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Acid-promoted metal-free synthesis of 3-ketoquinolines from amines, enaminones and DMSO

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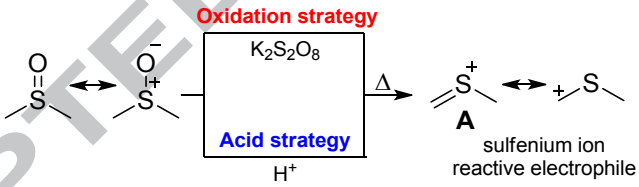
Abstract

A metal-free *p*-toluenesulfonic acid ($TsOH \cdot H_2O$) mediated synthesis of 3-ketoquinolines from anilines, enaminones and DMSO has been developed. In this transformation, DMSO was activated by $TsOH \cdot H_2O$ and provided the one-carbon unit of the 3-ketoquinolines. A plausible mechanism involving an electrophilic sulfenium ion intermediate was proposed.

Keywords: enaminones, DMSO, one carbon synthon, 3-ketoquinolines

1. Introduction

Dimethyl sulfoxide (DMSO) is an important aprotic polar solvent in organic synthesis and medicinal science due to its low toxicity, high solubility and ready availability.[1] In addition, it also has been widely used as an oxidant[2] and ligand.[3] In recent years, DMSO has attracted extensive interest as a versatile synthon donor which has expanded its applications.[4] For example, DMSO has been used as a sulfur source,[5] oxygen source[6] and one-carbon source.[7] In particular, strategies utilising DMSO as a one-carbon source to construct quinoline structures have attracted significant interest.[7c-d, 7h-j] Generally, DMSO can be activated in two ways under metal-free conditions to generate a reactive electrophilic intermediate sulfenium ion **A** *in situ* which could be easily captured by nucleophiles (Scheme 1). (i) Oxidation strategy: activation by a strong oxidant (e.g. $K_2S_2O_8$);[7] (ii) acid strategy: Pummerer rearrangement under acidic conditions.[8-10]

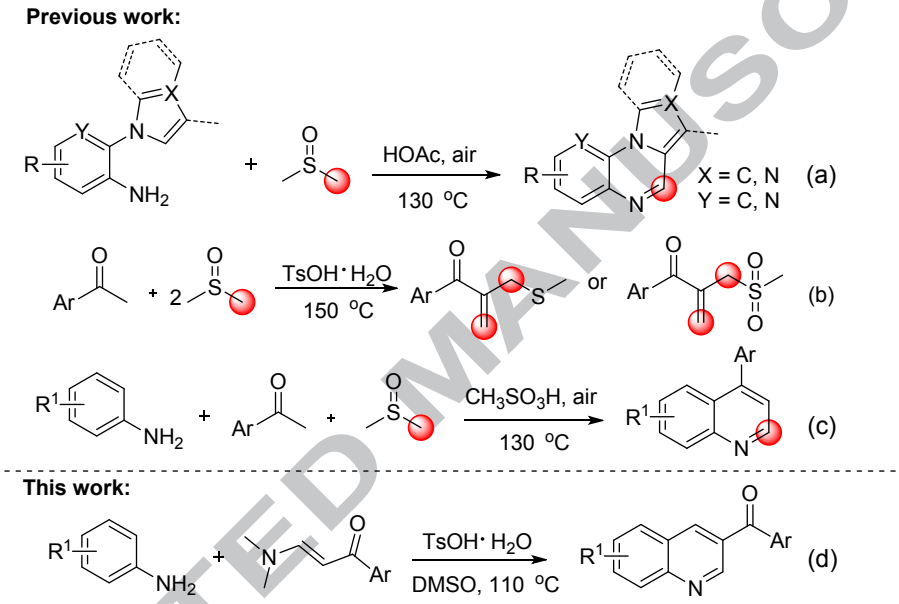


Scheme 1. Two methods for sulfenium ion **A** formation from DMSO.

