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Synthesis of β-keto-sulfones using ionic liquid [TPA][Pro] as an efficient and reusable reaction medium☆

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Abstract

Facile and an efficient synthesis of β-keto-sulfones is described by the reaction of α-haloketone with sodium alkyl/aryl sulphinates in ionic liquid [TPA][Pro] as an efficient and reusable reaction medium to afford the corresponding β-keto-sulfones in excellent yields.

Keywords: β-Keto-sulfones; α-Haloketones; Sodium alkyl/aryl sulphinates; Ionic liquid [TPA][Pro]

Sulfones are very important and fascinating branch of chemistry. 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, β-keto-sulfones are very important group of intermediates, as they are precursors in Michael and Knoevenagel reactions [2,3] in the preparation of acetylenes, allenes, chalcones [4–9], vinylsulfones [10] and polyfunctionalized 4*H*-pyrans [11]. β-Keto-sulfones are useful for the synthesis of ketones by facile reductive elimination of the sulfone group [12]. In addition, β-keto-sulfones are useful for the synthesis of synthetically as well as biologically important β-hydroxy-sulfones [13] and α-halomethyl sulfones [14]. Although several methods of synthesis of β-keto-sulfones have been reported in literature, which includes alkylation of metallic arene sulphinates with either α-haloketone [15] or α-tosyloxy ketones [16], acylation of alkyl sulfones [17], reactions of diazo sulfones with aldehydes catalyzed by $SnCl_2$ [18], reaction of an acid ester with α-sulfonyl carbanions [19], reaction of an acid anhydride with α-sulfonyl carbanions, addition of aldehydes to α-sulfonyl carbanions followed by oxidation of the resulting β-hydroxy-sulfones [20], oxidation of β-keto-sulphides [21], oxidation of β-keto-sulfoxides [22]. However, the direct and straightforward method for the preparation of β-keto-sulfones is treatment of haloketones with metal sulphinate salts but the low solubility of metal sulphinate salts in organic solvents is the inadequacy.

In recent years, the use of ionic liquids (I.L.s) as green solvents in organic synthetic processes has gained considerable importance due to their solvating ability, negligible vapor pressure, easy recyclability and reusability [23]. The synthesis and use of chiral ionic liquids (CILs) has received increasing attention of chemist. Maschmeyer and co-workers [24] have reported the synthesis of ionic liquids using quaternary ammonium hydroxide and chiral carboxylic acids, which are inexpensive and can be prepared easily. Recently, we have reported the facile synthesis of β-keto-sulfones, the direct synthesis of α-iodo β-keto-sulfones and α,α-symmetrical, asymmetrical dihalo β-keto-sulfones and their base-induced cleavage to afford halomethyl, dihalomethyl sulfones [25]. In continuation of our work, although not novel, we envisaged the synthesis of β-keto-sulfones in new chiral ionic liquid [TPA][Pro], as an efficient and reusable reaction medium.

In this report (Scheme 1), we describe an efficient method for the synthesis of β-keto-sulfones in [TPA][Pro]. This method does not need expensive reagents or special care to exclude the moisture from the reaction medium. We prepared ionic liquid [TPA][Pro] from readily available tetrapropyl ammonium hydroxide and L-proline in aqueous medium at 60 °C. The tetrapropyl ammonium hydroxide is a strong base, which readily deprotanates the carboxylic acid moiety of chiral amino acid like L-proline to form a carboxylic acid salt and water, the resulting salt being a liquid at room temperature. We first examined the reaction of sodium *p*-toluenesulphinate with phenacyl

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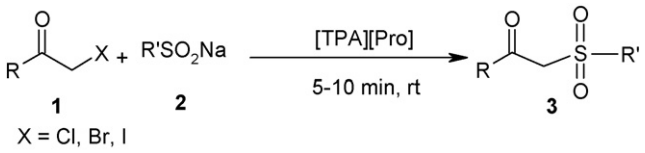
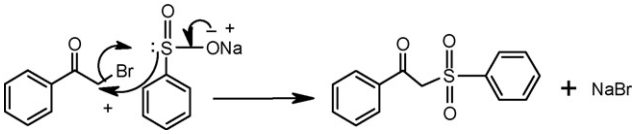


Scheme 1.



Scheme 2. Plausible mechanism.

