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COMMUNICATION

Iodination of β-keto-sulfones using molecular iodine and hydrogen peroxide in aqueous medium: facile synthesis of α-iodomethyl sulfones

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The reaction of β-keto-sulfones with molecular iodine in the presence of aqueous acidic hydrogen peroxide yielded α-iodo β-keto-sulfones, which on treatment with aqueous alkali at room temperature underwent base-induced cleavage to afford corresponding α-iodomethyl sulfones in excellent yields.

Keywords: β-Keto-sulfones; α-Iodomethyl sulfones; Iodination

1. Introduction

Sulfones are of great importance in organic synthesis. The presence of sulfone group in an organic compound adds variety to its chemical architecture [1] and also enhances the biological activity of the compound. Among sulfones, α-halomethyl sulfones, α, α-dihalomethyl sulfones are excellent α-carbanion stabilizing substituents [2], as they are precursors for the preparation of alkenes [3–4], aziridines [5] and epoxides [6–9]. Makosza *et al.* utilized chloromethyl phenyl sulfones and chloromethyl *p*-tolyl sulfones in vicarious nuclephilic substitution (VNS) reactions with nitro arenes to afford VNS adducts [10–13]. These adducts have been elaborated into both 3-sulfonyl substituted indole derivatives and the analogues indazoles [14]. In addition, haloalkyl sulfones are useful in preventing aquatic organisms from attaching to fishing nets and shiphulls [15], in herbicides compositions [16] and also used as bactericidal [17], anti fungal [18], algaecides [19] and insecticides [20]. Although the methods of synthesis of α-halomethyl sulfones and α, α-dihalomethyl sulfones have been reported in literature [21–25], the synthesis of

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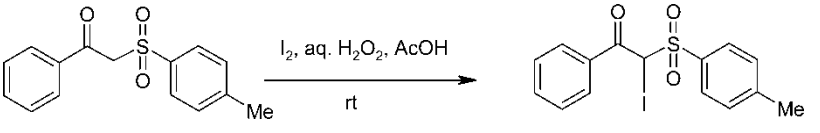
α-iodomethyl sulfones is less thoroughly investigated. The α-halo β-keto-sulfones and α-halomethyl sulfones (Halo = Cl or Br) do not undergo Finklestein reaction [26, 27] to yield α-iodo β-keto-sulfones and α-iodomethyl sulfones due to the strong retardation effect of the sulfone group [28, 29]. Kirihara *et al.* reported chemoselective bromination of active methylene and methine compounds using potassium bromide in the presence of hydrogen peroxide [30]. Recently, we have reported the facile synthesis of β-keto-sulfones and direct synthesis of α-iodo β-keto-sulfones and their base-induced cleavage to afford α-iodomethyl sulfones [31–34]. A literature survey revealed that the halogenation of β-keto-sulfones involves electro-positive halogen atom [25], which can readily provide iodine in the presence of hydrogen peroxide. In this connection, herein we report the synthesis α-iodomethyl sulfones by the reaction of β-keto-sulfones with molecular iodine in the presence of aqueous hydrogen peroxide followed by base-induced cleavage.