There have been several reports regarding DMSO activation under metal-free conditions. In this respect, Ma and co-workers reported an efficient AcOH-promoted method to construct *N*-heterocycle-fused quinoxalines using DMSO as a one-carbon unit (Scheme 2a).[8] More recently, Wen and co-workers developed a novel acid-promoted, direct cross-coupling reaction of methyl ketones and DMSO to prepare β-acyl allylic methylsulfides and sulfones in which DMSO serves as a dual synthon (Scheme 2b).[9] Our group also reported an efficient CH_3SO_3H-promoted synthesis of 4-arylquinolines from readily available anilines and acetophenones using DMSO as a one-carbon unit under air (Scheme 2c).[10]

Quinolines are ubiquitous in pharmacologically and medicinally relevant

compounds. Various quinoline syntheses have been developed including classical named reactions[11] and transition metal-catalyzed coupling reactions.[12] However, the development of simple and efficient organic synthetic routes is still desirable (particularly metal-free procedures using readily available and inexpensive starting materials). Herein, we report a facile metal-free Brønsted acid-promoted synthesis of 3-ketoquinolines from anilines, enaminones and DMSO (Scheme 2d).



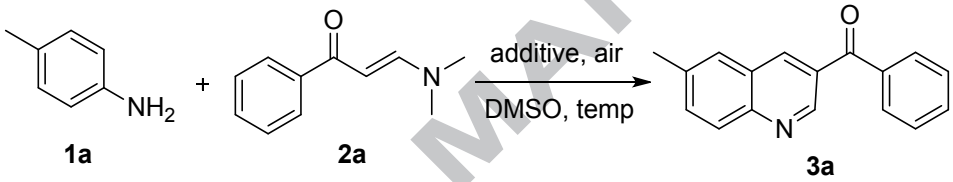
Scheme 2. Acid promoted DMSO activation and representative reactions.

2. Results and Discussion

We started by examining the model reaction of *p*-toluidine (**1a**), enaminone **2a**, CH_3SO_3H (1.0 equiv.) as the additive and DMSO (1 mL, also used as the solvent) at 120 ºC under air, in accordance with our previous work.[10] To our delight, 3-ketoquinoline **3a** was obtained in 30% isolated yield (Table 1, entry 1). Then different Brønsted acids were examined; TsOH·H_2O gave the best result and the desired product was isolated in 39% yield (Entry 2 vs. entries 1 and 2-7). The acid additive was determined to be necessary for this reaction (Entry 8). Next we examined the influence of the amount of the additive. When less than 1.0 equiv. of TsOH·H_2O was added, lower yields were obtained (Entries 9-10). Increasing the amount of TsOH·H_2O to 2.0 equiv. gave an improved 57% yield (Entry 12 vs. entries 11-13).

Gratifyingly, the yield was further improved to 69% (Entry 15) when the temperature was decreased to 110 ºC. Finally, prolonging the reaction time to 36 h did not increase the yield (Entry 17). Further attempts (e.g. changing the ratio of **1a** and **2a**, using mixed solvents) to improve the yield did not give better results (See ESI, Table 1). It should be noted that Wan and co-workers reported an unprecedented synthetic protocol to access 3-ketoquinolines *via* cleavage of the branched C=C and C=N bond in enaminones.[13] We therefore aimed to establish that DMSO was involved in the reaction, and other solvents (e.g. DMF, 1,4-dioxane, toluene) were examined (Entries 18-20) and the desired product **3a** was only obtained in DMF.[14]

Table 1. Optimization of the reaction conditions.[a]



1a **2a** **3a**

Entry	Additive (equiv.)	Temp (°C)	Yield **3a** (%)
1	CH_3SO_3H (1.0)	120	30
2	$TsOH·H_2O$(1.0)	120	39
3	D-CSA (1.0)	120	18
4	HOAc (0.1 mL)	120	trace
5	TFA (0.1 mL)	120	10
6	HCl(1.0)	120	trace
7	HCOOH(1.0)	120	NR
8	-	120	NR
9	$TsOH·H_2O$ (0.2)	120	15
10	$TsOH·H_2O$ (0.5)	120	26
11	$TsOH·H_2O$ (1.5)	120	46
12	$TsOH·H_2O$ (2.0)	120	57
13	$TsOH·H_2O$ (2.5)	120	53
14	$TsOH·H_2O$ (2.0)	130	52

