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Chemoselective one-pot synthesis of β-keto sulfones from ketones†

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A practical method to synthesize substituted β-keto sulfones directly from ketones at room temperature has been developed. This method involves the nucleophilic addition of a base generated enolate to sulfonyl iodide. The reaction shows high chemoselectivity for the addition of a sulfonyl group to an α-carbon over a hydroxyl group. In addition, the given protocol provides good to excellent yields of β-keto sulfones under mild reaction conditions. Moreover, the regiochemical aspect of the protocol is also explored.

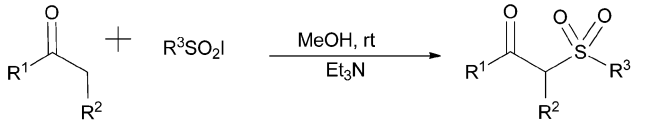
Introduction

Organo-sulfones are a highly important class of compounds in modern organic synthesis as the presence of a sulfonyl moiety in an organic compound aids in designing new complex structures/natural products and enhancing their biological activity.[1] Amongst the different derivatives of organo-sulfones, β-keto sulfones form a class of versatile intermediates in numerous transformations owing to the diverse reactivity of the active methylene sulfone[2] and ease of the removal of the sulfonyl group.[3] In the past β-keto-sulfones have been used as precursors in Michael[4] and Knoevenagel reactions.[5] Moreover, various useful compounds also have been prepared *via* the intermediacy of β-keto sulfones, like ketones *via* reductive desulfurization,[6] disubstituted acetylenes,[7] olefins,[7d] chalcones,[8] flavanones,[8] allenes,[9] vinyl sulfones,[10] amides,[11] aromatic amines,[12] polyfunctionalized 4*H*-pyrans,[4a,b] 2,3-dihydrofurans,[13] naphthols,[14] naphthalenes,[14] quinolines,[15] aryl 1*H*-1,2,3-triazol-4-yl sulfones,[16] 1,3-diketones,[17] epoxy sulfones,[18] α-halo β-keto sulfones,[19] α-halomethyl sulfones,[19b,20] and optically active β-hydroxy sulfones.[21] In addition, some of these derivatives also exhibit important biological activities like antifungicidal,[22] antibacterial[22b] and inhibiting 11β-hydroxysteroid dehydrogenase type 1.[23] Thus, the development of new efficient methods for β-keto sulfone synthesis continues to be a topic of immense importance.

Over the years a wide variety of procedures are available for the preparation of β-keto sulfones (see ESI†).[24] However, most of the methods are deficient in one or more aspect such as low yields, use of strong bases, multi-step synthesis, low functional group tolerance, prolonged reaction times, and the presence of side reactions, need for unavailable, expensive or toxic starting materials and harsh reaction conditions or complicated procedures involving high temperature or microwave heating. The use of inexpensive starting materials in a reaction emerged as an efficient and economical approach in modern organic synthesis. In this context ketones represent an ideal reagent for β-keto sulfone synthesis. In an attempt to address the aforementioned issues, Chen *et al.* reported the direct synthesis of β-keto sulfones from ketones *via in situ* generated α-tosyloxy ketones using a hypervalent iodine reagent – [hydroxy(tosyloxy)-iodo] benzene – followed by a reaction with sodium arenesulfinate.[25] However, this method also has limitations such as use of substrates with no oxidizable group[26] and the prohibitive price of [hydroxy(tosyloxy)iodo] benzene. Consequently, there remains a need for alternative straightforward strategies for the preparation of β-keto sulfones directly from cheap and commercially available ketones. In this regard, we herein report a one-pot chemoselective synthesis of β-keto sulfones directly from ketones (Scheme 1).

Results and discussion

The base mediated generation of an enolate from a ketone and their reaction with various electrophiles is one of the fundamental and most documented reactions in the literature.[27]



R^1, R^2 = alkyl, aryl or H
R^3= aryl

Scheme 1 Base mediated synthesis of β-keto sulfones directly from ketones.

