Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

Halogenation of β-keto-sulfones using KX/H_2O_2 in aqueous medium: Synthesis of α-halo β-keto-sulfones and α-halomethyl sulfones

N. Suryakiran[a]; M. Srinivasulu[a]; Y. Venkateswarlu[a]
[a] Natural Products Laboratory, Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad, India

To cite this Article Suryakiran, N. , Srinivasulu, M. and Venkateswarlu, Y.(2007) 'Halogenation of β-keto-sulfones using KX/H_2O_2 in aqueous medium: Synthesis of α-halo β-keto-sulfones and α-halomethyl sulfones', Journal of Sulfur Chemistry, 28: 4, 345 — 350
To link to this Article: DOI: 10.1080/17415990701418738
URL: http://dx.doi.org/10.1080/17415990701418738

Journal of Sulfur Chemistry
Vol. 28, No. 4, August 2007, 345–350

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

Halogenation of β-keto-sulfones using KX/H_2O_2 in aqueous medium: Synthesis of α-halo β-keto-sulfones and α-halomethyl sulfones†

N. SURYAKIRAN, M. SRINIVASULU and Y. VENKATESWARLU*

Natural Products Laboratory, Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 5000 07, India

(Received 7 March 2007; in final form 18 April 2007)

Synthesis of α-halo β-keto-sulfones and α-halomethyl sulfones is described by the reaction of β-keto-sulfones with potassium halides in the presence of hydrogen peroxide in aqueous acidic medium afforded the corresponding α-halo β-keto-sulfones at room temperature in excellent yields. Further the α-halo β-keto-sulfones on treatment of aqueous alkali underwent base-induced cleavage to yield α-halomethyl sulfones.

Keywords: α-Halo β-keto-sulfones; α-Halomethyl sulfones; Potassium halide; Hydrogen peroxide

1. Introduction

Among sulfur containing compounds, β-keto-sulfones are very important group of intermediates [1–3] as they are precursors in Michael and Knoevenagel reactions [4, 5] in the preparation of acetylenes, allenes, chalcones [6–11], vinylsulfones [12], polyfunctionalized 4*H*-pyrans [4, 13] and ketones [14–17]. In addition, β-keto-sulfones are useful for the synthesis of optically active β-hydroxy-sulfones [18–21] and α-halomethyl sulfones and α,α-dihalomethyl sulfones [22]. The α-halomethyl sulfones and α,α-dihalomethyl sulfones are very good α-carbanion stabilizing substituents [23] and they are precursors for the preparation of alkenes [24], aziridines [25], epoxides [26–29], β-hydroxy-sulfones and used as VNS adducts [30–33]. Haloalkyl sulfones are useful in preventing aquatic organisms from attaching to fishing nets and ship hulls [34], they also posses other biological properties such as herbicidal [35], bactiricidal [36], antifungal [37], algaecides [38] and insecticides [39]. In general, the α-halo β-keto-sulfones are obtained by halogenation of corresponding β-keto-sulfones with halogenating reagents such as bromine, pyrydinium perbromate, sulfuryl chloride in dichloromethane or chloroform. However, the above reagents and solvents are very toxic. Also α-chloro/bromo β-keto-sulfones and α-chloro/bromomethyl sulfones do not undergo Finkelstein reactions [40–43] to obtain

*Corresponding author. Tel.: +91 40 27193167; Fax: +91 40 27160512; Email: luchem@iict.res.in
†IICT Communication # 070408

Journal of Sulfur Chemistry
ISSN 1741-5993 print/ISSN 1741-6000 online © 2007 Taylor & Francis
http://www.tandf.co.uk/journals
DOI: 10.1080/17415990701418738

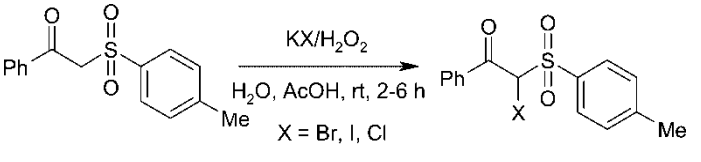
α-iodomethyl sulfones, due to a strong retardation effect by the sulfone group [44–45], so, to the best of our knowledge synthesis of α-iodomethyl sulfones is very difficult.