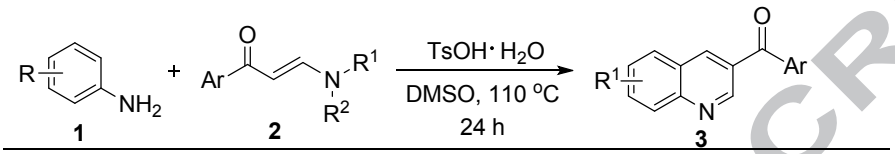
15	$TsOH·H_2O$ (2.0)	110	69
16	$TsOH·H_2O$ (2.0)	100	35
17[b]	$TsOH·H_2O$ (2.0)	110	68
18[c]	$TsOH·H_2O$ (2.0)	110	25
19[d]	$TsOH·H_2O$ (2.0)	110	NR
20[e]	$TsOH·H_2O$ (2.0)	110	NR

[a] Reagents and conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), additive, DMSO (1.0 mL), air, 24 h. [b] Reaction time was 36 h. [c] No DMSO, DMF (1.0 mL). [d] No DMSO, 1,4-dioxane (1.0 mL). [e] No DMSO, toluene (1.0 mL).

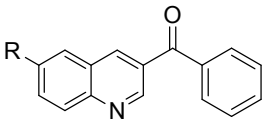
To illustrate the scope of this 3-ketoquinoline synthesis, the reactions of different anilines **1** and enaminones **2** were conducted under the optimized reaction conditions (Table 1, entry 15). As summarized in Scheme 3, a variety of anilines and enaminones with either electron-donating or electron-withdrawing groups afforded the desired products in good yields (**3a-z**). For anilines, electron-donating groups on the aromatic ring were generally preferable to weak electron-withdrawing groups which required heating at 130 ºC for 36 h (**3a-e**, **3j-m** vs **3f-g**). However, acetyl and hydroxyl substituted anilines, as well as pyridin-2-amine, were not suitable for this protocol (**3h-i**, **3n**). 3-Methylaniline gave the corresponding products in 77% yield, but as a mixture of two regioisomers **3j** and **3j'** in a ~5:1 ratio.

Then the scope of different enaminone partners with *p*-toluidine (**1a**) was explored. Various substituted enaminones gave the desired products (**3o-z**) in moderate to good yields (49-72%). To our delight, enaminones containing an iodine atom or a free hydroxyl group which could undergo further transformations were tolerated and afforded the corresponding 3-ketoquinolines **3t** (67%) and **3x** (55%), respectively. This protocol was also extended to heteroaryl enaminones including pyridine and thiophene, and moderate yields of the target products (**3y**, **3z**) were obtained. It should be noted that alkyl enaminones were not compatible with these reaction conditions.

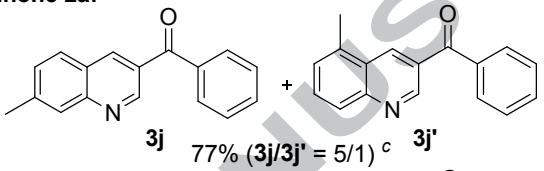
Finally, we examined the reactions of different *N*, *N*-substituted enaminones. Other *N*,*N*-disubstituted enaminones were suitable for this transformation and afforded the desired product **3a** in moderate yields (30-68%). Enaminones with primary and secondary amines were not suitable.



