Indian Journal of Chemistry
Vol. 48B, April 2009, pp. 611-616

Note

A simple and efficient PTT-mediated synthesis of α-azidoketones in [bmim][BF_4] ionic liquid

Anil Kumar*, Israr Ahmed, M Sudershan Rao,
Gautam Patel & Dalip Kumar

Chemistry Group, Birla Institute of Technology and Science,
Pilani 333 031, India

E-mail: anilkumar@bits-pilani.ac.in

Received 6 May 2008; accepted (revised) 20 January 2009

A simple and efficient one-pot method has been described for the direct synthesis of α-azidoketones from various ketones possessing α-hydrogen by reaction with phenyltrimethylammonium tribromide (PTT) and subsequent treatment with NaN_3 in ionic liquid. The procedure gives high yield and the ionic liquid can be reused.

Keywords: Phenyltrimethylammonium tribromide (PTT), α-azidoketones, ionic liquid

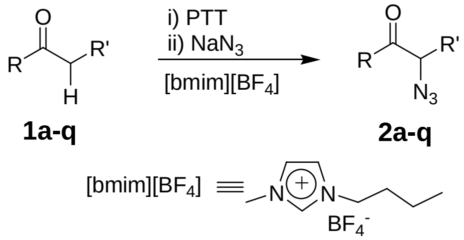
α-Azidoketones are useful starting compounds for the synthesis of biologically important heterocyclic compounds such as pyrroles, pyrazines, and oxazoles[1]. α-Azidoketones are photochemically and thermally labile compounds, and utilized in the generation of other functionalities such as amine *via* reduction, imines *via* rearrangements, and triazoles and related heterocycles *via* cycloaddition[1]. Therefore, many methods for the synthesis of α-azidoketones have been reported[2,3]. The traditional methods for the synthesis of α-azidoketones involve nucleophilic substitution reaction of α-haloketones or α-tosyloxy ketones using sodium azide[4]. α-Azidoketones have also been prepared from α-diazoketones in the presence of sodium azide and cerium(III) chloride heptahydrate[5]. Recently, a one-step synthesis of α-azidoketones was reported from the corresponding ketones using [hydroxyl(tosyloxy)iodo]-benzene and sodium azide in presence of a phase-transfer catalyst under solvent-free conditions[6]. However, all the known methods for α-azidoketones suffered from one or more limitations as regards tedious reaction procedure, long reaction times, and relatively low yields. Invariably all the reported reactions are conducted in volatile toxic organic solvents. In addition, there are the usual purification problems associated with distillation[7] of products from the incomplete reactions, since some azido compounds decompose rapidly posing the danger of explosion.

The ionic liquids, especially those based on 1,3-dialkylimidazolium cations, have gained considerable interest as green alternative to volatile organic solvents in recent years[8]. Their non-volatile nature without any detectable vapour pressure gives them significant advantage in minimizing solvent consumption and addresses the problem of emission of volatile organic solvents (VOS) in atmosphere and thus make these solvents environmentally attractive alternatives to classical organic solvents. They have unique chemical and physical properties such as excellent chemical and thermal stability and non-flammability, and these properties of ionic liquids can be tuned by changing the alkyl chains or anions[9].

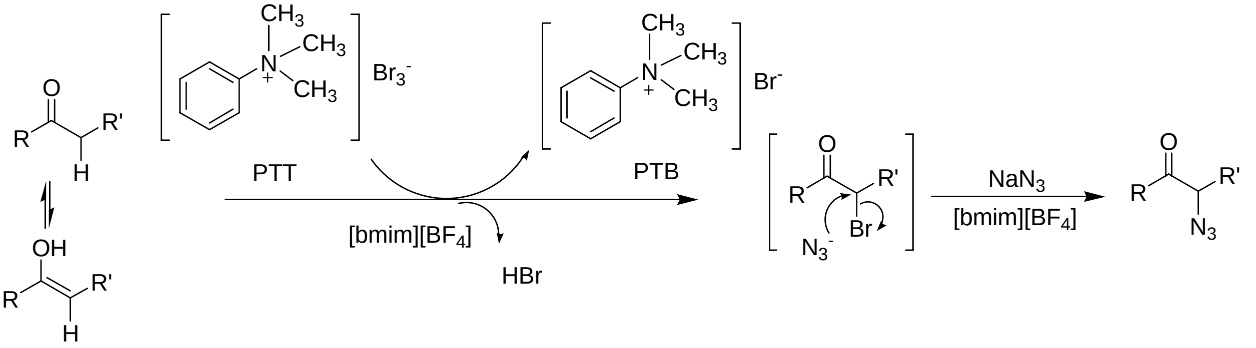
In continuation of our interest in ionic liquids as alternative reaction media for various organic transformations[10], herein are reported preliminary results of one-pot method for synthesis of α-azidoketones from ketones using phenyltrimethylammonium tribromide (PTT) and sodium azide in ionic liquid (**Scheme I**).

