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Solvent-free facile synthesis of novel α-tosyloxy β-keto sulfones using [hydroxy(tosyloxy)iodo]benzene

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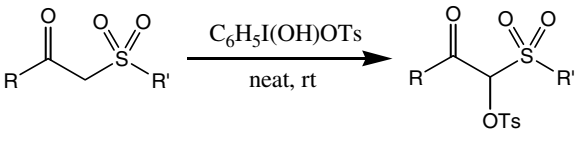
Abstract—A facile, general and high yielding protocol for the synthesis of novel α-tosyloxy β-keto sulfones is described utilizing relatively non-toxic, [hydroxy(tosyloxy)iodo]benzene, under solvent-free conditions at room temperature.

β-keto sulfones are an important group of valuable precursors in the synthesis of potentially bioactive molecules.[1] Compounds bearing sulfonyl functionality exhibit a range of pharmacological activities and are useful intermediates in the synthesis of a wide variety of heterocyclic compounds.[1] Further α-halogenation of β-keto sulfones followed by base-induced cleavage leads to the preparation of α-halo methylsulfones and α,α-dihalo methylsulfones, which are useful precursors for the synthesis of alkenes, epoxides and aziridines.[2] Recently, the synthesis of α-iodo β-keto sulfones, a building block for medicinally important α-iodo methylsulfones, has been achieved by the reaction of β-keto sulfones with iodine monochloride in acetic acid.[3] In yet another report, in situ generated α-bromo β-keto sulfones from phenyl trimethyl ammonium tribromide has been utilized in the synthesis of 2-amino-4-aryl-5-aryl-sulfonyl thiazoles.[4] However, to the best our knowledge, there is no literature report dealing with the synthesis of hitherto unknown α-tosyloxy β-keto sulfones which may be potentially very useful precursors in organic synthesis.

Hypervalent iodine reagents are widely used in organic synthesis and have attracted significant attention of organic chemists due to their simple experimental operation and low toxicity as they avoid the utility of transition metals commonly involved in such processes.[5] Particularly, [hydroxy(tosyloxy)iodo]benzene [HTIB], also known as Koser's reagent, is a useful entity for the α-tosyloxylation of ketones which serve as precursors for the construction of several heterocyclic compounds.[6] Koser and co-workers have found HTIB to be an effective reagent for one-step conversion of enolizable ketones to the corresponding α-tosyloxyketones.[6] Reactions for α-tosyloxylation of ketones have benefited by the use of silyl enol ethers although such reactions require longer time and the starting materials are often difficult to synthesize. Another common multi-step synthesis involves the reaction of α-hydroxyalkyl ketones with sulfonyl chloride.[7] The ultrasound promoted reaction of ketone with HTIB further improved reaction time and product yield.[8] However, most of the reported procedures for α-functionalization of β-keto sulfones require longer reaction times under refluxing conditions and afford products in moderate yields. In view of our recent endeavours in synthesizing β-keto sulfones under solventless benign conditions,[9] and because of our continued interest in the application of ensuing β-keto



Scheme 1.

Keywords: α-Tosyloxy β-keto sulfones; β-Keto sulfones; Solvent-free synthesis; [Hydroxy(tosyloxy)iodo]benzene.
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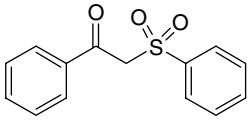
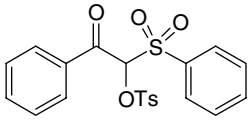
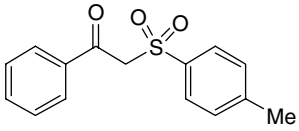
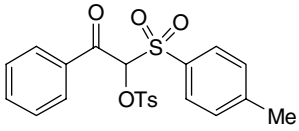
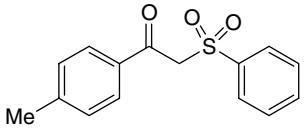
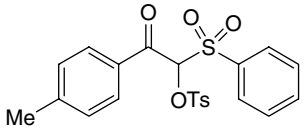
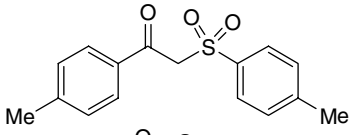
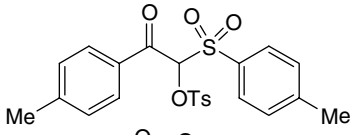
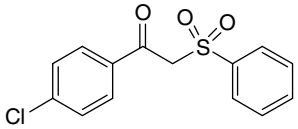
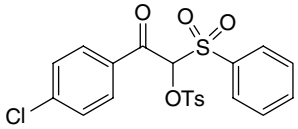
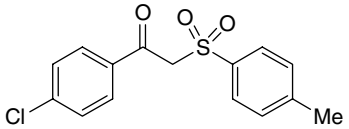
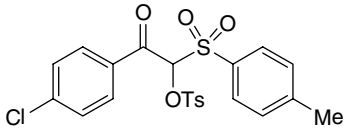
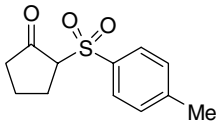
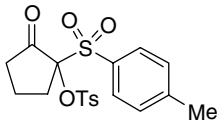
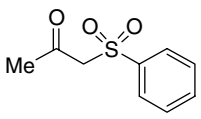
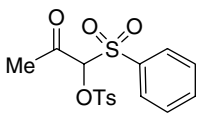
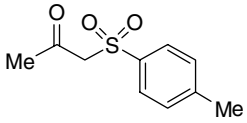
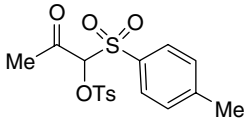
sulfones and the potential of related α-tosyloxy β-keto sulfones in organic synthesis, we report herein a useful HTIB-mediated α-tosyloxylation of β-keto sulfones that proceeds effortlessly under solvent-free conditions (Scheme 1).