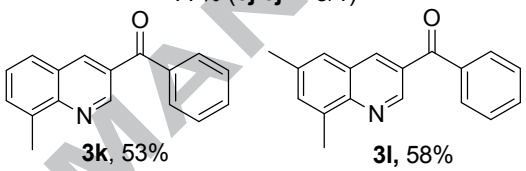
different anlines with enaminone 2a:



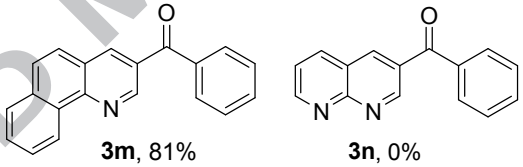
3a (R = CH_3), 69%
3b (R = H), 63%
3c (R = CH_3O), 58%
3d (R = Ph), 59%
3e (R = *i*-Pr), 73%
3f (R = F), 38% [b]
3g (R = Br), 40% [b]
3h (R = Ac), trace [b]
3i (R = OH), trace



3j 77% (**3j/3j'** = 5/1) [c] **3j'**

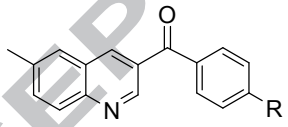


3k, 53% **3l,** 58%

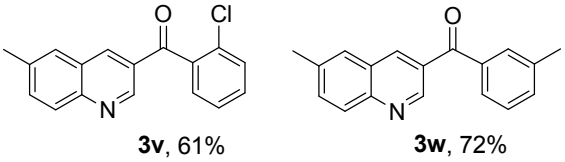


3m, 81% **3n**, 0%

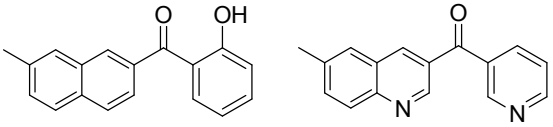
***p*-toluidine (1a) with different enaminones (R^1= R^2 = CH_3):**



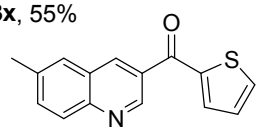
3o (R = CH_3O), 69%
3p (R = CH_3), 65%
3q (R = F), 62%
3r (R = Cl), 60%
3s (R = Br), 65%
3t (R = I), 67%
3u (R = NO_2), 49%



3v, 61% **3w**, 72%

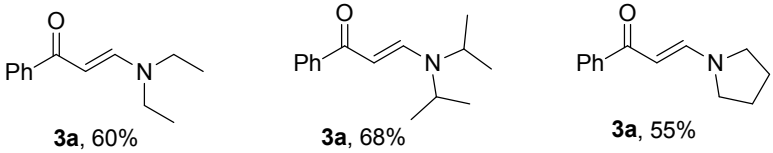


3x, 55% **3y**, 32%

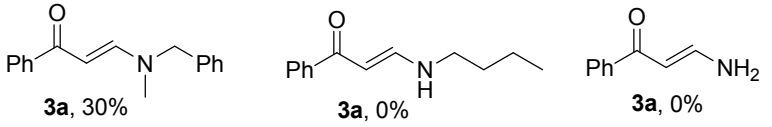


3z, 57%

3a was obtained from *p*-toluidine (1a) with different enaminones:



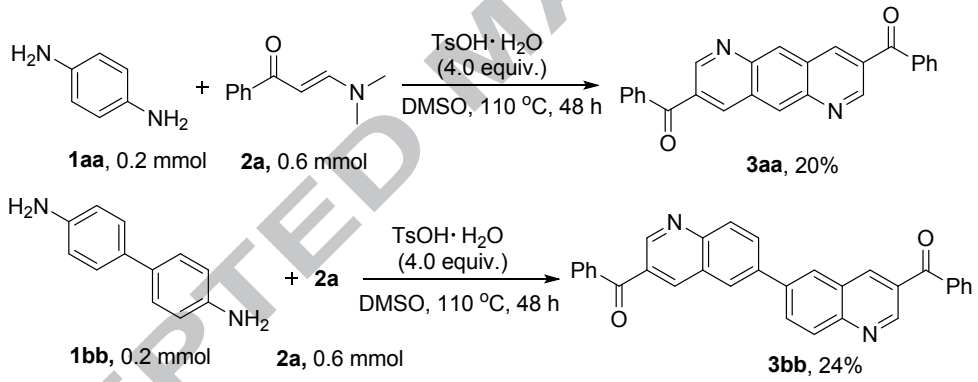
3a, 60% **3a**, 68% **3a**, 55%



3a, 30% **3a**, 0% **3a**, 0%

Scheme 3. Substrate scope. [a] Reagents and conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $TsOH \cdot H_2O$ (0.4 mmol), DMSO (1.0 mL), air, 110 ºC, 24 h. [b] 130 ºC for 36 h. [c] Ratio was determined by the ^1H NMR analysis.

