate) was stirred at room temperature for 24–72 h. The progress of the reaction was monitored by TLC. The products were isolated by direct flash column chromatography of the crude reaction product.

Typical procedure for the products 9a–w and 9ab–ah

Substituted isatin **7** (0.1 mmol), CF_3SO_3H (30.0 mg, 0.2 mmol), alcohol or amine (1.0 mmol) and HFIP (1 mL) were added in turn into a 10 mL glass sealed tube. The tube was tightly capped. The reaction mixture was stirred at 100 °C for 12 h. After cooling down to room temperature, the reaction mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated. Purification by thin layer chromatography afforded the products **9a–w** and **9ab–ah**.

Typical procedure for the products 11

To a stirred solution of methyl acridine-9-carboxylate (23.7 mg, 0.1 mmol) in $CHCl_3$ (1 mL) was added 70% *m*-CPBA (17.3 mg, 0.1 mmol) portionwise at 0 °C. The mixture was stirred at room temperature for 12 h. After complete consumption of the starting material was observed by TLC, the reaction mixture was diluted with $CHCl_3$, and solid K_2CO_3 (4.0 equiv.) was added. The resulting mixture was stirred for an additional 10 min and then washed with water three times. The organic layer was separated and dried with anhydrous Na_2SO_4, filtered,

and concentrated. The crude product was purified by flash chromatography to afford product **11** (26.1 mg, 100% yield).

Typical procedure for the products 12

To a stirred solution of methyl acridine-9-carboxylate (23.7 mg, 0.1 mmol) in Et_2O (1 mL) was added $BF_3{\cdot}OEt_2$ (42.6 mg, 0.3 mmol) portionwise at room temperature. Product **12** (27.5 mg, 90% yield) was obtained after filtration.

Typical procedure for the products 13

Methyl acridine-9-carboxylate (47.4 mg, 0.2 mmol) was dissolved in anhydrous THF (3 mL), and $LiAlH_4$ (1 M in THF, 0.25 mL) was added dropwise under an inert atmosphere. The reaction mixture was slowly heated to 80 °C and maintained at 80 °C for 3 h. The reaction was then quenched by the addition of 15% aq. NaOH. The resulting precipitate was filtered off. Then the filtrate was diluted with EtOAc, washed with water and saturated aq. $NaHCO_3$, and dried with anhydrous Na_2SO_4. Purification of the crude product by column chromatography (ethyl acetate/hexane, 1 : 4) yielded the alcohol as a pale, yellow solid (41.0 mg, 97%).

Conclusions

In summary, we developed an efficient CF_3SO_3H-promoted synthesis of substituted acridinium ester and amide derivatives in good to excellent yields and with high functional group tolerance. Large π-conjugated systems with polycyclic aromatic hydrocarbons were obtained. This method was applied to the formal synthesis of biologically active compounds with 9-ester acridines as the key intermediates. The photophysical properties of these acridine compounds were investigated, indicating that the sulfur heterocyclic acridine **9w** was obtained at a high quantum yield, which may provide some useful information for exploring potential applications in materials science in the future.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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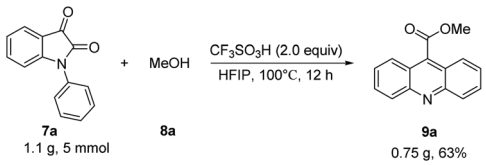
9 The CIF files of **9a** and **9r** have been deposited with Cambridge Crystallographic Data Centre (# CCDC 1960437 and 1968988).†

10 A gram scale reaction was carried out with **7a** as the substrate using our standard conditions to afford product **9a** in 63% yield.



7a 1.1 g, 5 mmol — **8a** — **9a** 0.75 g, 63%

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