In recent years, halogenation of organic compounds with non-polluting reagents is an important transformation [46]. Masayuki *et al.* reported chemoselective bromination of active methylene and methine compounds using potassium bromide, hydrochloric acid and hydrogen peroxide [47]. Recently, we have reported the facile synthesis of β-keto-sulfones [48] and direct synthesis of α-iodo β-keto-sulfones and their base-induced cleavage to afford α-iodomethyl sulfones [49]. In continuation of our work, we envisaged the synthesis of various α-halo β-keto-sulfones and their corresponding base-induced cleavage products using eco-friendly reagent.

2. Results and discussion

In this report (scheme 1), we describe an efficient and environmental friendly mono halogenation of β-keto-sulfones. A literature survey revealed that the halogenation of β-keto-sulfones involves electro-positive halogen atom. We reacted the β-keto-sulfones with potassium bromide in the presence of hydrogen peroxide in aqueous acidic medium at room temperature to give corresponding α-bromo β-keto-sulfones in 95% yield (scheme 1, table 2). In order to optimize the reaction conditions, we have carried out the above reaction in different solvents and using acetic acid (table 1). From these studies, it is found that the reaction in aqueous acidic medium afforded excellent yields of the corresponding α-bromo β-keto-sulfone. The acetic acid can easily enolises the β-keto-sulfones, and the resulting enol of β-keto-sulfones readily attacked by bromonium ion to give the corresponding α-bromo β-keto-sulfone (scheme 2). Here, the hydrogen peroxide plays a vital role, which produces the bromonium ion from potassium bromide, and in the absence of hydrogen peroxide no reaction was observed. When four equivalents of hydrogen peroxide is used in the reaction, only 80% of α-bromo β-keto-sulfone was obtained whereas, eight equivalents of hydrogen peroxide gave the excellent yields of α-bromo β-keto-sulfone (table 1). Similarly, we have reacted β-keto-sulfones with potassium iodide and chloride to give the corresponding α-iodo β-keto-sulfones and α-chloro β-keto-sulfones respectively, in good to excellent yields using eight equivalents of hydrogen peroxide. This success has encouraged us to react various β-keto-sulfones with different potassium halides in the presence of hydrogen peroxide in aqueous medium to afford corresponding α-halo β-keto-sulfones in excellent yields. In addition, we investigated the base-induced cleavage of α-halo β-keto-sulfones with aqueous alkali to give the corresponding α-halo methylsulfones in quantitative yields (scheme 3). Further, it is noticed that, this is the best method for the preparation of α-iodo β-keto-sulfones and α-iodomethyl sulfones.

The formation of α-halo β-keto-sulfones is observed by the downfield chemical shift of methine proton in α-halo *p*-toluenesulfonylacetophenone (table 2, entries 1–3), from $\delta = 4.56$ (2H) to 6.50 (1H), 6.30 (1H), 6.25 (1H) in α-iodo, α-bromo, α-chloro *p*-toluenesulfonylacetophenones respectively in the ^{1}H NMR spectrum.