Results and Discussion

Synthesis of α-azidoacetophenone **2a** was attempted by mixing acetophenone **1a** with equimolar PTT, followed by sodium azide in dichloromethane at RT. However, no formation of **2a** was detected even after 24 hr. On the other hand, when the reaction was carried out in ionic liquid [bmim][BF_4], exclusive formation of **2a** in high yield was observed. This is possibly due to high solubility of PTT in ionic liquid and also favourable enolization derived reaction of ketone to α-bromoacetophenone. The α-bromo acetophenone, *in situ* reacts with NaN_3 by substitution mechanism (**Scheme II**). Presence of ionic liquid is also expected to accelerate this substitution step. Similar effect of ionic liquid has been reported for fluorination by nucleophilic substitution[11], nucleophilic substitution of activated aryl halides with secondary amines[12] and reactivity of anionic nucleophiles in ionic liquids[13].



Scheme I



Scheme II — Plausible mechanism for the synthesis of α-azidoketones from ketones using phenyltrimethylammonium tribromide (PTT)

The reaction condition was optimized by varying amount of PTT, NaN_3, reaction time, and ionic liquids. It was found that the best yields are obtained by adding 1.1 equivalent of PTT, stirring reaction for 15-20 min followed by addition of 1.5 equivalent of NaN_3 at RT in [bmim][BF_4]. A mixture of acetopheneone **1a** (100 mg) and PTT (1.1 equiv.) in ionic liquid [bmim][BF_4] (3.0 mL) was stirred at RT for 15 min followed by addition of NaN_3 (1.5 equiv.) and stirring was continued for additional 2 hr. The reaction mixture was extracted with diethyl ether (2 × 5 mL). The organic phase was dried over anhydrous $NaSO_4$ and concentrated on a rotary evaporator. The residue was percolated through a column of silica gel using ethyl acetate/hexane (1:9, v/v) as eluent to afford the pure **2a** in 96% yield. The formation of **2a** was indicated by a characteristic peak of azide group in IR at 2110 cm^{-1}. Following the success of this reaction, the general scope of this method was examined with a number of aryl ketones, cyclic ketones, acyclic ketones and heterocyclic ketones. The procedure was found to be of general application and successfully gave various α-azidoketones **2b-q** in high yields (**Scheme I, Table I**).

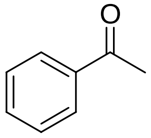
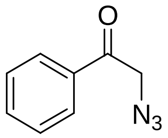
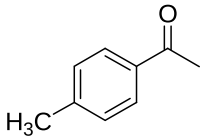
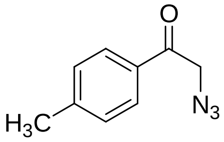
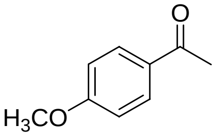
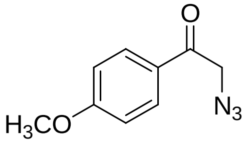
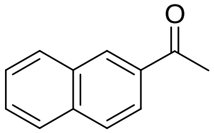
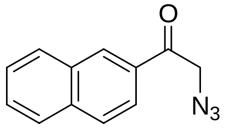
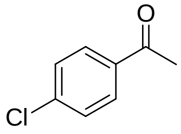
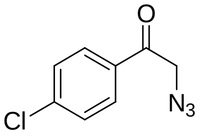
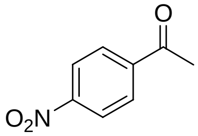
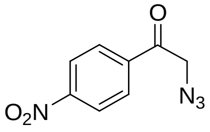
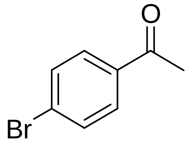
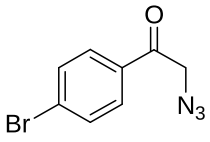
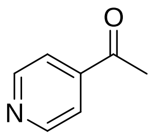
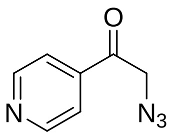
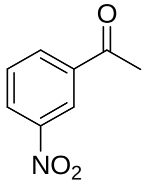
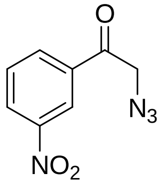
To study the reusability, the recovered ionic liquid was reused for reaction of **1a** with PTT followed by NaN_3 to give **2a**. After extraction of product from ionic liquid with diethyl ether, the ionic liquid was dried under vacuum for 10 min. To this dried ionic liquid, **1a** and PTT were added and stirred at RT for 15 min. To this reaction mixture, NaN_3 was added and the reaction mixture stirred at RT for 2 hr. After completion of reaction the product was extracted with diethyl ether. For the same reaction this cycle was repeated five times giving **2a** in 96, 92, 93, 89 and 87% yield, respectively. The ionic liquid showed good reusability even after five cycles with very little deterioration in yield of product which is expected due to accumulation of sodium bromide in ionic liquid making it more viscous.