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However, the related addition of an enolate to a sulfonyl halide leading to the formation of β-keto sulfones has not been studied so far. Initially, to optimize the reaction conditions we investigated which base and solvent system would work best for the reaction of the model substrate acetophenone (**1a**) with tosyl-iodide (**2**) (Table 1). As seen from Table 1, the reaction gave the desired product **3a** in 90% yield using Et_3N as the base in methanol (Table 1, entry 7). Further, the organic bases like Et_3N, piperdine or *N*-butyl amine (Table 1, entries 7–9) show better compatibility over the inorganic bases like K_2CO_3, Cs_2CO_3 or Ba_2CO_3 (Table 1, entries 1–3), due to the poor solubility of these bases in organic media.

Use of an excess amount of base, inert reaction conditions, higher temperatures (Table 1, entries 10 and 11) and longer reaction times (Table 1, entries 12 and 13) did not afford any better results. Carrying out the reaction in solvents like THF, DMSO, DMF, toluene, hexane and 1, 4-dioxane result in either no or poor yields (Table 1, entries 16–19, 21, 22) of **3a**. However, the reaction without solvent and with solvents like ethanol, water, ethyl acetate afforded the desired product **3a** in much better yields of 65, 78, 64, and 40%, respectively (Table 1, entries 14, 15, 20, 23).

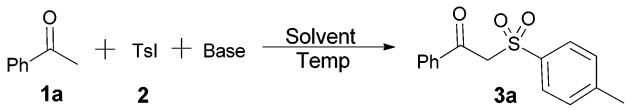
It is worth mentioning that no reaction took place without the base (Table 1, entry 24) and the output of the reaction lowered significantly when the reaction was performed in the presence of light and this can be attributed to the light sensitivity of tosyl iodide. Due to the stability issue associated with tosyl iodide as it is light sensitive, hygroscopic and commercially unavailable the given protocol was further investigated to consider the *in situ* generation of tosyl iodide. For this purpose a mixture of sodium *p*-toluenesulfinate (**4a**)–molecular iodine (1.2 : 1) was used in combination with Et_3N for the reaction with **1a** and to our delight a comparable 85% yield of **3a** was obtained (Table 1, entry 25). Furthermore, the reaction with tosyl bromide and tosyl chloride proved to be unfruitful, resulting in lower (32%) and no yields of **3a**, respectively (Table 1, entries 26 and 27).

After establishing the optimized reaction conditions, we further explored the generality and functional group compatibility of this reaction on various structurally diverse ketones, and the results are shown in Table 2.

As can be seen from the Table 2, the reaction proceeds smoothly with various aryl, alkyl and cyclic ketones with sodium *p*-toluenesulfinate (**4a**) and benzenesulfinic acid sodium salts (**4b**) to afford β-keto sulfones **3a–3v** in good to excellent yields. Notably, there is no appreciable difference in the yield with either of the two sulfinate salts. As seen from Table 2, the aromatic substituents have a minor effect on the yield of the reaction, for instance, ketones having a strong electron-donating substituent such as OMe in 1-(4-methoxyphenyl)-ethanone and a strong electron-withdrawing substituent such as NO_2 in 1-(4-nitrophenyl)ethanone provide the desired β-keto sulfones in high yield of **3e** and **3o** in 78 and 97%, respectively. However, output of the reaction favours ketones having electron withdrawing substituent and this can be attributed to aid of the inductive effect of the substituents on the ease of generation of the enolate.

