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Tetrahedron
Tetrahedron 63 (2007) 155–159

Ionic liquid promoted selective debromination of α-bromoketones under microwave irradiation

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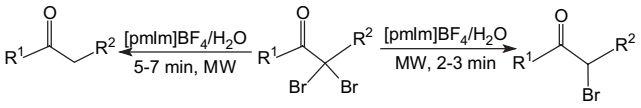
Received 17 July 2006; revised 27 September 2006; accepted 12 October 2006
Available online 9 November 2006

Abstract—The debromination of α-bromoketones with an easily accessible ionic liquid, 1-methyl-3-pentylimidazolium tetrafluoroborate, [pmIm]BF_4 under microwave irradiation has been investigated. By controlling the reaction time *gem*-α-dibromoketones are selectively debrominated to either monobromo or debromoketones. The α-monobromo- and α-monoiodoketones are dehalogenated while the corresponding chloroketones remain inert. The activated *vic*-bromoacetates are converted to the corresponding (*E*)-alkenes by the same procedure. These reactions do not require any organic solvent, any metal or any conventional reducing agent. The ionic liquid works here as catalyst as well as reaction medium and is recycled without any appreciable loss of its catalytic efficiency.

1. Introduction

The selective debromination of α-bromoketones is a useful transformation in organic synthesis and remains a challenging problem because of the presence of more than one reducible groups.[1] The problem becomes more complicated in α-dibromoketones particularly when selective debromination of one bromo group is required. Although, a number of methods have been reported[2] for the debromination of α-bromocarbonyl compounds using a variety of reagents[2] such as triphenyl phosphine in methanol,[2a] pyridinium salts,[2b] hydridotetracarbonylferrate anion,[2c] molybdenum hexacarbonyl on alumina,[2d] sodium iodide–chlorotrimethylsilane,[2e] triphenylphosphonium iodide,[2f] sodium borohydride–antimony tribromide,[2g] sodium amalgam in CH_3OD,[2h] HBr–ACOH–$Na_2S_2O_4$,[2i] *n*-Bu_3SnH,[2j] zinc in AcOH,[2k] none of these procedures addressed monodebromination of *gem*-α-dibromoketones. Our literature search (SciFinder, SCOPUS) also did not reveal any such method. This prompted us to find a suitable method for this challenging transformation.

We have been very actively engaged in exploring new facets of ionic liquids[3] in organic transformations for last few years and as a part of this program[4] we recently developed a simple procedure for the stereoselective debromination of *vic*-dibromides by an easily accessible ionic liquid 1-methyl-3-pentylimidazolium tetrafluoroborate, [pmIm]BF_4 under microwave irradiation.[4j] We report here another novel application of this ionic liquid for selective debromination of *gem*-α-dibromoketones to monobromo- and debromoketones by proper control of reaction time (Scheme 1).



R^1 = Ar, OEt; R^2 = COPh, COMe, Me, H

Scheme 1.

2. Results and discussion

The experimental procedure is very simple. A mixture of *gem*-α-dibromoketone and [pmIm]BF_4 with a drop of H_2O was heated under microwave (MW) irradiation. The monobromoketone was obtained by irradiation over 2–3 min (TLC) and the doubly debrominated ketone was isolated by irradiation for 5–7 min. In each case, the product was isolated by extraction with ethyl acetate followed by purification by column chromatography. The remaining ionic liquid after being washed and dried was reused for five runs without any appreciable loss of efficacy. After five runs fresh ionic liquid (half of the initial amount taken) was added and the reaction was continued without any difficulty.