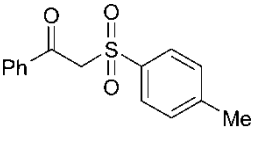
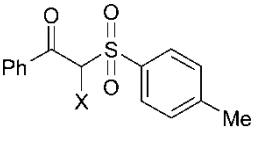
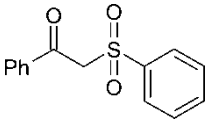
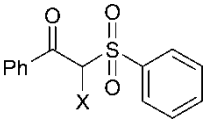
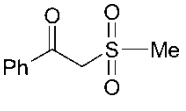
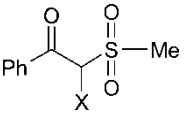
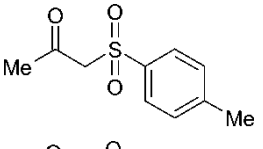
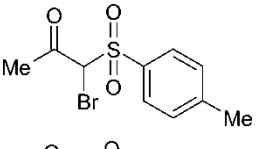
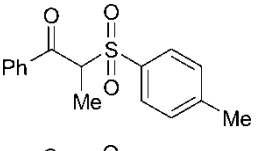
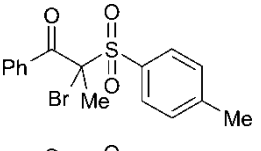
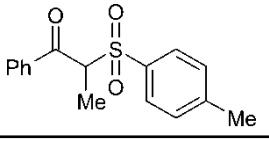
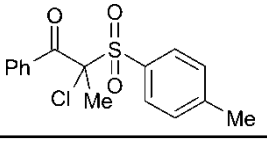


SCHEME 1

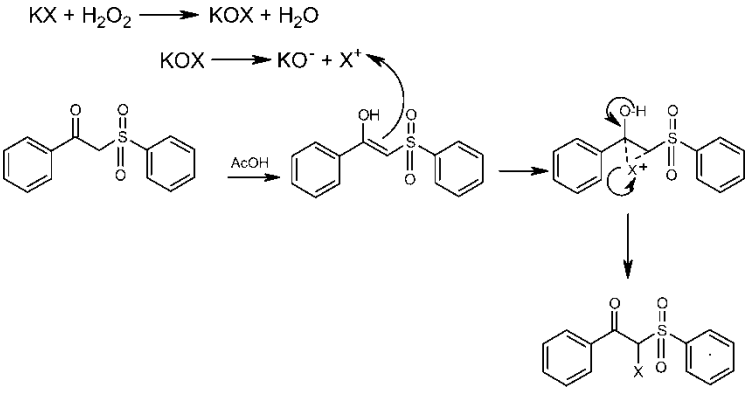
Table 1. Optimization of reaction conditions on halogenation of *p*-toluenesulfonylacetophenone using potassium bromide in the presence of hydrogen peroxide and acetic acid (0.5 mL).

Entry	Solvent	Hydrogen peroxide (equivalent)	Time (h)	Yield (%)
1	DCM	1	2	50
2	DCM	2	2	70
3	DCM	4	2	80
4	$CHCl_3$	8	2	50
5	Toluene	8	6	95
6	Benzene	8	6	70
7	DCM	8	2	90
8	H_2O	8	2	95

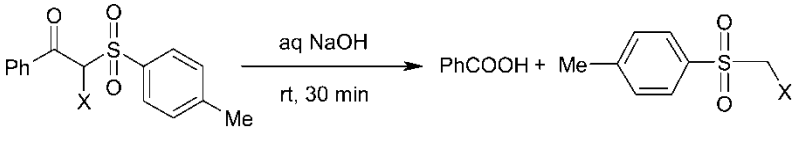
Table 2. Halogenation of β-keto-sulfones using potassium halides in the presence of hydrogen peroxide and aqueous acetic acid.

Entry	Substrate		Product	Time (h)	Yield[a] (%)
1		X = Br		2	95
				4	98
				6	95
2		X = I		4	96
3		X = Cl		4	95
4		X = Br		6	96
5		X = I		2	96
6		X = Cl		5	96
7		X = Br		6	96
8		X = I		5	96
9		X = Cl		6	96
10				2	97
11				3	98
12				6	96

[a]Isolated yields after column chromatography. All products gave satisfactory 1H NMR and Mass spectral data.