Chemoselectivity has been a long standing challenge in β-keto sulfone synthesis as these compounds are either synthesized by oxidative methods[28] or by using strong bases.[29] Consequently, it is noteworthy to mention here that the present protocol shows high chemoselectivity for the addition of tosyl iodide towards α-carbon in the presence of a stronger nucleophile, such as the hydroxyl group in 1-(2-hydroxyphenyl)ethanone[30] to provide **3g** and **3h** with excellent yields, and in addition the di- or tri-sulfonylation of ketones are also not observed. Moreover, halide substituents on the aryl ring were well tolerated, hence giving potential for further functionalization of the aryl ring (Table 2, **3i–3n**, **3p**). Furthermore, the heteroaromatic ketones 1-(pyridin-2-yl)ethanone and 1-(thiophen-2-yl)ethanone also afforded the desired products **3q** and **3r** in good yields of 73 and 78%, respectively. Although most of the reactions were conducted using methanol as the solvent; some ketones like acetone and cyclohexanone also afforded the desired products in high yield even without solvent (Table 2, **3s–3v**).

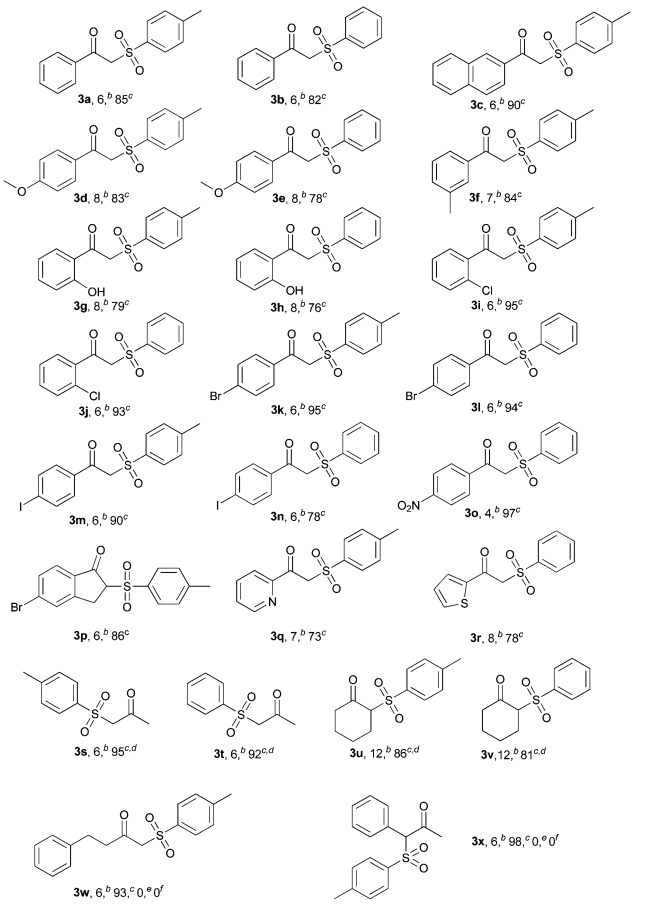
Table 1 Optimization of reaction condition for acetophenone **1a** with tosyl iodide **2**[a]



Entry	Base	Solvent	Time (h)	Yield[b] (%)
1	K_2CO_3	MeOH	6	15
2	Cs_2CO_3	MeOH	6	0
3	Ba_2CO_3	MeOH	6	5
4	DBU	MeOH	6	17
5	DABCO	MeOH	6	12
6	DMAP	MeOH	6	2
7	Et_3N	MeOH	6	90
8	Piperdine	MeOH	6	72
9	*n*-$BuNH_3$	MeOH	6	65
10	Et_3N	MeOH	6	50[c]
11	Et_3N	MeOH	6	25[d]
12	Et_3N	MeOH	8	90
13	Et_3N	MeOH	12	91
14	Et_3N	EtOH	6	78
15	Et_3N	H_2O	6	64
16	Et_3N	THF	6	39
17	Et_3N	DMSO	6	0
18	Et_3N	DMF	6	0
19	Et_3N	Toluene	6	15
20	Et_3N	EtOAc	6	40
21	Et_3N	Hexane	6	16
22	Et_3N	1,4-Dioxane	6	26
23	Et_3N	No solvent	6	65
24	No base	MeOH	6	0
25	Et_3N	MeOH	6	85[e]
26	Et_3N	MeOH	6	32[f]
27	Et_3N	MeOH	6	0[g]