Table 1
Solvent effect on the reaction of phenacyl bromide with sodium *p*-toluenesulphinate at room temperature

Entry	Solvent	Time	Yield (%)
1	[TPA][Pro]	5	98
2	[TPA][Pro]/CH_3CN (1:1)	5	98
3	PEG	10 min	96
4	1,4 Dioxane	24	55
5	EtOH	24 h	50
6	CH_3CN	24 h	49
7	IPA	24 h	40
8	C_6H_6	24 h	Nil
9	$CHCl_3$	24 h	Nil
10	DCM	24 h	Nil

bromide in ionic liquid [TPA][Pro] at room temperature to yield the corresponding β-keto-sulfones in 98% yield (Table 2, Entry 1). This result were encouraged us to carry out the reaction in ionic liquid. In order to optimize the reaction conditions, we carried out the reaction in different solvents (Table 1). The poor yields in hydroxylic solvents and less polar solvents are probably due to the lower solubility of the sulphinate salt in these solvents, coupled with the fact that the nucleophile (p-$MeC_6H_4SO_2^-$) is solvated in hydroxylic solvents thereby reducing its effective nucleophilicity. It was observed that ionic liquid ability to act as a phase transfer catalyst for this transformation and the reaction was complete very fast (Scheme 1). Reaction of different α-halo ketones with alkyl/aryl sulphinates proceeded efficiently and smoothly and the products were obtained in good to excellent yields. Various β-keto-sulfones have been synthesized in facile manner using ionic liquids as an efficient reaction medium (Scheme 1, Table 2). From the forgoing results, it is evident that the [TPA][Pro] is an efficient reaction medium for the synthesis of β-keto-sulfones. Further, it is noticed that the ionic liquid can be recovered and reused for next run.

The formation of the product β-keto-sulfones rather than β-keto-sulphinate ester can be explained by Soft and Hard Acid and Base (SHAB) terminology and it follows neucliophilic attack of sulphinate sulphur in a concerted manner (Scheme 2).

In conclusion, we have described the synthesis of β-keto-sulfones in ionic liquid [TPA][Pro] as new ionic liquids possessing chiral carboxylate, as efficient and reusable reaction medium. The present procedure for the synthesis of β-keto-sulfones has the advantage of high efficient reaction medium with high yields of products and simple work-up procedure, which makes it, is a useful and important addition to the present existing methods (Fig. 1).

1. Typical experimental procedure

A mixture of α-haloketone (10 mmol) and sodium alky/aryl sulphinate (11 mmol) in ionic liquid [TPA][Pro] (5 mL). The reaction was stirred at RT for an appropriate time (Table 1). After completion of the reaction, as monitored by TLC, the product was extracted into diethyl ether (3 × 20 mL). The combined organic extract was evaporated under reduced pressure to give crude product, which was purified by silica column chromatography. The ionic liquid was recovered and reused

Table 2
Synthesis of β-keto-sulfones using ionic liquid [TPA][Pro] as an efficient reaction medium.

Entry	Substrate			Product	Time (min)	Yield[a] (%)
	R	X	R′			
1	Ph	Br	*p*-Toluyl	3a	5	98
2	Me	Br	*p*-Toluyl	3b	5	98
3	*p*-Toluyl	Br	*p*-Toluyl	3c	5	95
4	*p*-Cl(C_6H_5)	Br	*p*-Toluyl	3d	5	98
5	Ph	Br	Ph	3e	5	96
6	Me	Br	Ph	3f	6	98
7	*p*-Toluyl	Br	Ph	3g	5	98
8	*p*-Cl(C_6H_5)	Br	Ph	3h	5	96
9	Ph	Br	Me	3i	6	96
10	Me	Br	Me	3j	6	98
11	*p*-Toluyl	Br	Me	3k	8	98
12	Ph	Br	Me	3l	10	98
13	Ph	Cl	*p*-Toluyl	3m	5	98
14	Me	Cl	*p*-Toluyl	3n	5	97
15	Ph	I	*p*-Toluyl	3o	5	97
16	*p*-Toluyl	I	*p*-Toluyl	3p	5	98