SCHEME 1

2. Results and discussion

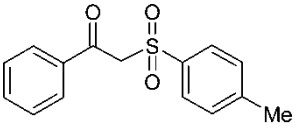
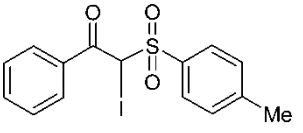
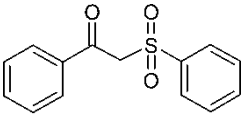
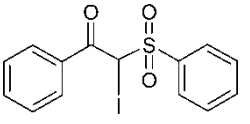
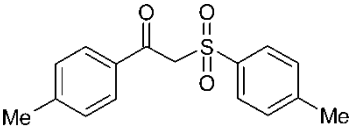
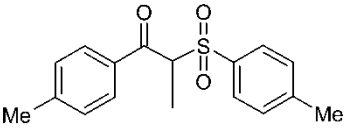
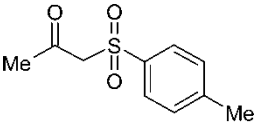
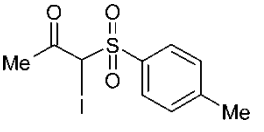
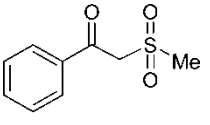
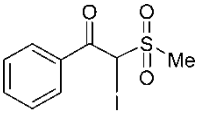
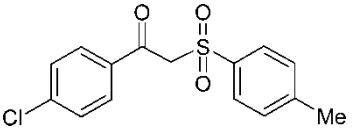
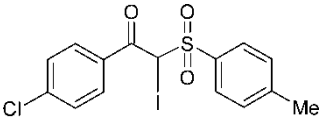
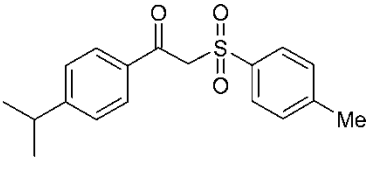
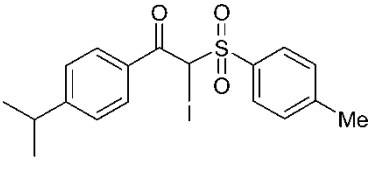
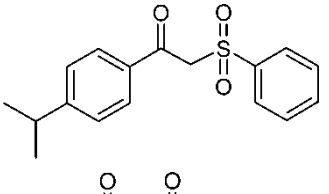
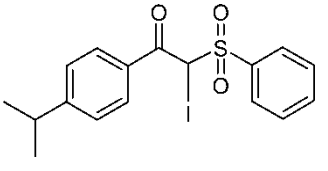
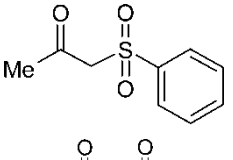
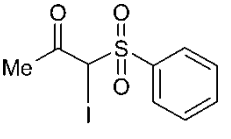
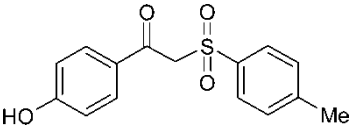
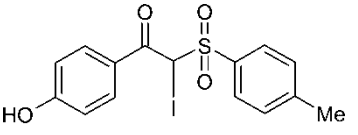
In this letter (scheme 1), we describe a facile synthesis of α-iodomethyl sulfones. This method is very inexpensive and no organic solvent used as reaction medium. The reaction proceeded efficiently and smoothly at room temperature and the products are obtained in excellent yields. Initially, *p*-toluene sulfonyl acetophenone (β-keto-sulfone) was reacted with molecular iodine in the presence of 10 equiv. of hydrogen peroxide in aqueous acetic acid medium to give the corresponding α-iodo β-keto-sulfone in 30 min in 100% yield. Encouraged by this result, we extended the generality of the reaction with different β-keto-sulfones to yield corresponding α-iodo β-keto-sulfones (scheme 1, table 1). Further, α-iodo β-keto-sulfones on treatment with aqueous alkali underwent base-induced cleavage to give α-iodomethyl sulfones in excellent yields (scheme 2, table 2).

It has been observed that, in the absence of acetic acid and hydrogen peroxide, the reaction do not proceed even after 24 h, indicating that the reaction proceeds through enolization of β-keto-sulfones followed by attack of halonium ion (scheme 3). The formation of halo products was characterized by their ^{1}H NMR spectral data. For example, the formation of α-iodo β-keto-sulfones is noticed by a downfield chemical shift of the methylene proton of *p*-toluenesulfonylacetophenone (table 1, entry 1) from δ 4.56 to around δ 6.50 in α-iodo *p*-toluenesulfonylacetophenone. Further, the methylene protons in iodomethyl *p*-toluylsulfones resonates at ∼δ 4.40 (table 2, entry 1).