Several activated *gem*-α-dibromoketones were reacted according to this procedure to produce either monobromoketones or doubly debrominated ketone when exposed to microwave irradiation for a selective period of time. The results are summarized in Table 1. It was found that the crude

Keywords: Ionic liquid; Bromoketones; Debromination; Microwave irradiation.
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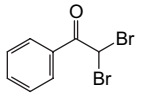
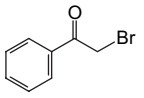
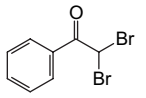
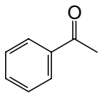
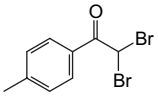
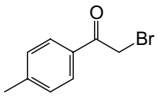
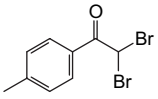
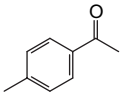
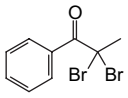
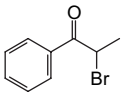
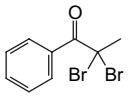
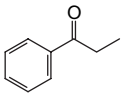
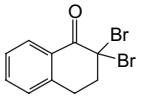
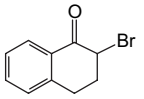
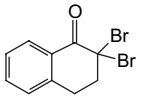
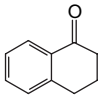
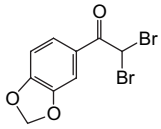
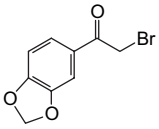
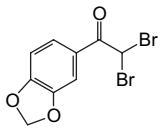
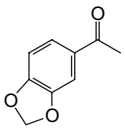
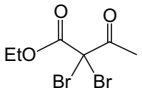
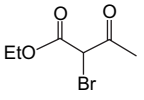
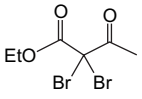
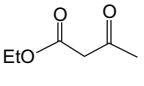
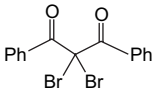
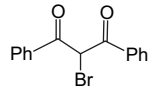
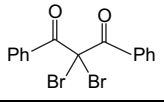
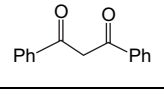
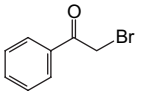
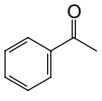
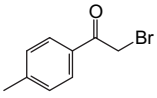
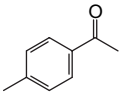
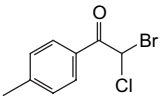
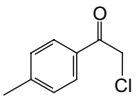
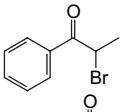
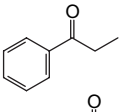
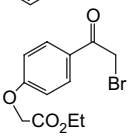
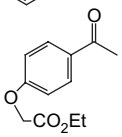
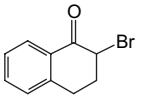
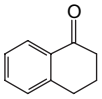
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.10.035

Table 1. Selective debromination of dibromo compounds catalyzed by [pmIm]BF_4

Entry	Substrate	Time (min)	Product	Yield (%)[a]	Ref.
1a		2.5		85	2i
1b		6.5		82	2i
2a		2.5		85	6
2b		7.0		80	6
3a		2.5		90	6
3b		7.0		75	2g
4a		2.0		86	7
4b		6.5		78	7
5a		2.5		75	
5b		7.0		70	
6a		2.0		85	2i
6b		5.0		85	2i
7a		2.0		85	7
7b		5.5		80	7