Solvent-free reactions are advantageous as they prevent pollution 'at-source', and are often economical with the associated ease of operational simplicity.[10] Many organic solvents, especially halogenated ones, are ecologically deleterious. Consequently, minimum usage of toxic reagents and volatile solvents is central towards the development of benign chemical processes. Furthermore, application of hypervalent iodine reagents will be the primary beneficiary of solvent-free conditions because of their low solubility in most of the organic solvents.

The simple procedure, in its entirety, involves grinding together a neat mixture of α-benzenesulfonyl-acetophenone and HTIB at room temperature using a pestle and mortar. Within 5 min, the reaction led to the formation of α-tosyloxybenzenesulfonylacetophenone in 94% yield (entry 1) via the formation of a eutectic semi-liquid phase. Encouraged by such a facile reaction, various β-keto sulfones were treated with HTIB and invariably in all cases pure α-tosyloxy β-keto sulfones were obtained in excellent yields (Table 1). The α-tosyloxylation of β-keto sulfones under these solvent-free conditions proceeded with very high efficiency. It was observed that alkyl and aryl β-keto sulfones (Table 1, entries 1–6, 8–9) were almost equally reactive towards HTIB, however, α-*p*-methylbenzenesulfonyl cyclopentanone (Table 1, entry 7) was relatively less reactive. In

Table 1. Synthesis of α-tosyloxy β-keto sulfones using [hydroxy(tosyloxy)iodo]benzene

Entry	β-Keto sulfones	Products[a]	Time (min)	Yield[b] (%)
1			7	94
2			9	92
3			6	94
4			5	90
5			5	90
6			5	86
7			10	72
8			4	85
9			5	88

[a] Satisfactory spectral data were obtained on all the products.
[b] Isolated yields after crystallization/chromatography.

contrast, the reaction of α-benzenesulfonyl-acetophenone and HTIB in acetonitrile at room temperature required 5 h for completion. Interestingly, mixing of β-keto sulfones and HTIB via grinding is essential for the success of reaction as the homogeneous mixture of β-keto sulfones and HTIB failed to generate the product at room temperature (after keeping the reaction mixture for 10 h only trace amount of the product was formed and the reaction remains incomplete even after 48 h).[11]

In conclusion, we have developed an efficient and general mechanochemical synthetic route to various novel α-tosyloxy β-keto sulfones that proceed expeditiously and deliver high yields of pure products under solvent-free conditions. Further applications of these α-tosyloxy β-keto sulfones are currently being explored in our laboratory for the rapid assembly of various heterocyclic compounds of therapeutic interests and will be reported in due course.

Typical experimental procedure: A mixture of α-*p*-methylbenzenesulfonyl acetophenone (0.087 g, 0.32 mmol) and [hydroxy(tosyloxy)iodo]benzene (0.140 g, 0.35 mmol) was placed in a mortar. The reaction mixture was ground together using a pestle at room temperature for 9 min wherein the contents turned to light yellow in color. After completion of the reaction, as monitored by TLC, the residue was triturated with hexane followed by crystallization from ethanol to afford the pure product in 92% yield, entry 2, Table 1, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (3H, s, CH_3), 2.48 (3H, s, CH_3), 6.37 (1H, s, CH), 7.20–7.36 (4H, m, Ar–H), 7.47–7.52 (2H, m, Ar–H), 7.62–7.71 (5H, m, Ar–H), 8.05–8.08 (2H, d, $J = 8.10$ Hz, Ar–H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 19.58, 19.74, 87.35, 126.41, 126.54, 126.72, 127.21, 127.47, 127.65, 127.79, 127.95, 129.65, 129.74, 132.24, 132.47, 143.91, 144.48, 184.42.

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