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A facile one-pot synthesis of β-keto sulfones from ketones under solvent-free conditions

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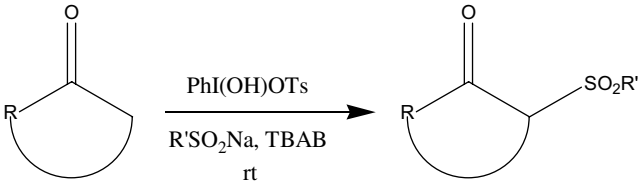
Abstract—An easy solvent-free method is described for the conversion of ketones into β-keto sulfones in high yields that involves the in situ generation of α-tosyloxyketones, followed by nucleophilic substitution with sodium arene sulfinate in the presence of tetrabutylammonium bromide at room temperature. The salient features of this one-pot protocol are short reaction times, cleaner reaction profiles, and simple work-up that precludes the use of toxic solvents.

β-Keto sulfones are an important class of compounds in organic synthesis.[1] Several useful compounds are prepared via the intermediacy of β-keto sulfones, such as olefins,[2] disubstituted acetylenes,[2] vinyl sulfones,[3] allenes,[4] and polyfunctionalized 4*H*-pyrans.[5] Facile reductive elimination of β-keto sulfones leads to the formation of ketones.[6] Additionally, β-keto sulfones are precursors for optically active β-hydroxy sulfones.[7] Some of the β-keto sulfones are found to possess fungicidal activity.[8] The common routes to β-keto sulfones involve oxidation of β-keto-sulfides,[9] reactions of sulfonyl chlorides with silyl enol ethers,[10] reactions of diazo sulfones with aldehydes,[11] alkylation of arene sulfinate salts with α-haloketones,[12] acylation of alkyl sulfones, reaction of alkyl sulfones with *N*-acylbenzotriazoles,[13] and a more recent approach involving the reaction of sulfonyl chloride with arylacetylenes.[14] Some of these methods require toxic substrates, multi-step synthesis, and prolonged reaction time, and yields of the products are moderate, at best. Consequently, there is a need for an alternative procedure involving milder reaction conditions. In the past, we have delineated the utility of hypervalent iodine reagents, particularly for the synthesis of heterocyclic compounds under solvent-free conditions.[15]

Organic reactions under solvent-free conditions are advantageous because of their enhanced selectivity and efficiency, ease of manipulation, cleaner product formation, and toxic or often volatile solvents are avoided.[16] Since many hypervalent iodine reagents have low solubility in most of the organic solvents, the development of solvent-free reactions will further widen the utility of these reagents in organic synthesis. In continuation of our interest to develop greener protocols, herein we report one-pot synthesis of β-keto sulfones from the corresponding ketones, using relatively benign [hydroxy(tosyloxy)iodo]benzene and sodium arene sulfinates in the presence of phase transfer catalyst under solvent-free conditions (Scheme 1). Initial efforts to synthesize β-keto sulfones by in situ generation of α-tosyloxyacetophenone from the reaction of acetophenone with [hydroxy(tosyloxy)iodo]benzene, followed by the



Scheme 1.

