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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 877–881

Chemoselective mono halogenation of β-keto-sulfones using potassium halide and hydrogen peroxide; synthesis of halomethyl sulfones and dihalomethyl sulfones☆

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Received 5 October 2006; revised 15 November 2006; accepted 22 November 2006
Available online 12 December 2006

Abstract—The synthesis of α-halo β-keto-sulfones using potassium halide and hydrogen peroxide as a chemoselective mono halogenation reagent and the synthesis of α,α-symmetrical and asymmetrical dihalo β-keto-sulfones and α-halo, α-alkyl and β-keto-sulfones is described. Base induced cleavage of α-halo β-keto-sulfones, α,α-dihalo β-keto-sulfones, and α-halo, α-alkyl β-keto-sulfones afforded the corresponding halomethyl sulfones, dihalomethyl sulfones and haloalkyl sulfones.

1. Introduction

β-Keto-sulfones are a very important group of intermediates[1] as they are precursors for Michael and Knoevenagel reactions[2,3] and are used in the preparation of acetylenes, allenes, chalcones,[4–9] vinyl sulfones,[10] polyfunctionalized 4*H*-pyrans[11] and ketones.[12] In addition, β-keto-sulfones can be converted into optically active β-hydroxy-sulfones,[13] halomethyl sulfones and dihalomethyl sulfones.[14] Halomethyl sulfones and dihalomethyl sulfones are very good α-carbanion stabilizing substituents[15] and precursors for the preparation of alkenes,[16] aziridines,[17] epoxides,[18] and β-hydroxy-sulfones,[13d] and have also been used as VNS adducts.[19] Haloalkyl sulfones are useful in preventing aquatic organisms from attaching to fishing nets and ship hulls.[20] They also possess other biological properties such as herbicidal,[21] bactericidal,[22] antifungal,[23] algaecidal[24] and insecticidal.[25]

α-Halo β-keto-sulfones and α,α-dihalo β-keto-sulfones[14] have been obtained by halogenation of β-keto-sulfones with halogenating reagents such as pyridinium perbromate, bromine and sulfuryl chloride in chloroform/dichloromethane. However, the α-chloro/bromo β-keto-sulfones and chloro/bromomethyl sulfones do not undergo Finkelstein reactions[26] to afford iodomethyl sulfones, due to a strong retardation effect by the sulfone; hence, the synthesis of iodomethyl sulfones has proved difficult.[27] To the best of our knowledge, α,α-asymmetrical dihalo β-keto-sulfones have not been synthesized so far.[14,28] Recently, we reported the synthesis of β-keto-sulfones and the direct synthesis of α-iodo β-keto-sulfones and iodomethyl sulfones.[29] In continuation of our work, we envisaged the chemoselective mono halogenation of β-keto-sulfones using potassium halide in the presence of hydrogen peroxide and the synthesis of α,α-symmetrical and asymmetrical dihalo β-keto-sulfones, α-halo, α-alkyl β-keto-sulfones and their corresponding base-induced cleavage products.

Halogenation of β-keto-sulfones requires electropositive halogen, which can be readily provided by potassium halide[30] in the presence of hydrogen peroxide. α-Iodo β-keto-sulfone **2** was prepared by the reaction of **1** with KI in the presence of hydrogen peroxide in acetic acid at room temperature; similarly the α-chloro and α-bromo β-keto-sulfones were prepared by reaction with KCl and KBr, respectively (Scheme 1, Table 1). In all cases, mono halogenation occurred selectively at the methylene carbon of the β-keto-sulfones and no by-products

Keywords: α-Halo β-keto-sulfones; α,α-Dihalo β-keto-sulfones; α-Halomethyl sulfones; α,α-Dihalomethyl sulfones; Potassium halide; Hydrogen peroxide.
☆ IICT Communication No. 061003.
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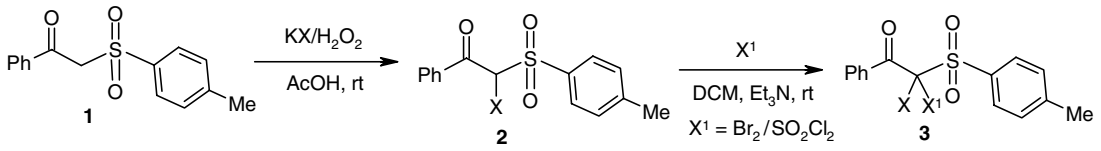
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.11.129



