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Synthesis of quinolines from anilines, acetophenones and DMSO under air

Tao-Shan Jiang [b,1,*], Xi Wang [a,1], Xiuli Zhang [a,c,*]

[a] Department of Applied Chemistry, Anhui Agricultural University, Hefei, Anhui 230036, PR China
[b] School of Life Sciences, Anhui Agricultural University, Hefei 230036, PR China
[c] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Shanghai 200032, PR China

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ABSTRACT

An efficient CH_3SO_3H-promoted synthesis of quinolines from readily available anilines, acetophenones and DMSO under air is reported. This protocol gives diverse substituted 4-arylquinolines in moderate to high yields with broad substrate/functional group tolerance. Preliminary mechanistic studies demonstrate that DMSO may be transformed to HCHO in this process and used as a one carbon source.

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Introduction

The quinoline substructure is an important heterocyclic motif which is found in many natural products, pharmaceuticals and functional materials [1]. Over the past few years, various methods have been established for the synthesis of quinolines, which has greatly enriched the development of quinoline chemistry [2–3]. However, many of the existing methods utilise expensive transition metals, pre-functionalized starting materials and possess limited substrate scope. These limitations have encouraged the development of new synthetic methods for the synthesis of quinolines. Recently, the one-pot synthesis of diverse quinolines from readily available and inexpensive anilines, acetophenones and a one carbon unit was reported which effectively circumvents the above drawbacks. For example, the direct synthesis of 4-arylquinolines *via* Co(III)-catalyzed C—H activation/carbonylation/cyclization of anilines with ketones using paraformaldehyde as a one carbon unit was reported by Yi and Zhang (Scheme 1a) [4].

In recent years, there have been additional reports regarding DMSO as a one-carbon synthon in organic synthesis [5]. DMSO could also serve as a "=CH—" fragment for the rapid access to heterocyclic compounds though sequential annulation/aromatization processes [3b,6,7]. Importantly, Singh and co-workers developed an elegant synthesis of 4-arylquinolines *via* a $K_2S_2O_8$ promoted oxidative annulation process involving anilines, aryl ketones, and DMSO as a one carbon source (Scheme 1b) [6]. In this reaction, *in situ* generated sulfenium ion could potentially react with two nucleophilic starting materials (anilines or acetophenones) which complicates the reaction. The addition of catalytic $FeCl_3$ attenuates the nucleophilicity of the aniline and enhances that of the acetophenone affording improved results in many cases. Although this represents an efficient strategy, we envisaged that strong electron-donating or phenolic hydroxyl anilines may not suitable in this protocol using $K_2S_2O_8$ as the oxidant. Inspired by the discovery of Singh and co-workers, we hypothesized that the efficiency and scope of the reaction would be improved by the addition of a Brønsted acid which would react to form the aniline salt, which may further attenuate the nucleophilicity of aniline, thus slowing down the undesired oxidation processes (Scheme 2). Herein, we disclose a CH_3SO_3H promoted quinolines synthesis involving anilines, acetophenones and DMSO under air (Scheme 1c).

Results and discussion

Initially, we tested the model reaction of *p*-toluidine (**1a**), acetophenone (**2a**) and DMSO (1 mL, also used as the solvent) with different Brønsted acids in the presence of $K_2S_2O_8$ at 120 °C. As a control experiment, the reaction with no additive was performed

* Corresponding authors at: Department of Applied Chemistry, Anhui Agricultural University, Hefei, Anhui 230036, PR China (X. Zhang).
E-mail addresses: jts2015@ahau.edu.cn (T.-S. Jiang), zhxiuli@163.com (X. Zhang).
[1] These authors contributed equally to this work.

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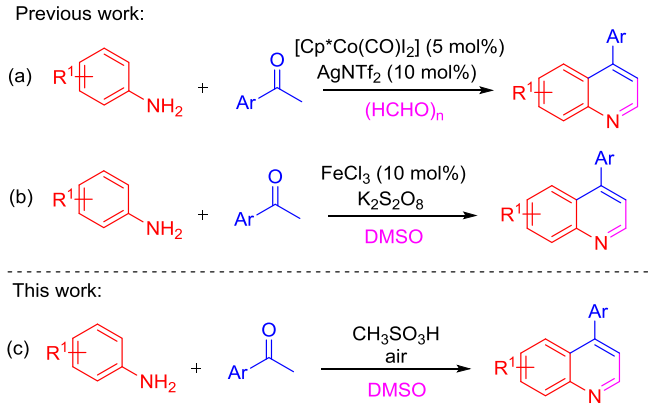
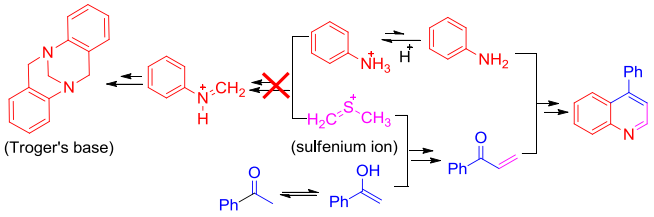


Scheme 1. Synthesis of 4-arylquinolines from anilines, acetophenones and C1 units.



