Synthesis of Quinolines from Anilines, Acetophenones and DMSO Under Air

Tao-Shan Jiang, Xi Wang, Xiuli Zhang

PII: S0040-4039(18)30820-7
DOI: https://doi.org/10.1016/j.tetlet.2018.06.054
Reference: TETL 50092

To appear in: *Tetrahedron Letters*

Received Date: 18 April 2018
Revised Date: 7 June 2018
Accepted Date: 21 June 2018

Please cite this article as: Jiang, T-S., Wang, X., Zhang, X., Synthesis of Quinolines from Anilines, Acetophenones and DMSO Under Air, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.06.054

Synthesis of Quinolines from Anilines, Acetophenones and DMSO Under Air

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

[a] Department of Applied Chemistry, Anhui Agricultural University, Hefei, Anhui 230036, P. R. China

[b] School of Life Sciences, Anhui Agricultural University, Hefei, 230036, P. R. China.

[c] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Shanghai 200032, P.R. China

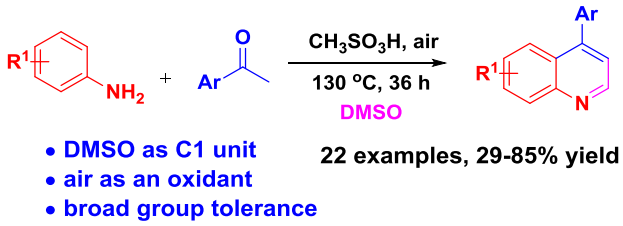
e-mail: jts2015@ahau.edu.cn; zhxiuli@163.com

[†] These authors contributed equally to this work.

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.

Graphical abstract

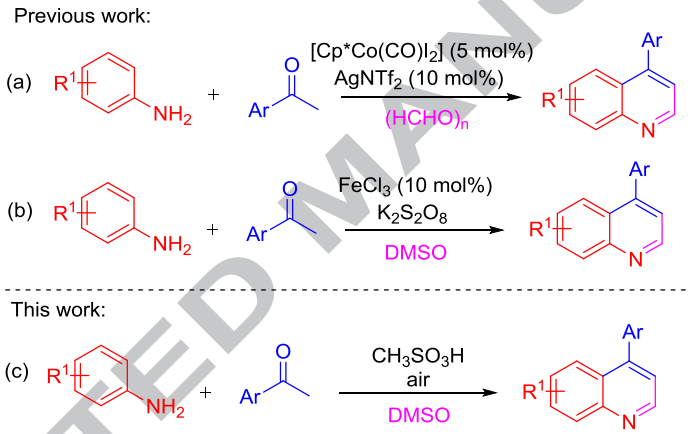


Keywords: Quinolines; Oxidative annulation; DMSO; Anilines; Acetophenones;

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

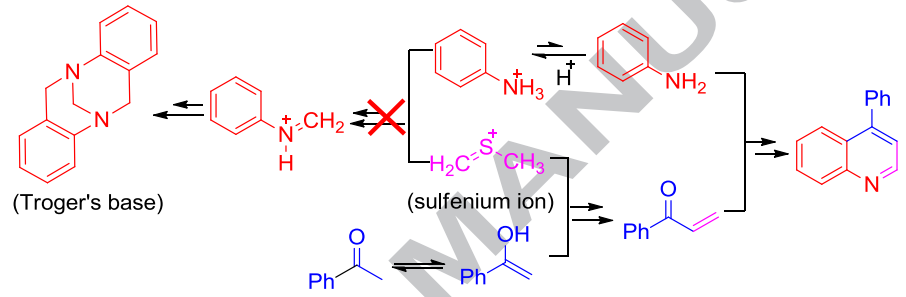
the existing methods utilise expensive transition metals, pre-functionalized starting materials and possess limited substrate scope. These limitations have encouraged the development of new synthetic methods for the synthesis of quinolines. Recently, the one-pot synthesis of diverse quinolines from readily 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]



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

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).

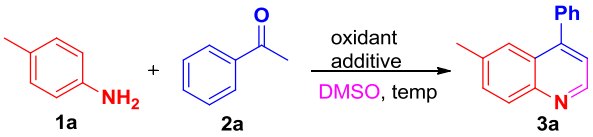


Scheme 2. Design of a Brønsted acid promoted synthesis of 4-arylquinolines.

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 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).