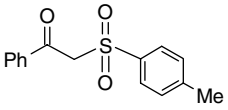
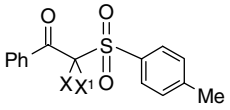
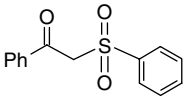
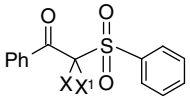
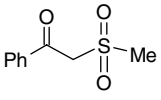
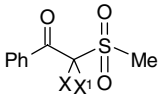
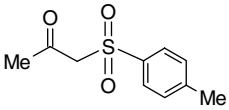
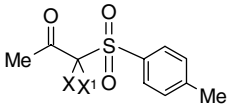
Scheme 1.

were observed. In contrast, halogenation of *p*-toluylsulfonylacetone (Table 1, entry 4) with Br_2 or SO_2Cl_2 gave 2-bromo/chloro *p*-toluylsulfonylacetone and 4-bromo/chloro *p*-toluylsulfonylacetone.

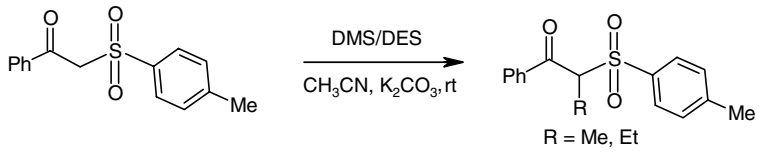
α,α-Symmetrical dihalo β-keto-sulfones can be prepared using reagents such as SO_2Cl_2 or Br_2 in the presence of one equiv of Et_3N as base in DCM. α,α-Asymmetrical dihalo β-keto-sulfones, for example, α-bromo, α-chloro β-keto-sulfones, can be prepared by treatment of α-chloro β-keto-sulfones with Br_2 in DCM in the presence of triethylamine or by reaction of α-bromo β-keto-sulfones with SO_2Cl_2 in DCM in the presence of triethylamine with equal ease. The α-iodo, α-chloro β-keto-sulfones and α-iodo, α-bromo β-keto-sulfones **3** were prepared by treatment of α-iodo β-keto-sulfones with SO_2Cl_2 and Br_2, in DCM in the presence of Et_3N, respectively (Scheme 1, Table 1).

The α-halo, α-alkyl β-keto-sulfones were synthesized by C-alkylation of β-keto-sulfones with alkylating reagents such as dimethyl sulfate (DMS) or diethyl sulfate (DES) in acetonitrile in the presence of K_2CO_3 (Scheme 2), followed by halogenation (Scheme 1) with potassium halide in the presence of hydrogen peroxide in excellent yields (Table 1, entries **1i–l** and **2i–l**).

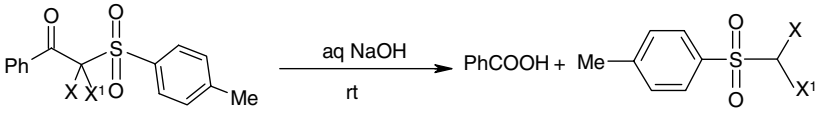
Table 1. Synthesis of α-halo β-keto-sulfones and α,α-dihalo β-keto-sulfones