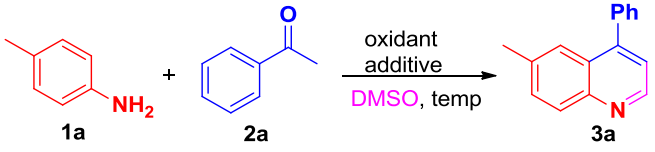
Scheme 2. Design of a Brønsted acid promoted synthesis of 4-arylquinolines.

and the desired product **3a** was obtained in 45% isolated yield (Table 1, entry 1). As expected, the yield was increased to 64% using 1.0 equivalent of CH_3SO_3H (Table 1, entry 2). Other acid such as PTSA, D-CSA, HOAc, TFA and HCl did not further improve the yield (Table 1, entries 3–7). Several oxidants were tested and the reaction proceeded well under an O_2 atmosphere (Table 1, entries 8–10). Replacing the O_2 balloon with air as the oxidant resulted in a 69% yield (Table 1, entry 11). Decreasing the temperature did not improve the yield (Table 1, entry 12), however, the yield was increased to 78% at 130 °C (Table 1, entry 13). Running the reaction at a higher concentration (DMSO: 0.5 mL) resulted in a further improvement in yield (Table 1, entry 14).

Using the optimized reaction conditions, the scope and efficiency of this oxidative cyclization were examined (Table 2). Initially, *p*-toluidine (**1a**) was used as a reaction partner to investigate the scope of the acetophenones. In general, a variety of acetophenones with diverse functional groups afforded the corresponding products in moderate to high yields (29–84%). Acetophenones with electron-donating substituents on the aryl ring (**3b**–**e**) gave better results than those with electron-withdrawing groups (**3i**–**l**). α-Substituted or heterocyclic ketones also proceeded smoothly and the desired products were isolated in moderate yields (**3g, 3h, 3m**). However, the presence of a substituent at the *ortho*-position of acetophenone gave no product due to steric hindrance (**3f**). Next, the reactions of various anilines with acetophenone (**2a**) were evaluated. Weak electron-donating substituents on the aniline, such as alkyl and phenyl, gave excellent results (**3n**-**p**). In previous literature reports, there were no examples of anilines bearing strong electron-donating groups (e.g. MeS, MeO), which may not be compatible under the $K_2S_2O_8$ promoted conditions. However, in our reaction system, methylthio or methoxy substituted anilines reacted with acetophenone and DMSO to give the desired products in 32% (**3q**) and 37% (**3r**) yield, respectively. Additionally, anilines with electron-withdrawing groups afforded the corresponding quinoline derivatives in moderate yield (**3t**-**w**). Gratifyingly, 4-aminophenol or 4′-hydroxyacetophenone was also tolerated, and the corresponding hydroxy-substituted quinolines were obtained in 36% (**3w**) and 55% (**3x**) yield, respectively.

Although a thorough mechanistic study regarding this reaction has been presented [6,7], we wanted to gain further insight into the mechanism of this aerobic oxidation. Several control experiments were conducted (Scheme 3). First, *p*-toluidine (**1a**) was reacted under the standard conditions and trace amounts of Troger's base was detected by GC–MS. This result indicates that CH_3SO_3H could inhibit by-product formation. It is known that acetophenone could generate the corresponding α,β-enone upon reaction with DMSO and $K_2S_2O_8$ [8]. However, the

Table 1
Optimization of the reaction conditions[a].



Entry	Additive (equiv.)	Oxidant	temp (°C)	Yield **3a** (%)
1	None	$K_2S_2O_8$	120	45
2	CH_3SO_3H (1.0)	$K_2S_2O_8$	120	64
3	PTSA (1.0)	$K_2S_2O_8$	120	50
4	D-CSA (1.0)	$K_2S_2O_8$	120	46
5	HOAc (1.0)	$K_2S_2O_8$	120	33
6	TFA (0.1 mL)	$K_2S_2O_8$	120	48
7	HCl(1.0)	$K_2S_2O_8$	120	15
8	CH_3SO_3H (1.0)	TBHP	120	Trace
9	CH_3SO_3H (1.0)	H_2O_2	120	Trace
10	CH_3SO_3H (1.0)	O_2	120	60
11	CH_3SO_3H (1.0)	Air	120	69
12	CH_3SO_3H (1.0)	air	110	46
13	CH_3SO_3H (1.0)	Air	130	78
14[b]	CH_3SO_3H (1.0)	Air	130	84

[a] Unless otherwise specified, all reactions were carried out using **1a** (0.2 mmol), **2a** (0.3 mmol), oxidant (2.0 equiv.), CH_3SO_3H (1.0 equiv.), DMSO (1.0 mL), 36 h.
[b] DMSO (0.5 mL).

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