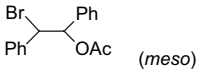
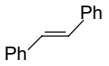
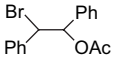
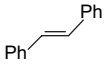
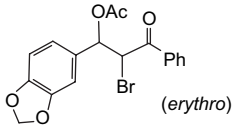
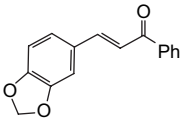
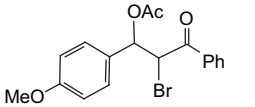
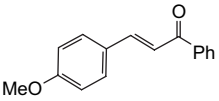
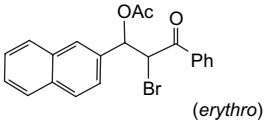
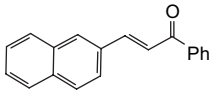
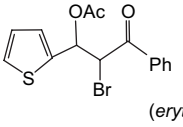
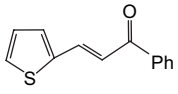
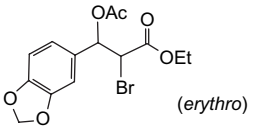
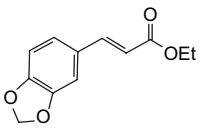
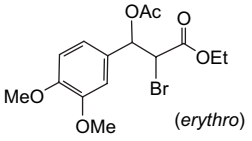
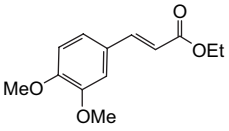
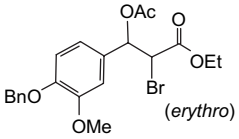
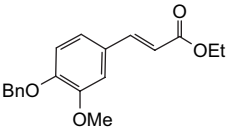
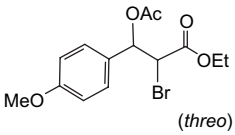
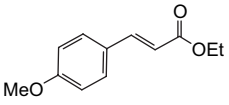
[a] The yields refer to those of pure isolated products characterized by IR, ^1H and ^{13}C NMR spectroscopic data.

Table 2. Dehalogenation of α-halo ketones and esters catalyzed by [pmIm]BF_4

Entry	Substrate	Time (min)	Product	Yield (%)[a]	Ref.
1		4.0		85	2i
2		3.5		90	6
3		4.0		85	8
4		4.0		85	2g
5		4.5		80	
6		4.0		95	7
7		2.0		70	9
8		2.0		85	7
9		2.5		85	
10		2.0		90	7
11		2.0		95	2i
12		2.0		90	11
13		2.0		85	7
14		1.5		70	9
15		2.0		90	9

[a] The yields refer to those of pure isolated products characterized by IR, ^1H and ^{13}C NMR spectroscopic data.

Table 3. Stereoselective debromination–eliminationn of *vic*-bromo acetates catalyzed by [pmIm]BF_4

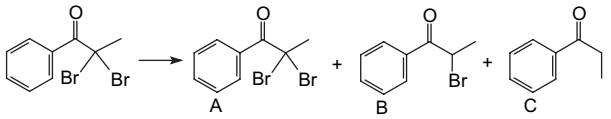
Entry	Substrate	Time (min)	Product	Yield (%)[a]	Ref.
1	 (*meso*)	3		82	5b
2	 (*dl*)	3.5		67	5b
3	 (*erythro*)	3		80	4j
4	 (*erythro*)	3		85	4j
5	 (*erythro*)	3		80	4j
6	 (*erythro*)	3		60	4j
7	 (*erythro*)	3		82	10
8	 (*erythro*)	3		85	10
9	 (*erythro*)	3.5		85	10
10	 (*threo*)	3		80	10

[a] The yields refer to those of pure isolated products characterized by IR, ^1H and ^{13}C spectroscopic data.

monobromo products contain 2–5% of the corresponding doubly debrominated ketones; however, pure compounds were obtained easily by chromatographic purification. On the other hand, debrominated compounds were obtained in high purity after just a simple work up. α-Monobromoketones also underwent facile debromination to the parent ketone when exposed to this procedure. The results are reported in Table 2.

It was observed that chloride remained inert under the reaction condition (entry 3, Table 2) while iodides were rapidly removed (entries 12–14, Table 2). Thus, this procedure can lead to the selective removal of a bromide in the presence of a chloride functionality. By simple manipulation this reaction was also successfully utilized for stereoselective olefin formation by debromination–elimination of *vic*-acetoxybromo