In conclusion, α-azidoketones are prepared in high yields from cyclic, acyclic, aromatic and heterocyclic ketones possessing α-hydrogen with PTT and subsequent treatment with NaN_3 in one-pot procedure in ionic liquid. This is a novel and efficient method for direct synthesis of α-azidoketones from various ketones under milder and environment friendly conditions.

Experimental Section

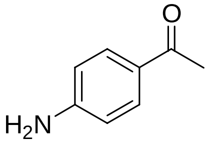
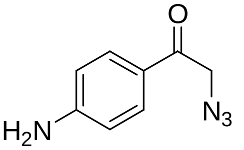
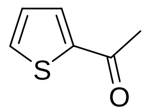
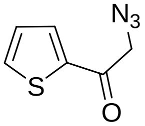
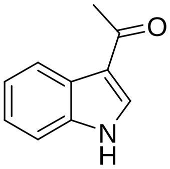
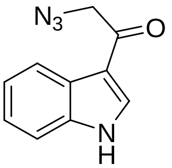
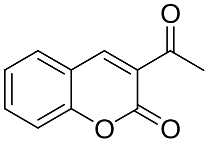
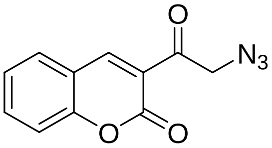
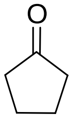
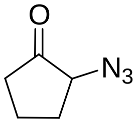
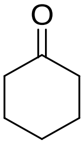
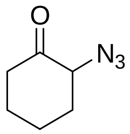
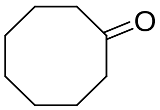
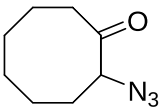
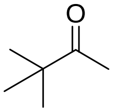
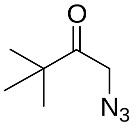
The ^1H NMR spectra were recorded on a Brucker Heaven Avance 11 400 (400 MHz) spectrometer using TMS as internal standard and $CDCl_3$ as solvent and the chemical shifts were expressed in ppm. The IR spectra were recorded using KBr pellets on Shimadzu Prestige-21 FTIR spectrometer and ν_{max} was expressed in cm^{-1}. EI-MS spectra were recorded on a Jeol SX 102/DA-6000 (6 KV, 10 mA) mass spectrometer. The required ionic liquid [bmim][BF_4] was prepared according to the reported procedure by alkylation of 1-methylimidazole with 1-bromobutane followed by substitution of bromide anion with tetrafluoroborate in dry acetone[14]. PTT was synthesized by modification of reported procedure from the reaction of *N*,*N*-dimethyl aniline and dimethyl sulfate

Table I — Synthesis of α-azidoketones from ketones catalyzed by PTT in ionic liquid

Compd	Ketone	Product	Time (hr)	Yield (%)[a]
2a			2	96
2b			2	95
2c			2	96
2d			2	92
2e			3	94
2f			3	91
2g			3	92
2h			3	89
2i			3	91

—Contd

Table I — Synthesis of α-azidoketones from ketones catalyzed by PTT in ionic liquid—*Contd*

Compd	Ketone	Product	Time (hr)	Yield (%)[a]
2j			2	93
2k			2	94
2l			2	88
2m			2	92
2n			2	93
2o			2	92
2p			2	90
2q			3	81

[a]All the compounds showed satisfactory IR, ^{1}H NMR and mass spectra.

followed by addition of hydrobromic acid and bromine[15]. Ketones and sodium azide were purchased form SD Fine and Spectrochem, India. Sodium tetrafluoroborate and 1-methylimidazole were purchased from Aldrich. The homogeneity of the products was determined on silica-coated aluminium TLC plates (Merck).