Table 1. Optimization of the reaction conditions [a]



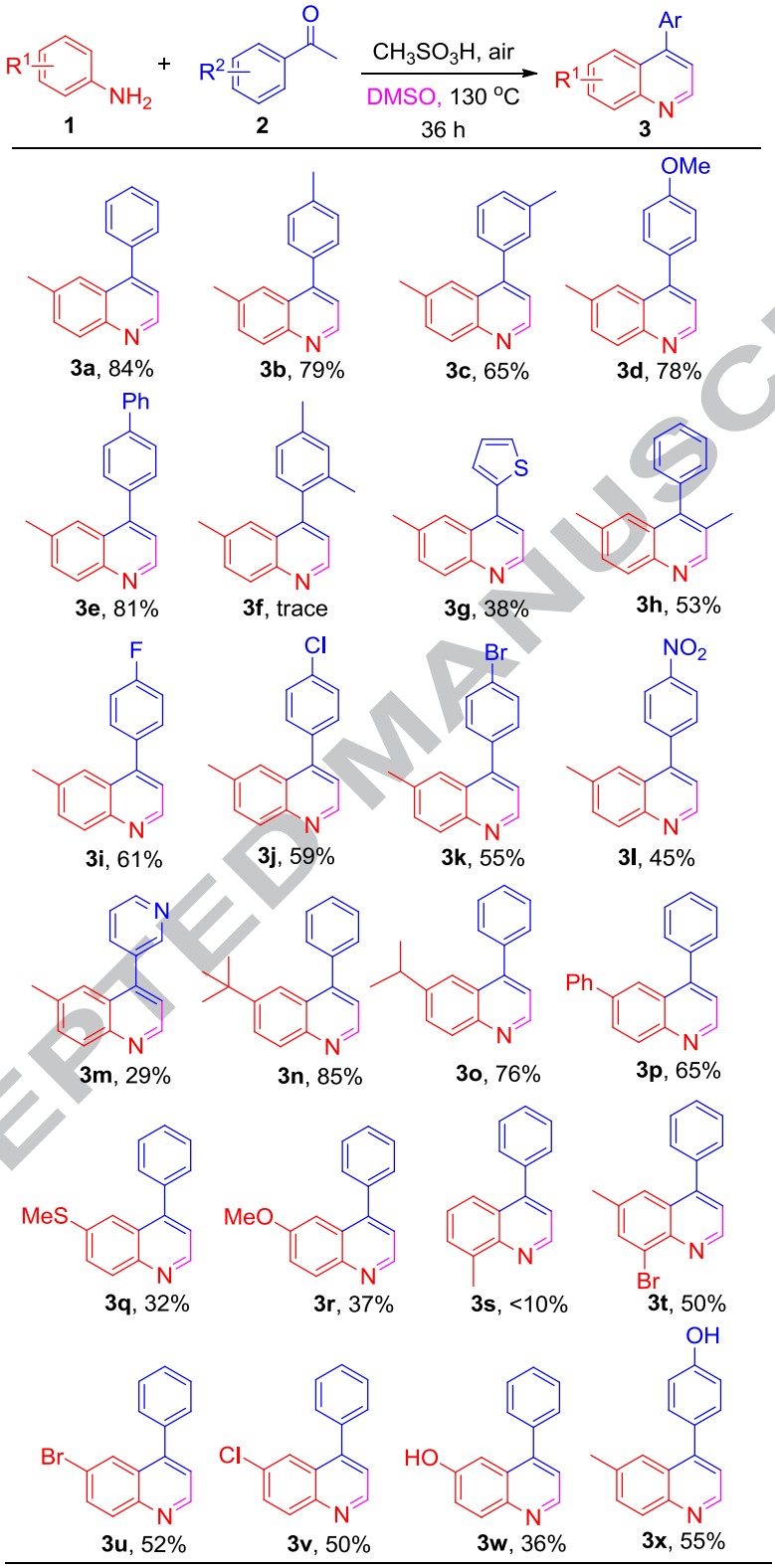
Entry	Additive (equiv.)	Oxidant	temp (^{o}C)	Yield **3a** (%)
1	none	$K_2S_2O_8$	120	45
2	CH_3SO_3H (1.0)	$K_2S_2O_8$	120	64
3	PTSA (1.0)	$K_2S_2O_8$	120	50
4	D-CSA (1.0)	$K_2S_2O_8$	120	46
5	HOAc (1.0)	$K_2S_2O_8$	120	33
6	TFA (0.1 mL)	$K_2S_2O_8$	120	48
7	HCl(1.0)	$K_2S_2O_8$	120	15
8	CH_3SO_3H (1.0)	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).