Entry	Substrate	Product			Time (h)	Yield[a] (%)
1			(**1a**) X = Cl	X^1 = H	6	98
			(**1b**) X = Br	X^1 = H	2	99
			(**1c**) X = I	X^1 = H	4	96
			(**1d**) X = Cl	X^1 = Cl	6	96
			(**1e**) X = Br	X^1 = Br	6	98
			(**1f**) X = Cl	X^1 = Br	12	95
			(**1g**) X = I	X^1 = Cl	10	90
			(**1h**) X = I	X^1 = Br	10	93
			(**1i**) X = Me	X^1 = Cl	5	95
			(**1j**) X = Me	X^1 = Br	5	96
			(**1k**) X = Et	X^1 = Cl	6	96
			(**1l**) X = Et	X^1 = Br	6	90
2			(**2a**) X = Cl	X^1 = H	6	96
			(**2b**) X = Br	X^1 = H	2	98
			(**2c**) X = I	X^1 = H	4	98
			(**2d**) X = Cl	X^1 = Cl	6	95
			(**2e**) X = Br	X^1 = Br	6	99
			(**2f**) X = Cl	X^1 = Br	12	91
			(**2g**) X = I	X^1 = Cl	12	90
			(**2h**) X = I	X^1 = Br	12	95
			(**2i**) X = Me	X^1 = Cl	6	96
			(**2j**) X = Me	X^1 = Br	7	95
			(**2k**) X = Et	X^1 = Cl	6	96
			(**2l**) X = Et	X^1 = Br	7	96
3			(**3a**) X = Cl	X^1 = H	4	97
			(**3b**) X = Br	X^1 = H	2	98
			(**3c**) X = I	X^1 = H	4	95
			(**3d**) X = Cl	X^1 = Cl	6	95
			(**3e**) X = Br	X^1 = Br	6	98
			(**3f**) X = Cl	X^1 = Br	14	96
			(**3g**) X = I	X^1 = Cl	12	90
			(**3h**) X = I	X^1 = Br	12	98
4			(**4a**) X = Cl	X^1 = H	6	96
			(**4b**) X = Br	X^1 = H	2	99
			(**4c**) X = I	X^1 = H	5	98
			(**4d**) X = Cl	X^1 = Cl	6	98
			(**4e**) X = Br	X^1 = Br	6	95
			(**4f**) X = Cl	X^1 = Br	12	90

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



Scheme 2.

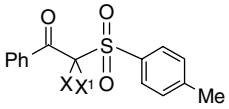
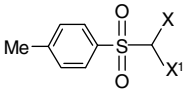
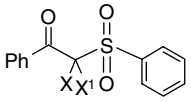
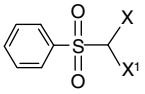
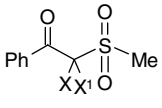
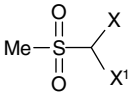
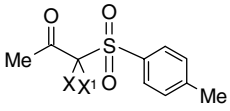
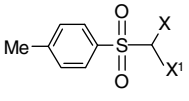


X = hydrogen/ alkyl/ halogen
X^1 = halogen

Scheme 3.

All the above α-halo β-keto-sulfones, α,α-symmetrical and asymmetrical dihalo β-keto-sulfones and α-halo, α-alkyl β-keto-sulfones underwent base-induced cleavage with aqueous alkali to give the corresponding halomethyl sulfones, dihalomethyl sulfones and α-halo, α-alkylmethyl sulfones, respectively (Scheme 3, Table 2).

Table 2. Synthesis of α-halomethyl sulfones and α,α-dihalomethyl sulfones via base-induced cleavage

Entry	Substrate	Product			Yield[a] (%)
1			(**1a**) X = Cl	X^1 = H	99
			(**1b**) X = Br	X^1 = H	99
			(**1c**) X = I	X^1 = H	98
			(**1d**) X = Cl	X^1 = Cl	98
			(**1e**) X = Br	X^1 = Br	98
			(**1f**) X = Cl	X^1 = Br	98
			(**1g**) X = I	X^1 = Cl	99
			(**1h**) X = I	X^1 = Br	98
			(**1i**) X = Me	X^1 = Cl	97
			(**1j**) X = Me	X^1 = Br	99
			(**1k**) X = Et	X^1 = Cl	99
			(**1l**) X = Et	X^1 = Br	98
2			(**2a**) X = Cl	X^1 = H	98
			(**2b**) X = Br	X^1 = H	98
			(**2c**) X = I	X^1 = H	98
			(**2d**) X = Cl	X^1 = Cl	99
			(**2e**) X = Br	X^1 = Br	99
			(**2f**) X = Cl	X^1 = Br	98
			(**2g**) X = I	X^1 = Cl	97
			(**2h**) X = I	X^1 = Br	98
			(**2i**) X = Me	X^1 = Cl	99
			(**2j**) X = Me	X^1 = Br	98
			(**2k**) X = Et	X^1 = Cl	97
			(**2l**) X = Et	X^1 = Br	95
3			(**3a**) X = Cl	X^1 = H	98
			(**3b**) X = Br	X^1 = H	98
			(**3c**) X = I	X^1 = H	99
			(**3d**) X = Cl	X^1 = Cl	99
			(**3e**) X = Br	X^1 = Br	98
			(**3f**) X = Cl	X^1 = Br	99
			(**3g**) X = I	X^1 = Cl	98
			(**3h**) X = I	X^1 = Br	98
4			(**4a**) X = Cl	X^1 = H	96
			(**4b**) X = Br	X^1 = H	99
			(**4c**) X = I	X^1 = H	98
			(**4d**) X = Cl	X^1 = Cl	98
			(**4e**) X = Br	X^1 = Br	98
			(**4f**) X = Cl	X^1 = Br	99