Representative procedure

To a 10 mL round bottom flask containing ionic liquid [bmim][BF$_4$] (3.0 mL) was added **1a** (100 mg, 0.83 mmole) and PTT (342 mg, 0.91 mmole). The reaction mixture was stirred at RT for 15 min. Sodium azide (81 mg, 1.25 mmole) was added to the reaction-mixture and continued stirring for 2 hr at RT. After completion of the reaction as indicated by TLC, the reaction-mixture was extracted with diethyl ether (2 × 5 mL). The combined organic layer was dried and evaporated under reduced pressure. The residue was percolated through a bed of silica gel 60-120 mesh using hexane-ethyl acetate (95:5 v/v) as eluent to give pure **2a** (150 mg, 96%). The obtained **2a** was characterized by ^{1}H NMR, IR and mass spectroscopic data. Similarly, other substituted α-azidoketones **2b-q** were prepared by the reaction of corresponding ketones **1b-q** and characterized by comparison of IR, ^{1}H NMR and EI-MS spectroscopic data.

Spectroscopic data for selected α-azidoketones

α-Azidoacetophenone, 2a: IR (KBr): 2210 (N_3), 1694 (C=O), 1660 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.57 (2H, s, $COCH_2$), 8.10 (m, 1H, ArHs), 7.92 (m, 1H, ArHs), 7.48 (m, 3H, ArHs); EI-MS: *m/z* 183.32 $(M + Na\text{-}H)^+$.

α-Azido-4-methylacetophenone, 2b: IR (KBr): 2210 (N_3), 1687 (C=O), 1658 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.43 (3H, s, CH_3), 4.55 (s, 2H, $COCH_2$), 7.11 (d, *J* = 6.8 Hz, 2H, ArHs), 7.81 (d, *J* = 6.8 Hz, 2H, ArHs); EI-MS: *m/z* 176.13 $(M + H)^+$.

α-Azido-4-chloroacetophenone, 2e: IR (KBr): 2213 (N_3), 1698 (C=O), 1661 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.53 (s, 2H, $COCH_2$), 7.41 (d, *J* = 6.4 Hz, 2H, ArHs), 7.90 (d, *J* = 6.4 Hz, 2H, ArHs); EI-MS: *m/z* 195.82 $(M + H)^+$.

α-Azido-4-nitroacetophenone, 2f: IR (KBr): 2210 (N_3), 1701 (C=O), 1660 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.61 (s, 2H, $COCH_2$), 8.10 (m, 2H, ArHs), 8.33 (m, 2H, ArHs); EI-MS: *m/z* 206.98 $(M + H)^+$.

α-Azido-4-bromoacetophenone, 2g: IR (KBr): 2212 (N_3), 1697 (C=O), 1663 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.53 (s, 2H, $COCH_2$), 7.64 (d, *J* = 8.4 Hz, 2H, ArHs), 7.79 (d, *J* = 8.4 Hz, 2H, ArHs); EI-MS: *m/z* 241.14 and 238.13.

α-Azido-4-aminoacetophenone, 2j: IR (KBr): 3314 and 3308 (brs, NH_2), 2215 (N_3), 1693 (C=O), 1661 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.62 (s, 2H, $COCH_2$), 6.73 (d, *J* = 8.4 Hz, 2H, ArHs), 7.71 (d, *J* = 8.4 Hz, 2H, ArHs), 8.0 (2H, NH_2); EI-MS: *m/z* 216.14 $(M + K)^+$.

2-(α-Azidoacetyl)thiophene, 2k: IR (KBr): 2212 (N_3), 1688 (C=O), 1643 (C=C), 1009 (C-O), cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.74 (s, 2H, $COCH_2$), 7.13 (s, 1H, C_5-H), 7.63 (d, *J* = 8.4 Hz, 1H, C_4-H), 7.70 (m, 1H, C_2-H); EI-MS: *m/z* 191. 08 $(M + Na)^+$.

3-(α-Azidoacetyl)coumarin, 2m: IR (KBr): 2221 (N_3), 1714 (C=O), 1698 (-O-C=O), 1663 (C=C), 1110 and 1053 (C-O), cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.74 (s, 2H, $COCH_2$), 7.41 (m, 2H, ArHs), 7.71 (m, 2H, ArHs), 8.70 (s, 1H, C_4-H); EI-MS: *m/z* 230.19 $(M + H)^+$.

α-Azidopentanone, 2n: IR (KBr): 2115, (N_3), 1724 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.68 (t, *J* = 7.82 Hz, 1H, CHN_3), 2.23 (t, *J* = 7.80 Hz, 2H, $COCH_2$), 1.72-1.96 (m, 4H, CH_2CH_2); EI-MS: *m/z* 126.1389 $(M + H)^+$.