Keywords: β-Keto sulfones; Solvent-free synthesis; [Hydroxy(tosyloxy)iodo]benzene; Phase transfer catalyst.
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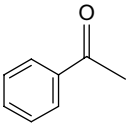
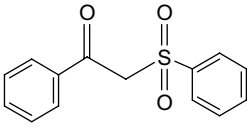
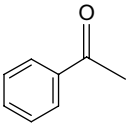
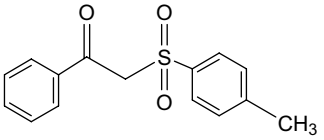
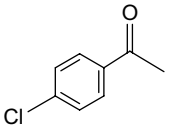
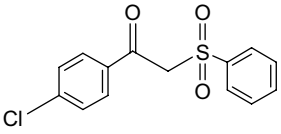
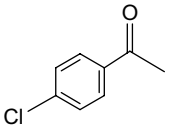
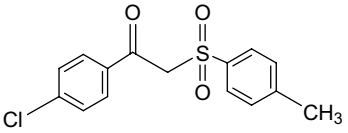
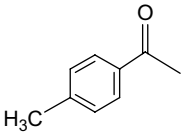
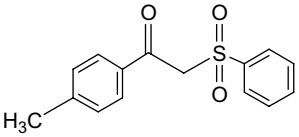
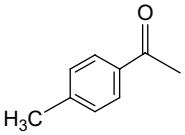
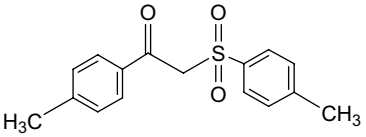
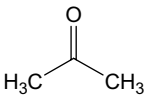
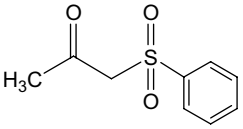
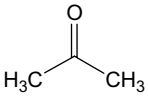
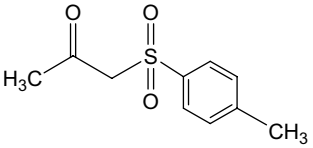
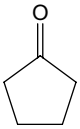
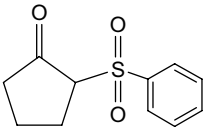
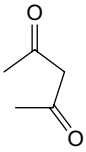
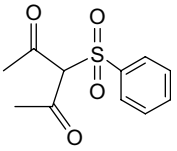
addition of sodium benzene sulfinate in the same pot, failed to generate the product; β-keto sulfones were not formed even in trace amounts after 48 h and upon using the excess of sodium benzene sulfinate. Encouraged by our synthesis of azides promoted by phase transfer catalysts (PTC), we explored the reaction by adding an equimolar quantity of tetrabutylammonium bromide (TBAB) to the above reaction mixture and intimately grinding the contents together for 3 min.[17] We observed exclusive and rapid formation of β-keto sulfones in high yields (Table 1, entry 1), as confirmed by their spectral analysis.[18] Various phase transfer catalysts, such as triethylbenzylammonium chloride, trimethylcetylammonium bromide, and tetrabutylammonium hydrogen sulfate, were also examined for this conversion. TBAB proved to be most effective in terms

Table 1. Synthesis of β-keto sulfones from ketones using hydroxy(tosyloxy)iodobenzene[a]

Entry	Substrate	Product	Time (min)	Yield[b] (%)
1			7	91
2			8	92
3			5	87
4			5	89
5			8	88
6			7	90
7			6	84
8			5	85
9			6	82
10			7	81

[a] Reactions conducted at room temperature using 1 mol equiv of TBAB.

[b] Yields refer to pure isolated products, which were identified by the comparison of IR and NMR spectral data with those of the known compounds.

of reaction time and yield of the product. The addition of PTC converts the solid reaction mixture to a semi-solid state, thus facilitating the attack of a nucleophile on the ensuing α-tosyloxyketone substrates. Further, the enhanced nucleophilicity of the $ArSO_2$ anion in the salt form, $ArSO_2N(t\text{-But})_4$, generated from TBAB and $ArSO_2Na$ may be responsible for the facile reaction.

Subsequently, the molar ratio of TBAB was varied and it was found that the 25 molar percentage is adequate to complete the reaction rapidly; with lesser amounts of TBAB, the reaction gets completed but takes longer time (10–48 h). The scope of this protocol was further extended for the synthesis of a variety of substituted β-keto sulfones (Table 1, entries 2–10). It was observed that all the ketones require almost the same reaction time, and yields are relatively better in the case of acetophenone and its derivatives.

In conclusion, we have developed a rapid, one-pot and high yielding protocol for the synthesis of β-keto sulfones from readily available ketones via in situ generation of α-tosyloxyketones, followed by nucleophilic substitution with sodium arene sulfinates, under solvent-free conditions.