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

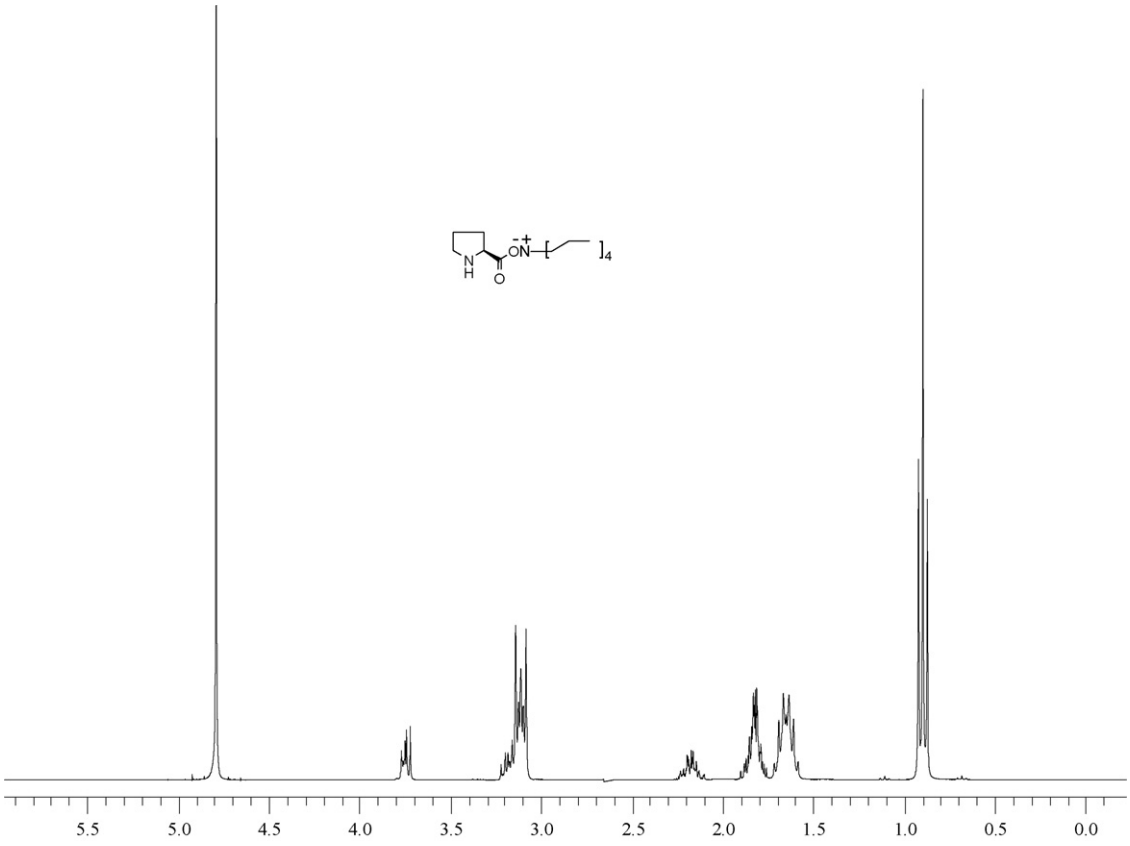


Fig. 1. ^{1}H NMR (300 MHz, D_2O) of ionic liquid [TPA][Pro] possessing chiral carboxylate.