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

The halo products were characterized by their ^{1}H NMR spectral data. For example, the formation of α-halo β-keto-sulfones led to a downfield chemical shift of the methylene proton of *p*-toluenesulfonylacetophenone (Table 1, entry 1), from δ 4.56 to around δ 6.50, 6.30, 6.25 in α-iodo, α-bromo and α-chloro *p*-toluenesulfonyl-acetophenones, respectively, and no corresponding signal was present in the spectra of the α,α-dihalo *p*-toluenesulfonylacetophenones. The ^{1}H NMR spectra of iodo, bromo, and chloromethyl *p*-toluylsulfones had methylene signals at δ 4.40, 4.50, and 4.45, respectively. Further the methine protons of α,α-dibromo, α,α-di-chloro, α-chloro, α-bromo, α-chloro, α-iodo, and α-bromo, α-iodo methyl *p*-toluylsulfones appeared at δ 6.15, 6.21, 6.21, 6.50 and 6.61, respectively.

In conclusion, we have reported in this Letter a facile route to α-halo β-keto-sulfones using potassium halide (halogen = I, Br, Cl) in the presence of hydrogen peroxide, and the synthesis of α,α-symmetrical and asymmetrical dihalo β-keto-sulfones, and α-halo, α-alkyl β-keto-sulfones and their base induced cleavage products.

2. Synthesis of α-halo β-keto-sulfones

To a solution of β-keto-sulfone (10 mmol) in acetic acid (10 mL) was added KI/KBr/KCl (11 mmol) and 30% hydrogen peroxide (80 mmol). The reaction was stirred at room temperature for the appropriate time (Table 1). After completion of the reaction, as monitored by TLC, the acetic acid was removed under reduced pressure, water (10 mL) was added and the product extracted into ethyl acetate (3 × 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure to give the crude product, which was purified on a silica gel column using hexane:ethyl acetate (9:1) as eluent.

3. Synthesis of α,α-dihalo β-keto-sulfones

To a solution of α-halo β-keto-sulfones (1 mmol) in DCM (10 mL) were added SO_2Cl_2/Br_2 (1.1 mmol) and Et_3N (1 mmol). The reaction mixture was stirred at room temperature for the appropriate time (Table 1). After completion of the reaction, as monitored by TLC, the solvent was removed under reduced pressure, water (10 mL) was added and the product extracted into ethyl acetate (3 × 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure to give the crude product, which was purified on a silica gel column using hexane:ethyl acetate (9:1) as eluent.

4. Synthesis of halomethyl sulfones and dihalomethyl sulfones

To a solution of 10% aqueous NaOH (5 mL) was added the α-halo β-keto-sulfone/α,α-dihalo β-keto-sulfone/α-halo, α-alkyl β-keto-sulfone (1 mmol) at room temperature and the mixture stirred for 30 min. After completion of the reaction as monitored by TLC, the reaction was extracted into diethyl ether (3 × 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated to give the corresponding crude products, which was purified on a silica gel column using hexane:ethyl acetate (9:1) as eluent.

Acknowledgements

The authors are thankful to Dr. J. S. Yadav, Director of IICT, for his constant encouragement and DOD, DBT and CSIR New Delhi, for financial support.

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