3. Conclusion

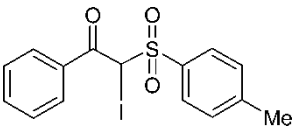
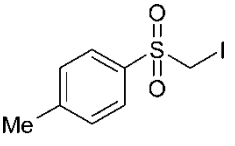
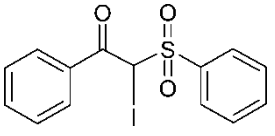
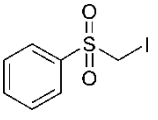
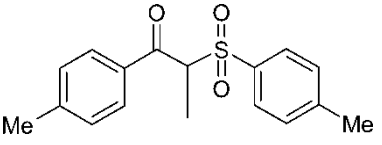
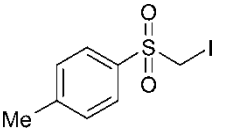
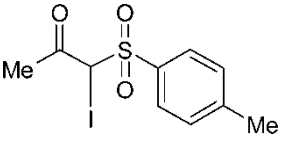
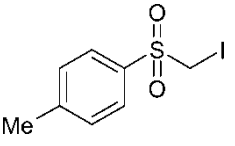
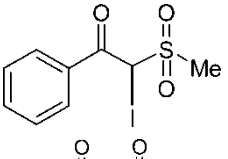
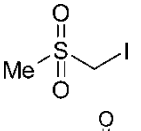
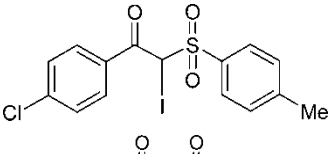
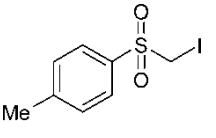
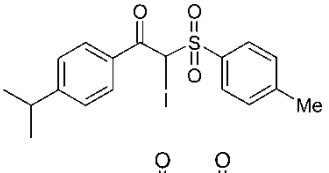
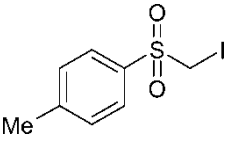
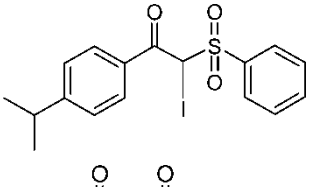
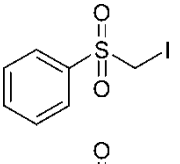
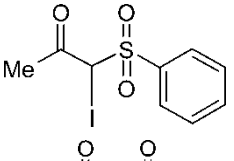
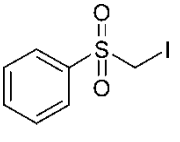
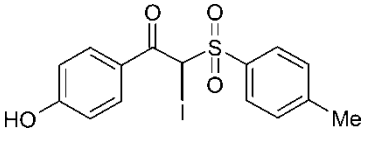
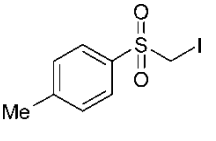
In conclusion, we have described a facile synthesis of various α-iodo β-keto-sulfones and α-iodomethyl sulfones, by the reaction of β-keto-sulfones with molecular iodine in the presence of hydrogen peroxide followed by a base-induced cleavage.

Table 1. Synthesis of α-iodo β-keto-sulfones using molecular iodine and hydrogen peroxide in aqueous acidic medium.

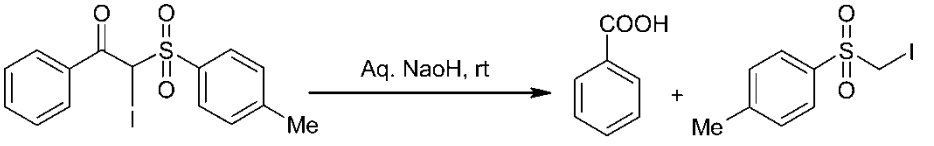
Entry	Substrate	Product[b]	Time (min)	Yield (%)[a]
1			30	100
2			30	99
3			30	96
4			30	95
5			45	96
6			45	94
7			45	92
8			30	96
9			30	94
10			60	95

[a]Isolated yields after column chromatography.
[b]All products gave satisfactory spectral data (^{1}H NMR, Mass)