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),

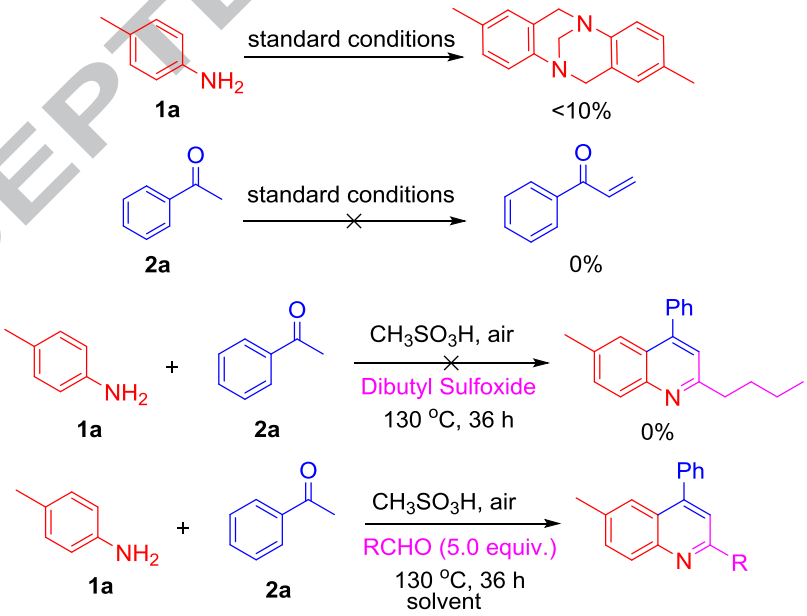
which may not be compatible under the $K_2S_2O_8$ promoted conditions. However, in our reaction system, methylthio or methoxy substituted anilines reacted with acetophenone and DMSO to give the desired products in 32% (**3q**) and 37% (**3r**) yield, respectively. Additionally, anilines with electron-withdrawing 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.

Table 2. Synthesis of quinolines from anilines and acetophenones.



[a] Reagents and conditions: **1** (0.2 mmol), **2** (0.3 mmol), CH_3SO_3H (1.0 equiv.), DMSO (0.5 mL), 130 °C under air, 36 h .

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 reaction of acetophenone **2a** under the standard conditions did not give the intermediate α,β-enone. Using dibutyl sulfoxide instead of DMSO as the reactant and solvent did not afford the corresponding product. To further explore this aerobic oxidation process, DMSO was replaced with paraformaldehyde as a one carbon unit and examined under different solvents.[9] The desired product **3a** was obtained in lower yield. Other aldehydes such as acetaldehyde or benzaldehyde did not give the corresponding products. These results indicated that the HCHO may be the key intermediate rather than the sulfenium ion, which is produced by DMSO reacting with O_2 at high temperature.



RCHO	Solvent	Yield
R = H	1,4-dioxane	16% (**3a**)
R = H	DCE	27% (**3a**)
R = H	DMA	37% (**3a**)
R = Me	DMA	0%
R = Ph	DMA	0%

Scheme 3. Preliminary mechanistic studies.

Conclusion

In summary, we have developed an efficient method for the one-pot synthesis of quinolines from anilines and acetophenones with DMSO as a one carbon unit under air. Compared to previous studies, this process has excellent substrate/functional group tolerance. Further studies on the synthetic applications of this methodology are ongoing in our group.

Acknowledgements

Financial support from the National Natural Science Foundation of China (21702002) and the Natural Science Foundation of Anhui Province (1608085MB26) is gratefully acknowledged.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at

References

(1) (a) Zhang J-Q, Luo Y-J, Xiong Y-S, Yu Y, Tu Z-C, Long Z-J, Lai X-J, Chen H-X, Luo Y, Weng J, Lu G. *J Med Chem.* 2016; *59*: 7268; (b) Solomon VR, Lee H. *Curr Med Chem.* 2011; *18*: 1488; (c) Parker WB. *Chem Rev.* 2009; *109*: 2880; (d) Suresh K, Sandhya B, Himanshu G. *Mini-Rev Med Chem.* 2009; *9*: 1648; (e) Michael JP. *Nat Pro Rep*. 2008; 25: 166; (f) Abele E, Abele R, Lukevics E. *Chem Heterocycl Compd*. 2008; 44: 769; (g) Xu H, Chen R, Sun Q, Lai W, Su Q, Huang W, Liu X. *Chem Soc Rev.* 2014; 43: 3259; (h) Danel A, Gondek E, Kityk I. *Opt Mater.* 2009; 32: 267.