for next run. The formation of the products has been characterized by spectral data, for example appearance of methylene signal at $\delta \sim 4.50$ indicates the formation of β-keto-sulfones in corresponding ^{1}H NMR spectrum. Entry 1. ^{1}H NMR ($CDCl_3$, 300 MHz), $\delta = 2.49$ (s, 3H, Ar–CH_3), 4.62 (s, 2H, CH_2), 7.34 (d, 2H, $J = 8.50$ Hz, Ar–H), 7.50 (t, 2H, $J = 8.05$ Hz, Ar–H), 7.60 (t, 1H, $J = 3.5$ Hz, Ar–H), 7.75 (d, 2H, $J = 8.05$ Hz, Ar–H), 8.00 (d, 2H, $J = 8.50$ Hz, Ar–H); EIMS: 274 ($M^{\bullet+}$); Entry 2. ^{1}H NMR ($CDCl_3$, 300 MHz), $\delta = 2.40$ (s, 3H, CH_3), 2.49 (s, 3H, Ar–CH_3), 4.19 (s, 2H, CH_2), 7.40 (d, 2H, $J = 8.55$ Hz, Ar–H), 7.80 (d, 2H, $J = 8.55$ Hz, Ar–H); EIMS: 212 ($M^{\bullet+}$); Entry 3. ^{1}H NMR ($CDCl_3$, 300 MHz), $\delta = 2.42$ (s, 3H, Ar–CH_3), 2.49 (s, 3H, Ar–H), 4.62 (s, 2H, CH_2), 7.34 (d, 2H, $J = 8.50$ Hz, Ar–H), 7.51 (d, 2H, $J = 8.00$ Hz, Ar–H), 7.80 (d, 2H, $J = 8.00$ Hz, Ar–H), 8.00 (d, 2H, $J = 8.50$ Hz, Ar–H); EIMS: 288 ($M^{\bullet+}$); Entry 4. ^{1}H NMR ($CDCl_3$, 300 MHz), $\delta = 2.49$ (s, 3H, Ar–CH_3), 4.62 (s, 2H, CH_2), 7.34 (d, 2H, $J = 8.50$ Hz, Ar–H), 7.45 (d, 2H, $J = 8.15$ Hz, Ar–H), 7.65 (d, 2H, $J = 8.15$ Hz, Ar–H), 8.00 (d, 2H, $J = 8.50$ Hz, Ar–H); EIMS: 308 ($M^{\bullet+}$); Entry 5. ^{1}H NMR ($CDCl_3$, 300 MHz), $\delta = 4.50$ (s, 2H, CH_2), 7.34 (d, 2H, $J = 8.50$ Hz, Ar–H), 7.49–7.55 (m, 5H, Ar–H), 7.60 (t, 1H, $J = 3.5$ Hz, Ar–H), 8.00 (d, 2H, $J = 8.50$ Hz, Ar–H); EIMS: 260 ($M^{\bullet+}$); Entry 11. ^{1}H NMR ($CDCl_3$, 300 MHz), $\delta = 2.25$ (s, 3H, Ar–CH_3), 3.15 (s, 3H, CH_3), 4.59 (s, 2H, CH_2), 7.34 (d, 2H, $J = 8.50$ Hz, Ar–H), 8.00 (d, 2H, $J = 8.25$ Hz, Ar–H); EIMS: 212 ($M^{\bullet+}$); Entry 12. ^{1}H NMR ($CDCl_3$, 300 MHz), $\delta = 3.14$ (s, 3H, CH_3), 4.59 (s, 2H, CH_2), 7.49 (t, 2H, $J = 8.25$ Hz, Ar–H), 7.62 (t, 1H, $J = 3.44$ Hz, Ar–H), 8.00 (d, 2H, $J = 8.25$ Hz, Ar–H); EIMS: 198 ($M^{\bullet+}$).

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References

[1] (a) T. Durst, in: D.H.R. Barton, W.D. Ollis (Eds.), Comprehensive Organic Chemistry, Peragmon Press, Oxford, UK, 1979;
(b) N.S. Simpkins, in: J.E. Baldwin (Ed.), Sulfones in organic synthesis, Peragmon press, Oxford, 1993;
(c) B.M. Trost, Comprehensive Organic Chemistry, Peragmon Press, Oxford, 1991.
[2] J.L. Macro, I. Fernandez, N. Khira, P. Fernandez, A. Romero, J. Org. Chem. 60 (1995) 6678.
[3] M.V.R. Reddy, S. Reddy, Acta Chim. Hung. 115 (1984) 269.
[4] M. Ihara, S. Suzuki, T. Taniguchi, Y. Tokunaga, K. Fukumoto, Tetrahedron 51 (1995) 9873.
[5] J.E. Baldwin, R.M. Adlington, N.P. Crouch, R.L. Hill, T.G. Laffeg, Tetrahedron Lett. 36 (1995) 7925.
[6] M.V.R. Reddy, S. Reddy, Acta Chim. Hung. 120 (1985) 275.
[7] J.J. Looker, J. Org. Chem. 31 (1966) 2714.
[8] S. Sengupta, D.S. Sarma, S. Mondal, Tetrahedron 54 (1998) 9791.
[9] S. Sengupta, D.S. Sarma, S. Mondal, Tetrahedron: Asymmetry 12 (2001) 513.
[10] S. Sengupta, D.S. Sarma, S. Mondal, Tetrahedron: Asymmetry 9 (1998) 2311.
[11] (a) J.L. Marco, I. Fernandez, N. Khiar, P. Fernandez, A. Romero, J. Org. Chem. 60 (1995) 6678;
(b) J.L. Marco, J. Org. Chem. 62 (1997) 6575.