Table 4. Results of debromination with conventional reagents

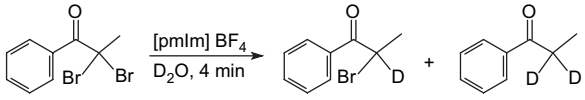


Reducing agent	Time (h), condition	Ratio of A, B and C
$(n\text{Bu})_3\text{SnH}$[2j]	12, reflux (85 °C)	42:58:00
NaI, TMSCl[2e]	12, rt	24:61:15
Zn in AcOH(1 equiv)[2k]	9, rt	40:32:28
Ph_3P (1.2 equiv) in CH_3OH and C_6H_6[2a]	12, reflux	10:65:21

derivatives.[5] The results are summarized in Table 3. Interestingly, only (*E*)-alkenes were obtained from all the substrates illustrated in Table 3 in accordance with the earlier observations in the debromination of *vic*-dibromides by this ionic liquid, $[pmIm]BF_4$.[4j]

The selective debromination of *gem*-dibromoketones to monobromoketones by this reagent is unique since no reports of such selectivity for this transformation have been found in the literature. Our own findings on the use of conventional reagents for this debromination reaction were also very disappointing (Table 4). None of these reagents showed appreciable selectivity towards monodebromination.

The ionic liquid, $[pmIm]BF_4$, plays a vital role in this transformation as no reaction was observed in the absence of ionic liquid. It was also found that this reaction did not proceed at all at room temperature or under conventional heating. A similar imidazolium based ionic liquid, [pmIm]Br, also catalyzed this reaction; however, the reaction with $[pmIm]BF_4$ was both faster and cleaner. Thus, this ionic liquid was chosen for all the reactions. As mentioned earlier, the ionic liquid remained intact after the reaction and was recycled in subsequent runs without any difficulty. In consideration of all these views, probably the reaction is going through an enolate formed by abstraction of one bromonium ion, which was then protonated by traces of H_2O present in the ionic liquid. This hypothesis gets support by the isolation of the deuterated bromoketone and ketone from a reaction carried out in the presence of D_2O (Scheme 2).



Scheme 2.

In general, reactions by this procedure are very clean, high yielding and fast. Although, the reaction proceeds with a 5 mol % of ionic liquid, the best condition for a clean and faster reaction was found by using 5 equiv of ionic liquid. One good feature of this reagent is that reducible groups such as carbonyl and carboxylic ester are safe under this procedure, as this ionic liquid does not function like a conventional reducing agent.

3. Conclusion

This procedure using an easily accessible ionic liquid, $[pmIm]BF_4$, as catalyst demonstrates a novel and efficient protocol for highly selective debromination of *gem*-α-dibromoketones to monobromoketones or debromoketones by proper control of reaction time. To the best of our knowledge, we are not aware of any such use of ionic liquid for this transformation. The significant advantages offered by this procedure are operational simplicity, fast reaction, high selectivity, excellent yields of products, no reduction of other reducible functionalities, recyclable catalyst and use of no organic solvent and toxic reagent in the reaction. We believe, this reaction will find suitable applications in organic synthesis and will lead to further useful chemistry.

4. Experimental

4.1. General

The ionic liquid, $[pmIm]BF_4$, was prepared by the metathesis reaction of [pmIm]Br[12a] with $NaBF_4$ following a reported procedure.[12b] The dibromides were prepared following known procedures.[13a,b] IR spectra were taken as thin films for liquid compounds and as KBr pellets for solids. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 300 and 75 MHz, respectively.