SCHEME 2



SCHEME 3

3. Conclusion

In summary, we have described a novel and environmental friendly halogenation of β-keto-sulfones to synthesis α-halo β-keto-sulfones and their base-induced cleavage to yield the corresponding α-halomethyl sulfones.

4. Experiment

4.1 *Synthesis of α-halo β-keto-sulfones:*

To a stirred solution of β-keto-sulfone (1 mmol) in water (10 mL) and acetic acid (0.5 mL) was added KBr/KI/KCl (1.1 mmol) followed by H_2O_2 (8 mmol 30%). The reaction mixture was further stirred at room temperature for the appropriate time (table 2). After completion of the reaction, as monitored by TLC, diluted with water (10 mL), extracted into ethyl acetate (3×20 mL). The combined organic extract was dried over anhydrous sodium sulphate and evaporated under reduced pressure to give the crude product, which was purified on a silica gel column. Entry **1**. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 2.45$ (s, 3H), 6.21 (s, 1H), 7.40 (d, 2H, $J = 8.4$ Hz), 7.45 (t, 2H, $J = 8.5$ Hz), 7.49 (t, 1H, $J = 2.4$ Hz), 7.81 (d, 2H, $J = 8.5$ Hz), 8.00 (d, 2H, $J = 8.4$ Hz); EIMS: m/z, 354 ($M^{+\cdot}+1$). Entry **2**. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 2.43$ (s, 3H), 6.50 (s, 1H), 7.40 (d, 2H, $J = 8.4$ Hz), 7.45 (d, 2H, $J = 8.4$ Hz), 7.70 (t, 1H, $J = 2.4$ Hz), 7.75 (d, 2H, $J = 8.5$ Hz), 7.85 (d, 2H, $J = 8.4$ Hz); EIMS: m/z, 401 ($M^{+\cdot}+1$). Entry **3**. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 2.51$ (s, 3H), 6.20(s, 1H), 7.40 (d, 2H, $J = 8.4$ Hz), 7.59 (t, 2H, $J = 8.5$ Hz), 7.65 (t, 1H, $J = 2.4$ Hz), 7.90 (d, 2H, $J = 8.5$ Hz), 8.10 (d, 2H, $J = 8.4$ Hz); EIMS: m/z, 309 ($M^{+\cdot}+1$). Entry **6**. ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 6.16$ (s, 1H), 7.40–7.60 (m, 3H), 7.80 (d, 2H, $J = 8.5$ Hz), 8.10 (d, 2H, $J = 8.5$ Hz); EIMS: m/z, 295 ($M^{+\cdot}+1$). Entry **9**. ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 3.20$ (s, 3H), 5.95 (s, 1H), 7.45–7.75 (m, 5H); EIMS: m/z, 232 ($M^{+\cdot}+1$).

4.2 *Base-induced cleavage of α-halo β-keto-sulfones: synthesis of α-halomethyl sulfones:*

To a solution of 10% aqueous NaOH (5 mL) was added the α-halo 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 contents were extracted into diethyl ether (3 × 20 mL). The combined organic extract was dried over anhydrous sodium sulphate and evaporated to give the corresponding crude α-halo methylsulfones in quantitative yields, which was purified on a silica gel column to give pure α-halomethyl sulfones. Entry **1**.^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 2.50$ (s, 3H), 4.20 (s, 2H), 7.40 (d, 2H, $J = 8.4$ Hz), 7.82 (d, 2H, $J = 8.4$ Hz); EIMS: m/z 250 ($M^{+\cdot}+1$). Entry **2**.^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 2.46$ (s, 3H), 4.41 (s, 2H), 7.30 (d, 2H, $J = 8.4$ Hz), 7.84 (d, 2H, $J = 8.4$ Hz); EIMS: m/z 297 ($M^{+\cdot}+1$). Entry **3**.^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 2.50$ (s, 3H), 4.44 (s, 2H), 7.40 (d, 2H, $J = 8.4$ Hz), 7.85 (d, 2H, $J = 8.4$ Hz); EIMS: m/z 205 ($M^{+\cdot}+1$). Entry **9**.^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 3.20$ (s, 3H), 3.40 (s, 2H); EIMS: m/z 129 ($M^{+\cdot}+1$).