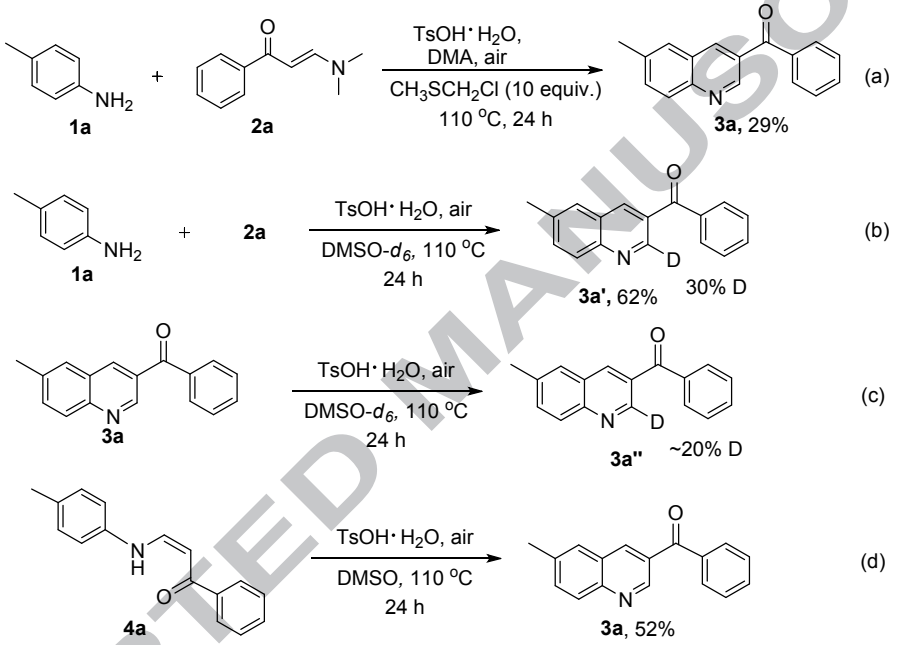
To demonstrate additional applications of this protocol, we examined the two-fold cyclization of 1,4-diaminobenzene (**1aa**) with enaminone **2a.** To our delight, the novel hetero-anthracene derivative **3aa** was obtained in 20% isolated yield. Although lower yielding, this method represents a simple synthesis of hetero-anthracene derivatives. Similarly, 4,4'-diaminobiphenyl (**1bb**) reacted with **2a** to give the corresponding product **3bb** in 24% isolated yield (Scheme 4).