α-Azidohexanone, 2o: IR (KBr): 2117 (N_3), 1715 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.56 (t, *J* = 7.45 Hz, 1H, CHN_3), 2.27 (t, *J* = 7.36 Hz, 2H, $COCH_2$), 1.75-1.99 (m, 6H, $(CH_2)_3$); EI-MS: *m/z* 129.6245 $(M + H)^+$.

Acknowledgement

The financial support by Department of Science and Technology, New Delhi (SR-FTP-CS-34-2007) and Birla Institute of Technology and Science, Pilani is gratefully acknowledged. The authors are also thankful to Mr. Avtar Singh at SAIF, Punjab University, Chandigarh, Punjab for recording ^{1}H NMR of the samples.

References

1 (a) Majo V J & Perumal P T, *J Org Chem,* 63, **1998**, 7136; (b) Fan X & Zhang Y, *Tetrahedron Lett,* 43, **2002**, 1863; (c) Nakajima M, Loeschorn C A, Cimberlo W E & Anselme J P, *Org Prep Proced,* 12, **1980**, 265; (d) Molina P, Fresenda P M & Almendros P, *Synthesis,* **1993**, 54; (e) Takeuchi H, Yanagida S, Ozaki T, Hagiwara S & Eguchi S, *J Org Chem,* 54, **1989**, 431; (f) Scriven E F V & Turnbull K, *Chem Rev* 88, **1988,** 297.

2 (a) Varma R S, Naicker K P & Kumar D, *J Mol Catl A: Chem,* 149, **1999**, 153; (b) Varma R S & Kumar D, *Catal Lett,* 53, **1998**, 225.

3 (a) Lee J C & Lee J S, *Bull Korean Chem Soc,* 26, **2005**, 1493; (b) Lee J C, Kim S & Shin W C, *Synth Comm,* 30, **2000**, 4271.

4 (a) Alvarez S G & Alvarez M T, *Synthesis,* **1997**, 413; (b) Patonay T & Hoffman R V, *J Org Chem,* 59, **1994**, 2902; (c) Benati L, Nanni D, Sangiorgi C & Spagnolo P, *J Org Chem,* 64, **1999**, 7836; (d) Magnus P & Barth L, *Tetrahedron Lett,* 33, **1992**, 2111.

5 Yadav J S, Reddy B V S & Srinivas M, *Chem Lett,* 33, **2004**, 882.

6 Kumar D, Sundaree S & Rao V S, *Synth Comm,* 36, **2006**, 1893.

7 Marsh F D, *J Org Chem,* 37, **1972**, 2966.

8 For recent reviews on ionic liquids see (a) Parvulescu V I & Hardacre C, *Chem Rev,* 107, **2007,** 2615; (b) Jain N, Kumar A, Chauhan S & Chauhan S M S, *Tetrahedron,* 61, **2005**, 1015; (c) Song C E, *Chem Commun,* **2004,** 1033; (d) Dupont J, DeSouza R F & Suarez P A Z, *Chem Rev,* 102, **2002**, 3667.

9 (a) Tao G-H, He L, Sun N & Kou Y, *Chem Commun,* **2005**, 3562; (b) Freemantle M, *Chem Eng News,* 76, **1998**, 32.

10 (a) Kumar A, Jain N & Chauhan S M S, *Synlett,* **2007**, 411; (b) Chhikara B S, Tehlan S & Kumar A, *Synlett,* **2005**, 63; (c) Kumar A, Jain N, Rana S & Chauhan S M S, *Synlett,* **2004**, 2785; (d) Kumar A, Jain N & Chauhan S M S, *Synth*

Commun, 34, **2004**, 2835; (e) Chauhan S M S, Kumar A & Srinivas K A, *Chem Commun,* **2003**, 2348.

11 (a) Kim D W, Soong C E & Chi C Y, *J Am Chem Soc,* 124, **2002**, 10278.

12 (a) Yadav J S, Reddy B V S, Basak A K & Naraiash A V, *Tetrahedron Lett,* 44, **2003**, 2217; (b) Angrish C, Kumar A & Chauhan S M S, *Indian J Chem,* 44B, **2005**, 1515.

13 Betti C, Landini D & Maia A, *Tetrahedron,* 64, **2008**, 1689.

14 Srinivas K A, Kumar A & Chauhan S M S, *Chem Commun,* **2002,** 2456.

15 (a) Marquet A & Jacques J, *Tetrahedron Lett,* 1, **1959**, 24; (b) Marquet A & Jacques, *Organic Syntheses*, Coll. Vol. 6, **1988**, p.175.