Acknowledgements

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

References

[1] T. Durst. *Comprehensive Organic Chemistry*, Edited by D.H.R. Barton and W.D. Ollis, Pergamon Press, Oxford, UK (1979).
[2] B.M. Trost. *Comprehensive Organic Chemistry*, Pergamon Press, Oxford (1991).
[3] N.S. Simpkins. *Sulfones in Organic Synthesis,* Pergamon Press, Oxford (1993).
[4] J.L. Macro, I. Fernandez, N. Khira, P. Fernandez, A. Romero. *J. Org. Chem.*, **60**, 6678 (1995).
[5] M.V.R. Reddy, S. Reddy. *Acta Chim. Hung.*, **115**, 269 (1984).
[6] M. Ihara, S. Suzuki, T. Taniguchi, Y. Tokunaga, K. Fukumoto. *Tetrahedron*, **51**, 9873 (1995).
[7] J.E. Baldwin, R.M. Adlington, N.P. Crouch, R.L. Hill, T.G. Laffeg. *Tetrahedron Lett.*, **36**, 7925 (1995).
[8] M.V.R. Reddy, S. Reddy. *Acta Chim. Hung.*, **120**, 275 (1985).
[9] J.J. Looker. *J. Org. Chem.*, **31**, 2714 (1966).
[10] S. Sengupta, D.S. Sarma, S. Mondal. *Tetrahedron*, **54**, 9791 (1998).
[11] S. Sengupta, D.S. Sarma, S. Mondal. *Tetrahedron*: *Asymmetry*, **12**, 513 (2001).
[12] S. Sengupta, D.S. Sarma, S. Mondal. *Tetrahedron*: *Asymmetry*, **9**, 2311 (1998).
[13] J.L. Marco. *J. Org. Chem.*, **62**, 6575 (1997).
[14] E.J. Corey, M. Chavosky. *J. Am. Chem. Soc.*, **86**, 1639 (1964).
[15] B.M. Trost, H.C. Arndt, P.E. Strege, T.R. Verhowever. *Tetrahedron Lett.*, **27**, 3477 (1976).
[16] M.J. Kurth, M.J. Brien. *J. Org. Chem.*, **50**, 3846 (1985).
[17] M. Fuju, K. Nakamura, H. Mekata, S. Oka, A. Ohno. *Bull. Chem. Soc. Jpn.*, **61**, 495 (1988).
[18] A. Svatos, Z. Hun Kova, V. Kren, M. Hoskovec, D. Saman, I. Valterova, J. Vrkoc, B. Koutek. *Tetrahedron*: *Asymmetry*, **7**, 1285 (1996).
[19] P. Betus, P. Phansavath, V.R. Vidal, J.P. Genet, A.R. Touati, T. Homri, B.B. Hassine. *Tetrahedron*: *Asymmetry*, **10**, 1369 (1999).
[20] V. Gotor, F. Rebolledo, R. Liz. *Tetrahedron*: *Asymmetry*, **12**, 513 (2001).
[21] C. Ni, Y. Li, J. Hu. *J. Org. Chem.*, **71**, 6829 (2006).
[22] J.S. Grossert, P.K. Dubey, G.H. Gill, T.S. Cameron, P.A. Gardner. *Can. J. Chem.*, **62**, 798 (1984).
[23] A. Jonczyk, K. Banko, M. Makosza. *J. Org. Chem.*, **40**, 266 (1975).
[24] (a) J.W. Lee, D.Y.S. Oh. D.Y.S. *Synth. Commun.*, **20**, 273 (1990). (b) F.G. Bardwell, G.D. Coopert. *J. Am. Chem. Soc.*, **73**, 5184 (1951).
[25] V. Reutrakal, V. Prapansiri, C. Panyachotipun. *Tetrahedron Lett.*, **25**, 1949 (1984).
[26] M. Adamczyk, E.K. Dolence, D.S. Watt, M.R. Christy, J.H. Reibenspies, O.P. Anderson. *J. Org. Chem.*, **49**, 1378 (1984).
[27] E.K. Dolence, M. Adamczyk, D.S. Watt, G.B. Rasell, D.H.S. Horn. *Tetrahedron Lett.*, **26**, 1189 (1985).
[28] S. Arai, T. Ishidu, T. Shioiri. *Tetrahedron Lett.*, **39**, 8299 (1998).
[29] E. Nagashima, K. Suzuki, M. Ishikawa, M. Sekiya. *Heterocycles*, **23**, 1873 (1985).
[30] J. Golinski, M. Makosza. *Tetrahedron Lett.*, **37**, 3495 (1978).
[31] M. Makosza, B. Chylinska, B. Mudryk. *Ann. Chem.*, **1**, 8 (1984).