Scheme 4. Reactions of diamino compounds with enaminone **2a.**

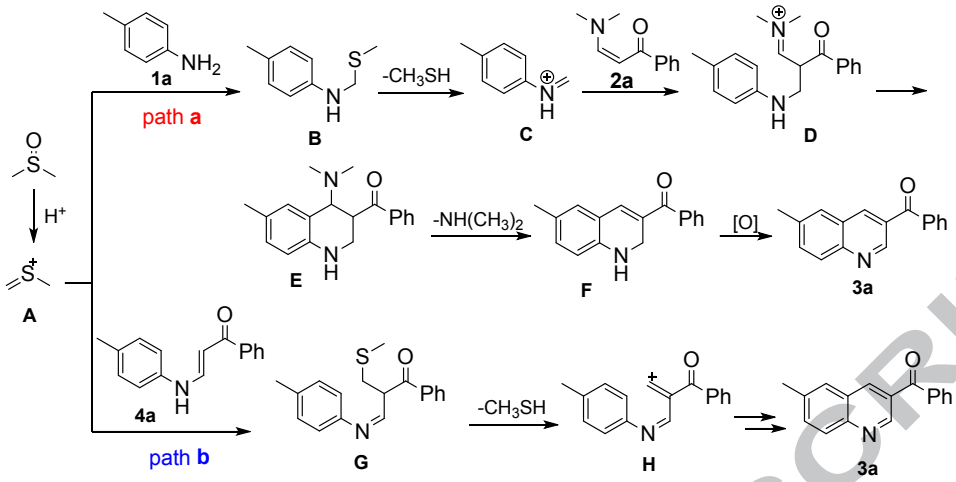
To understand the reaction mechanism and the position of the one-carbon unit, several control experiments were conducted (Scheme 5). Considering the *in situ* formed electrophilic intermediate sulfenium ion **A**,[9] the reaction was performed by adding chloromethyl methyl sulfide (10 equiv.) in the absence of DMSO, to give product **3a** in 29% yield (Scheme 5a). A deuterium-labeling experiment in DMSO-d_6 was carried out, and only 30% deuteration at the C-2 position was observed (Scheme 5b). Interestingly, when product **3a** was subjected to a deuterium-labeling experiment, product **3a″** was obtained with approximately 20% incorporation of deuterium at the C-2 position (Scheme 5c). These results indicated that DMSO provided the one-

carbon unit at the C-2 position of the desired product and H-D exchange of quinoline occurred under the acidic conditions.[15] However, enaminone intermediate **4a** was observed during the reaction and disappeared at the end.[16] The reaction of **4a** was performed under the standard reaction conditions, and surprisingly product **3a** was isolated in 52% yield which inferred that the one-carbon unit at the C-4 position of quinoline was derived from DMSO (Scheme 5d).



Scheme 5. Control experiments.

Plausible mechanisms (path a and path b) are shown below (Scheme 6). In path a, the *in situ* formed reactive intermediate **A** is attacked by **1a** to give intermediate **B** which undergoes demethylthioation to form iminium ion **C**. Then intermediate **D** is obtained *via* nucleophilic addition of enaminone **2a** to **C** and subsequent cyclization occurs to produce intermediate **E**. The elimination of $HNMe_2$ and subsequent oxidation leads to the formation of 3-ketoquinoline **3a**.[17] In path b, intermediate **G** which is formed from **A** and **4a** undergoes demethylthioation to form intermediate **H**, then subsequent cyclization and oxidation furnishes the desired product **3a**. Based on the above experiments, path a and path b both occur in this system.



Scheme 6. Proposed mechanism.

3. Conclusion

We have developed an efficient acid promoted synthesis of 3-ketoquinolines from anilines, enaminones and DMSO under metal-free conditions. In this protocol, DMSO was used as a one-carbon synthon. Mechanistically, DMSO may undergo a Pummerer rearrangement to generate a reactive electrophilic intermediate sulfenium ion **A** *in situ* under acidic conditions.

Acknowledgments

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A. Supplementary data

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

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Acid-promoted metal-free synthesis of 3-ketoquinolines from amines, enaminones and DMSO

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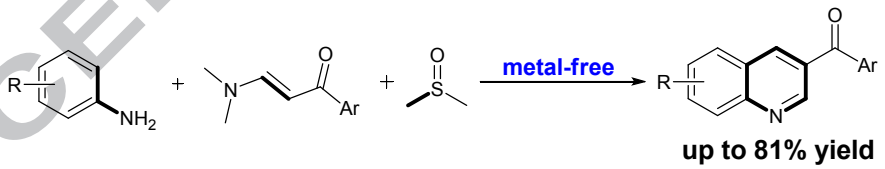

up to 81% yield

- Readily available starting materials
- DMSO serves a one-carbon unit
- Electrophilic sulfenium ion via Pummerer rearrangement

Highlights:

A metal-free synthesis of 3-ketoquinolines directly from anilines, enaminones and DMSO

DMSO was activated by the acid and provided the one-carbon unit

An easy synthetic route to hetero-anthracene derivatives.