Acknowledgments

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References and notes

1. Simpkins, N. S. In *Sulfones in Organic Synthesis*; Baldwin, J. E., Ed.; Pergamon Press: Oxford, 1993.
2. (a) Ihara, M.; Suzuki, S.; Taniguchi, T.; Tokunaga, Y.; Fukumoto, K. *Tetrahedron* **1995**, *51*, 9873; (b) Bartlett, P. A., ; Green, F. R., III; Rose, E. H. *J. Am. Chem. Soc.* **1978**, *100*, 4852; (c) Mandai, T.; Yanagi, T.; Araki, K.; Morisaki, Y.; Kawada, M.; Otera, J. *J. Am. Chem. Soc.* **1984**, *106*, 3670; (d) Lythgoe, B.; Waterhouse, I. *Tetrahedron Lett.* **1978**, *29*, 2625.
3. Sengupta, S.; Sarma, D. S.; Mondal, S. *Tetrahedron: Asymmetry* **1998**, *9*, 2311.
4. Baldwin, J. E.; Adlington, R. M.; Crouch, N. P.; Hill, R. L.; Laffey, T. G. *Tetrahedron Lett.* **1995**, *36*, 7925.
5. (a) Marco, J.-L.; Fernandez, I.; Khiar, N.; Fernandez, P.; Romero, A. *J. Org. Chem.* **1995**, *60*, 6678; (b) Marco, J. L. *J. Org. Chem.* **1997**, *62*, 6575.
6. (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1964**, *86*, 1639; (b) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, *27*, 3477; (c) Kurth, M. J.; O'Brien, M. J. *J. Org. Chem.* **1985**, *50*, 3846; (d) Fuju, M.; Nakamura, K.; Mekata, H.; Oka, S.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 495; (e) Sengupta, S.; Sarma, D. S.; Mondal, S. *Tetrahedron* **1998**, *54*, 9791; (f) Guo, H.; Zhang, Y. *Synth. Commun.* **2000**, *30*, 2564.
7. (a) Svatos, A.; Hunkova, Z.; Kren, V.; Hoskovec, M.; Sÿaman, D.; Valterova, I.; Vrkoc, J.; Koutek, B. *Tetrahedron: Asymmetry* **1996**, *7*, 1285; (b) Bertus, P.; Phansavath, P.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Touati, A. R.; Homri, T.; Hassine, B. B. *Tetrahedron: Asymmetry* **1999**, *10*, 1369; (c) Gotor, V.; Rebolledo, F.; Liz, R. *Tetrahedron: Asymmetry* **2001**, *12*, 513.
8. Wolf, W. M. *J. Mol. Struct.* **1999**, *474*, 113.
9. (a) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287; (b) Fan, A.-L.; Cao, S.; Zhang, Z. *J. Heterocycl. Chem.* **1997**, *34*, 1657.
10. Kamigata, N.; Udodaira, K.; Shimizu, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 783.
11. Holmquist, C. R.; Roskamp, E. J. *Tetrahedron Lett.* **1992**, *33*, 1131.
12. (a) Vennstra, G. E.; Zwaneburg, B. *Synthesis* **1975**, 519; (b) Wildeman, J.; Van Leusen, A. M. *Synthesis* **1979**, 733.
13. Katrizky, A. R.; Abdel-Fattah, A. A. A.; Wang, M. *J. Org. Chem.* **2003**, *68*, 1443.
14. Lai, C.; Xi, C.; Jiang, Y.; Hua, R. *Tetrahedron Lett.* **2005**, *46*, 513.
15. Varma, R. S.; Kumar, D.; Liesen, P. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4093.
16. (a) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025; (b) Varma, R. S. *Green Chem.* **1999**, 43; (c) Varma, R. S. *Pure Appl. Chem.* **2001**, *73*, 193.
17. Varma, R. S.; Naicker, K. P.; Kumar, D. *J. Mol. Catal. A: Chem.* **1999**, *149*, 153.
18. A representative procedure is as follows: A neat mixture of *p*-chloroacetophenone (1 mmol) and [hydroxy(tosyloxy)iodo]benzene (1.1 mmol) was ground together for 3 min, using a pestle and mortar at room temperature. Subsequently, sodium benzene sulfinate (1 mmol) and TBAB (0.25 mmol) were added, and the grinding process continued further for 2 min. The semi-solid reaction mixture was taken into water and extracted with dichloromethane (5 mL). Organic phase was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was percolated through a column of silica gel using ethyl acetate/hexane (1:9, v/v) as eluent to afford the pure product **3**, yield 91%, mp 130–32 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (2H, s, CH_2), 7.45–7.71 (5H, m, Ar–H), 7.81–7.94 (4H, m, Ar–H); ^{13}C NMR ($CDCl_3$) δ 186.81, 141.17, 138.56, 134.36, 134.05, 130.74, 129.27, 129.24, 128.54, 63.61. Compound **4**, yield 89%, mp 136–38 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (3H, s, CH_3), 4.68 (2H, s, CH_2), 7.35 (2H, dd, $J = 1.8$, 7.2 Hz, Ar–H), 7.47 (2H, dd, $J = 1.8$, 6.9 Hz, Ar–H), 7.75 (2H, dd, $J = 1.8$, 6.6 Hz, Ar–H), 7.91 (2H, dd, $J = 1.8$, 6.6 Hz, Ar–H); ^{13}C NMR ($CDCl_3$) δ 186.99, 145.54, 141.10, 135.59, 134.11, 130.78, 129.89, 129.20, 128.55, 63.77, 21.70.