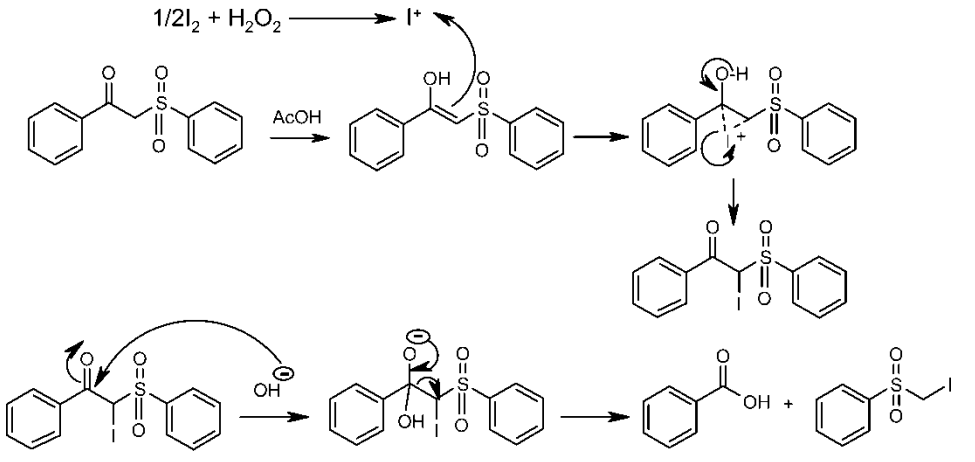
Table 2. Synthesis of α-iodomethyl sulfones via base induced cleavage in aqueous NaOH.

Entry	Substrate	Product[b]	Time (min)	Yield (%)[a]
1			30	90
2			30	90
3			30	85
4			30	95
5			30	95
6			30	90
7			30	92
8			30	95
9			30	89
10			30	95

[a]Isolated yields after column chromatography.
[b]All products gave satisfactory spectral data (^{1}H NMR, Mass)



SCHEME 2



SCHEME 3 Plausible mechanism.

4. Experiment

4.1 *Synthesis of α-iodo β-keto-sulfones*

To an aqueous solution (10 mL) of β-keto-sulfone (1 mmol) was added molecular iodine (0.6 mmol) in acetic acid (0.5 mL), and hydrogen peroxide (30% v/v) (10 mmol). The mixture was stirred at room temperature for an appropriate time (table 1). After completion of the reaction as monitored by TLC, the reaction mixture was diluted with water (10 mL) and the product was extracted into ethyl acetate (3 × 15 mL). The combined extract was dried over anhydrous sodium sulphate and evaporated to give the corresponding crude α-iodo β-keto-sulfones, which was purified on silica gel column to obtain pure products. Table 1 entry 1. α-iodo *p*-toluenesulfonylacetophenone: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.5 (s, 3H, CH_3), 6.45 (s, 1H, CH), 7.40 (d, 2H, J = 8.4 Hz, Ar-H), 7.45 (d, 2H, J = 8.4 Hz, Ar-H), 7.49 (t, 1H, J = 2.4 Hz, J = 8.4 Hz Ar-H), 7.75 (d, 2H, J = 8.4 Hz, Ar-H), 7.85 (d, 2H, J = 8.4 Hz, Ar-H); EIMS. m/z = 401 ($M^{+\cdot}$ + 1).

4.2 *Synthesis of α-iodomethyl sulfones*

The crude α-iodo β-keto-sulfone was stirred with 10% aq NaOH (W/V) for 30 min. After completion of the reaction as monitored by TLC, the reaction contents were extracted into diethyl ether (3 × 15 mL). The combined extract was dried over anhydrous sodium sulfate and evaporated to give the corresponding crude α-iodomethyl sulfone, which was purified on a silica gel column. Table 2, entries 1, 3, 4, 6, 7 and 10: α-Iodomethyl *p*-tolyl sulfone: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.50 (s, 3H, CH_3), 4.41 (s, 2H, CH_2), 7.40 (d, 2H, d, J = 8.4 Hz, Ar-H), 7.85 (2H, d, J = 8.4 Hz, Ar-H); EIMS m/z M^+ = 296. Table 2, entries 2, 8 and 9: α-Iodomethyl phenyl sulfone: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.40 (s, 2H, CH_2), 7.42 (d,

2H, $J = 8.5$ Hz, Ar-H), 7.50 (m, 1H, $J = 8.4$, 2.5 Hz Ar-H), 7.85, (d, 2H, $J = 8.5$ Hz, Ar-H); EIMS: $m/z = 283(M^{+\cdot} + 1)$. Table 2, entry 5: α-Iodomethyl methyl sulfone: ^{1}H NMR (300 MHz, $CDCl_3$) δ3.40 (s, 3H, CH_3), 4.39 (s, 2H, CH_2); EIMS $m/z = 221(M^{+\cdot} + 1)$.

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