[32] K. Wojciechowski, M. Makosza. *Tetrahedron Lett*., **62**, 4793 (1989).
[33] K. Wojciechowki, M. Makosza. *Synthesis*, **8**, 651 (1986).
[34] Y. Oishi, T. Watanabe, K. Kusa, M. Kazama, K. Koniya. *Japanese Patent*, JP 63243067, *Chem. Abstr.*, **110**, 212359 (1989).
[35] S. Shigematsy, Y. Yamada, I. Kimura, *Japanese Patent*, JP58128305, *Chem. Abstr.*, **99**, 171339 (1984).
[36] F.C. Baker, J.P.N. Li. *United States Patent* January 27, (1981) US4247559, (C07D 207/452; A61K 031/40).
[37] Z. Eckstein, M. Zavistowska, D. Palut, E. Polubiec. *Pol. J. Chem*., **45**, 314 (1966).
[38] Z. Ejmocki, B.K. Krassowska, I. Olezak, Z. Eckstein. *Pol. J. Chem.*, **54**, 11 and 2153 (1980).
[39] S. Antane, R. Bernotas, Y. Li, R. David. Mc. Y. Yan. *Synth. Commun.*, **34**, 2443 (2004).
[40] W. Middlebos, J. Strating, B. Zwanenberg. *Tetrahedron Lett.*, **12**, 351 (1971).
[41] W.M. Ziegler, R. Conner. *J. Am. Chem. Soc*., **62**, 2596 (1940).
[42] E. Barr, W.M. Ziegler, R. Conner. *ibid*, **63**, 106 (1941).
[43] G. Kresze, W.M. Schram, G. Cleve. *Chem. Ber*., **94**, 2060 (1961).
[44] F.G. Bordwell, W.T. Brannen, Jr. *J. Am. Chem. Soc*., **86**, 4645 (1964).
[45] F.G. Bordwell, B.J. Bruce. *J. Org. Chem*., **32**, 1182, (1967).
[46] A.T. Khan, P. Goswamy, L.H. Choudhury. *Tetrahedron Lett*., **47**, 2751 (2006).
[47] M. Kirihara, S. Ogawa, T. Noguchi, K. Okubo, Y. Monma, I. Shimizu, R. Shimosaki, A. Hatano, Y. Hirai. *Synlett*, 2287 (2006).
[48] N. Suryakiran, T. Srikanth Reddy, K. Asha Latha, M. Lakshman, Y. Venkateswarlu. *Tetrahedron Lett*., **47**, 3853 (2006).
[49] N. Suryakiran, T. Srikanth Reddy, V. Suresh, M. Lakshman, Y. Venkateswarlu. *Tetrahedron Lett*., **47**, 4319 (2006).