(2) For selected reviews, see: (a) Fallah-Mehrjardi M, *Mini-Rev Org Chem.* 2017; 14: 187; (b) Ramann GA, Cowen BJ. *Molecules*. 2016; 21: 986; (c) Marco-Contelles J, Pérez-Mayoral E, Samadi A, Carreiras MDC, Soriano E. *Chem Rev.* 2009; 109: 2652.

(3) For recently selected articles and references therein, see: (a) Ahmed W, Zhang S, Xu X, Yamamoto Y, Bao M. *Green Chem.* 2018; 20: 261; (b) Yuan J, Yu J-T, Jiang Y, Cheng J. *Org*

Biomol Chem. 2017, 15: 1334: (c) Mahfoudh M, Abderrahim R, Leclerc E, Campagne J-M. *Eur J Org Chem.* 2017; 2017: 2856; (d) Zhou Y, Tang Z, Song Q. *Adv Synth Catal.* 2017; 359: 952; (e) Wang S, Lu H, Li J, Zou D, Wu Y, Wu Y. *Tetrahedron Lett.* 2017; 58: 2723; (f) Zhan J-L, Wu M-W, Chen F, Han B. *J Org Chem.* 2016; 81: 11994; (g) Pollack SR, Kuethe JT. *Org Lett.* 2016; 18: 6388; (h) Zhong M, Sun S, Cheng J, Shao Y. *J Org Chem.* 2016; 81: 10825; (i) Wang L, Ferguson J, Zeng F, *Org Biomol Chem.* 2015; 13: 11486; (j) Frutos RP, Wei X, Patel N D, Tampone TG, Mulder JA, Busacca CA, Senanayake CH. *J Org Chem*. 2013; 78: 5800; (k) Yan R, Liu X, Pan C, Zhou X, Li X, Kang X, Huang G. *Org Lett*. 2013; 15: 4876; (l) Wang Y, Chen C, Peng J, Li M. *Angew Che In Ed*. 2013; 52: 5323.

(4) Xu X, Yang Y, Chen X, Zhang X, Yi W. *Org Biomol Chem.* 2017; 15: 9061.

(5) For select reviews about DMSO as a synthon in organic synthesis, see: (a) Jones-Mensah E, Karki M, Magolan J. *Synthesis* 2016; 48: 1421; (b) Wu X-F, Natte K. *Adv Synth Catal.* 2016; 358: 336.

(6) Jadhav , S. D.; Singh , A.; *Org. Lett.* 2017; 19: 5673.

(7) (a) Pan X, Liu Q, Chang L, Yuan G. *RSC Adv.* 2015; 5: 51183; (b) Lv Y, Li Y, Xiong T, Pu W, Zhang H, Sun K, Liu Q, Zhang Q. *Chem Commun.* 2013; 49: 6439; (c) Wang F, Shen J, Cheng G, Cui X. *RSC Adv.* 2015; 5: 73180; (d) Xie C, Zhang Z, Li D, Gong J, Han X, Liu X, Ma C. *J Org Chem.* 2017; 82: 3491; (e) Wakade SB, Tiwari DK, Ganesh PSKP, Phanindrudu M, Likhar PR, Tiwari DK. *Org Lett*. 2017; 19: 4948; (f) Xu X, Yang Y, Zhang X, Wei Y. *Org Lett*. 2018; 20: 566.

(8) Liu Y-F, Ji P-Y, Xu J-W, Hu Y-Q, Liu Q, Luo W-P, Guo C-C. *J Org Chem.* 2017; 82: 7159.

(9) HCHO could be produced by DMSO reacting with O_2 at high temperature under acidic condition, see ref. 7d and references therein.

Highlights:

metal-free Brønsted acid promoted quinoline synthesis

simple anilines, acetophenones and DMSO as the starting materials

air as a sole oxidant