[12] (a) E.J. Corey, M. Chavosky, J. Am. Chem. Soc. 86 (1964) 1639;
(b) B.M. Trost, H.C. Arndt, P.E. Strege, T.R. Verhowever, Tetrahedron Lett. 27 (1976) 3477;
(c) M.J. Kurth, M.J. Brien, J. Org. Chem. 50 (1985) 3846;
(d) M. Fuju, K. Nakamura, H. Mekata, S. Oka, A. Ohno, Bull. Chem. Soc. Jpn. 61 (1988) 495;
(e) H. Guo, Y. Zhang, Synth. Commun. 30 (2005) 2564.
[13] (a) A. Svatos, Z. Hun Kova, V. Kren, M. Hoskovec, D. Saman, I. Valterova, J. Vrkoc, B. Koutek, Tetrahedron: Asymmetry 7 (1996) 1285;
(b) P. Betus, P. Phansavath, V.R. Vidal, J.P. Genet, A.R. Touati, T. Homri, B.B. Hassine, Tetrahedron: Asymmetry 10 (1999) 1369;
(c) V. Gotor, F. Rebolledo, R. Liz, Tetrahedron: Asymmetry 12 (2001) 513.
[14] (a) F.C. Baker, J.P.N. Li, United States Patent, US 4,247,559 (C07D 207/452; A61K 031/40) January 27 1981;
(b) Z. Eckstein, M. Zavistowska, D. Palut, E. Polubiec, Pol. J. Chem. 45 (1966) 314;
(c) Z. Ejmocki, B.K. Krassowska, I. Olezak, ZEckstein, Pol. J. Chem. 54 (1980), p. 11 and 2153;
(d) S. Antane, R. Bernotas, Y. Li, M.R. David, Y. Yan, Synth. Commun. 34 (2004) 2443;
(e) J.S. Grossert, P.K. Dubey, G.H. Gill, T.S. Cameron, P.A. Gardner, Can. J. Chem. 62 (1984) 798.
[15] (a) G.E. Vennstra, B. Zwaneburg, Synthesis (1975) 519;
(b) J. Wildeman, A.M. Van Leusen, Synthesis (1979) 733.
[16] (a) Y.-Y. Xie, Z.-C. Chen, Synth. Commun. 31 (2001) 3145;
(b) D. Kumar, S. Sundaree, V.S. Rao, S.V. Rajender, Tetrahedron Lett. 47 (2006) 4197.
[17] (a) A.R. Kartizky, A.A. Abdel-Fattah, M.Y. Wang, J. Org. Chem. 68 (2003) 1443;
(b) W.E. Truce, R.H. Knospe, J. Am. Chem. Soc. 77 (1955) 5063.
[18] C.R. Holmquist, E.J. Roskamp, Tetrahedron Lett. 33 (1992) 1131.
[19] (a) K. Schank, A. Weber, Synthesis (1970) 367;
(b) K. Schank, Annalen 75 (1967) 702.
[20] M. Julia, J.M. Paris, Tetrahedron Lett. 14 (1973) 4833.
[21] T. Durst, in: D.H.R. Barton, W.D. Ollis (Eds.), Comprehensive Organic Chemistry, vol. 4, Peragmon Press, Oxford, UK, 1979, p. 174 (Chapter 11.8).
[22] B.M. Trost, Chem. Rev. 78 (1978) 363.
[23] (a) K. Fukumoto, M. Yoshizavwa, H. Ohno, J. Am. Chem. Soc. 127 (2005) 2398;
(b) K. Fukumoto, M. Yoshizavwa, H. Ohno, Chem. Commun. (2006) 3081;
(c) C. Wang, L. Guo, H. Li, Y. Wang, J. Weng, L. Wu, Green Chem. 8 (2006) 603.
[24] C.R. Allen, P.L. Richard, A.J. Ward, L.G.A. van de Water, A.F. Masters, T. Maschmeyer, Tetrahedron Lett. 47 (2006) 7367.
[25] (a) N. Suryakiran, T. Srikanth Reddy, K. Asha Latha, M. Lakshman, Y. Venkateswarlu, Tetrahedron Lett. 47 (2006) 3853;
(b) N. Suryakiran, T. Srikanth Reddy, V. Suresh, M. Lakshman, Y. Venkateswarlu, Tetrahedron Lett. 47 (2006) 4319;
(c) N. Suryakiran, P. Prabhakar, T. Srikanth Reddy, K.C. Mahesh, K. Rajesh, Y. Venkateswarlu, Tetrahedron Lett. 48 (2007) 877.