[a] *Reaction conditions*: acetophenone (1 mmol), TsI (1.2 mmol) and base (1.2 mmol) in solvent (5 mL) at room temperature. [b] Isolated yield. [c] Temp. = 50 °C. [d] Temp. = 70 °C. [e] *Reaction conditions*: acetophenone (1 mmol), TsNa (1.2 mmol), I_2 (1 mmol) and base (1.2 mmol) in methanol (5 mL) at room temperature. [f] Reaction with tosyl bromide. [g] Reaction with tosyl chloride.

Table 2 Scope of synthesis of β-keto sulfones **3** from various ketones[a]



[a] *Reaction conditions*: ketone (1 mmol), TsNa (1.2 mmol), I_2 (1 mmol) and Et_3N (1.2 mmol) in 5 mL methanol at room temperature. [b] Time (h). [c] Isolated yield. [d] Reaction without solvent. [e] *Reaction conditions*: ketone (1 mmol), LDA (1.2 mmol in THF) at −78 °C for 1 h then TsI (1.2 mmol in THF) then room temperature for 16 h. [f] Ketone (1 mmol), TMSCl (1.2 mmol), DBU (1.2 mmol) in toluene at 60 °C for 4 h and then TsI (1.2 mmol) at room temperature for 6 h.

Further, we directed our attention towards the regioselectivity of the reaction. For this, tosyl iodide was made to react with the enolate that was generated from the unsymmetrical alkyl ketones (benzyl acetone and 1-phenylpropan-2-one) by two methods – one by using LDA at −78 °C and the other using a TMSCl generated silyl enolate at high temperature (60 °C) and the results are compared with the present protocol (see ESI†). The reaction of the LDA generated lithium enolate of the ketones at −78 °C does not result in the formation of the desired β-keto sulfones (Table 2, **3w–3x**), and this may be attributed to the fact that under these condition the sulfonyl halide tends to generate a halonium ion (electrophile), which on reaction with the enolate gives α-halogenated ketones.[31] However, only in the case of sulfonyl fluoride, due to the high electronegativity of fluorine, does the reaction result in β-keto sulfone formation, and this also tends to support our mechanism of the generated enolate reacting with sulfonyl iodide.[31b]

Further, the reaction of the generated silyl enolate of the ketones with tosyl iodide was not fruitful (Table 2, **3w–3x**), as reported by Kamigata *et al.*,[32] the sulfonyl chloride reacts only with silyl enolate in the presence of a ruthenium(II) phosphine complex and at high temperature to yield β-keto sulfones with the reaction pathway that involves an *in situ* generated electrophilic sulfonyl radical intermediate. Moreover, the reactions of these ketones using the protocol developed above results in the formation of one of the regio-isomer products preferentially over the other. However, this regio-selectivity is found to be substrate dependent, as in the case of benzyl acetone the exclusive formation of **3w** *via* the sulfonylation of the terminal alpha CH_3– carbon was observed, while 1-phenylpropan-2-one **3x** was formed exclusively *via* the sulfonylation of the internal alpha CH_2– carbon.

Based on the above results, it is conclusive that the equilibrium amount of the enolate generated from a ketone in the presence of triethylamine is most likely the species that reacts with the sulfonyl iodide to afford β-keto sulfone.

Conclusions

In conclusion, we have developed a highly chemoselective one-pot protocol for the synthesis of β-keto sulfones directly from ketones affording good to excellent yields of the desired products. The reaction proceeds *via* the nucleophilic addition of an enolate to sulfonyl iodide resulting in the cleavage of the S–I bond and consequently to the formation of β-keto sulfone. The reaction shows high chemoselectivity for the addition of the sulfonyl group to an α-carbon over the hydroxyl group. The notable advantages of this methodology over the existing procedures are simple operation, mild conditions, inexpensive and wide substrate scope, and so it is highly interesting from both an economical and scientific point of view.

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