4.1.1. General experimental procedure for the debromination of *gem*-α-dibromoketones; representative one for debromination of 2,2-dibromo-1-phenylethanone (entry 1, Table 1). A mixture of 2,2-dibromo-1-phenylethanone (277 mg, 1 mmol) and ionic liquid, 1-methyl-3-pentylimidazolium tetrafluoroborate, $[pmIm]BF_4$ (1.2 g, 5 mmol) mixed with one drop of H_2O was subjected to microwave irradiation in a microwave reactor (CEM Corporation, 300 W, 125 °C, 50 psi) for 2.5 min (TLC). The reaction mixture was allowed to cool and extracted with ethyl acetate (3×5 mL). Evaporation of the solvent left the crude product, which was purified by column chromatography (hexane–ethyl acetate, 97:3; R_f for monobromo compound: 0.32 and R_f for doubly debrominated compound: 0.27) to give the pure monobromo-product, 2-bromo-1-phenylethanone (169 mg, 85%) as a colorless oil. IR (neat) 3057, 1697 cm^{-1}; ^1H NMR δ 4.43 (s, 3H), 7.41–7.46 (m, 2H), 7.53–7.58 (m, 1H), 7.91–7.94 (m, 2H); ^{13}C NMR δ 190.9, 133.8, 133.7, 128.7 (2C), 128.6 (2C), 31.1. These values are in good agreement with the reported data.[2i]

When this reaction was irradiated for 6.5 min, the completely debrominated product, acetophenone (R_f value: 0.27) (82%) was obtained. The spectroscopic data were in good accord with those of an authentic sample.

This procedure was followed for all the reactions listed in Tables 1–3. All these products except compounds in entries (Table 1) and entry (Table 2) are known compounds and their spectroscopic data (IR, ^1H and ^{13}C NMR) were identical with those reported (references in Tables 1–3).[2i,g,6–11,5b,4j,] The spectroscopic data of these three compounds and elemental analysis were provided below:

4.1.2. 1-Benzo[1,3]dioxol-5-yl-2-bromoethane (entry 5a, Table 1). White solid, mp (pet ether) 90–93 °C; IR (KBr) 2999, 2952, 2914, 1683, 1602, 1504, 1488, 1288, 1248, 933, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.39 (s,

2H), 6.08 (s, 2H), 6.09 (d, 1H, J=8.2 Hz), 7.46 (s, 1H), 7.60 (d, 1H, J=8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.0, 102.5, 108.5, 108.9, 126.0, 129.0, 148.8, 152.9, 189.9. Anal. Calcd for $C_9H_7BrO_3$: C, 44.47; H, 2.9. Found: C, 44.09; H, 2.6.

4.1.3. 1-Benzo[1,3]dioxol-5-yl-ethanone (entry 5b, Table 1). White solid, mp (pet ether) 84–86 °C; IR (KBr) 3072, 2974, 2916, 2854, 1662, 1602, 1448, 1348, 1282, 1114, 855, 709, 603 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 5.91 (s, 2H), 6.75 (d, 1H, J=8.3 Hz), 7.30 (s, 1H), 7.45 (d, 1H, J=8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 102.2, 108.1, 108.2, 125.1, 132.4, 148.5, 152.1, 196.5. Anal. Calcd for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.79; H, 4.88.

4.1.4. (4-Acetyl-phenoxy)acetic acid ethyl ester (entry 5, Table 2). Colorless oil; IR (neat) 2983, 2937, 1755, 1678, 1600, 1508, 1427, 1359, 1271, 1174, 1116, 985, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, 3H, J=7.1 Hz), 2.30 (s, 3H), 4.03 (q, 2H, J=7.1 Hz), 4.47 (s, 2H), 6.71 (d, 2H, J=8.8 Hz), 7.71 (d, 2H, J=8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 26.6, 61.8, 65.4, 114.6, 130.8, 131.4, 161.8, 168.5, 196.9. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.77; H, 6.30.

The ionic liquid remaining in the flask was rinsed with ethyl acetate and dried under vacuum at 80 °C to be used for subsequent reactions. This can be used for reactions for up to five runs without any appreciable loss of efficacy. After five runs, about 50% fresh ionic liquid was added to it, and the mixture was found to be good for several more reactions.

Although, the representative procedure is based on a milligram scale, it has been scaled up to multigram level without any difficulty.

Acknowledgements

This investigation has enjoyed financial support from CSIR [grant no. 01(1936)/04], New Delhi. K.C. and R.J. are also thankful to CSIR for their fellowships.

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