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A green approach for efficient α-halogenation of β-dicarbonyl compounds and cyclic ketones using *N*-halosuccinimides in ionic liquids

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Abstract—Room temperature ionic liquids (ILs) are used as a green recyclable reaction media for the α-monohalogenation of 1,3-diketones, β-keto-esters and cyclic ketones with *N*-halosuccinimides in excellent yields in the absence of a catalyst. The recovered ionic liquid was reused five to six times with consistent activity.

α-Halogenation of 1,3-dicarbonyl compounds is an important transformation as the α-halogenated products are versatile intermediates in organic synthesis[1] since their high reactivity makes them prone to react with a large number of nucleophiles to provide a variety of useful compounds. α-Monobromination of 1,3-dicarbonyl compounds without α-substituents has been a challenging problem since the monosubstituted product is always accompanied by a small amount of disubstituted product. A number of methods have been described previously for the halogenation of 1,3-dicarbonyl compounds.[2] Conventional methods for the bromination of β-keto-esters involve the use of various reagents include bromine,[3] copper(II) bromide[4] and *N*-bromosuccinimide.[5] In terms of accessibility and ease of handling, *N*-bromosuccinimide is a superior and inexpensive brominating reagent. Previously, NBS has been utilized for bromination of carbonyl compounds using a radical initiator such as, azobisisobutyronitrile (AIBN) or dibenzoyl peroxide (BPO),[6] or in the presence of $Mg(ClO_4)_2$,[7] NH_4OAc[8] and $NaHSO_4{\cdot}SiO_2$.[9] Several methods have been developed for the 2-chlorination[10] and 2-iodination[11] of 1,3-dicarbonyl compounds using NCS or NIS, respectively. Most of these methods involve strongly acidic or basic conditions and the undesirable formation of α,α-dihalogenated products in significant amounts. Other problems associated with these methods are the use of hazardous chemicals, tedious work-up procedures and long reaction times. Furthermore, the use of polar solvents like DMF, DMSO and CH_3CN causes serious environmental pollution. Very recently, we have reported the use of Amberlyst-15 for efficient 2-halogenation of 1,3-keto-esters and cyclic ketones using *N*-halosuccinimides.[12] However, to the best of our knowledge, α-halogenation of 1,3-dicarbonyl compounds and cyclic ketones using ionic liquids has not been previously reported.

Room temperature ionic liquids (RTLs) are recognized as green recyclable alternatives to the traditional volatile organic solvents because of their unique chemical and physical properties.[13] In particular, 1,3-dialkylimidazolium-based ionic liquids have emerged as alternative reaction media for the immobilization of transition metal based catalysts, Lewis acids and enzymes.[14] They are referred to as 'designer solvents' as their properties such as hydrophilicity, hydrophobicity, Lewis acidity, viscosity and density can be altered by changing the cations and/or the counteranions. Their high polarity and ability to solubilize both organic and inorganic compounds can result in enhanced reaction rates and can provide higher selectivities compared to conventional solvents. As a result of their green credentials and potential to enhance rates and selectivities, ionic liquids are finding increasing applications in organic synthesis.[15] Recent reports have shown that they can also promote and

Keywords: Ionic liquids; Halogenation; *N*-Halosuccinimides; β-Dicarbonyl compounds; Cyclic ketones.
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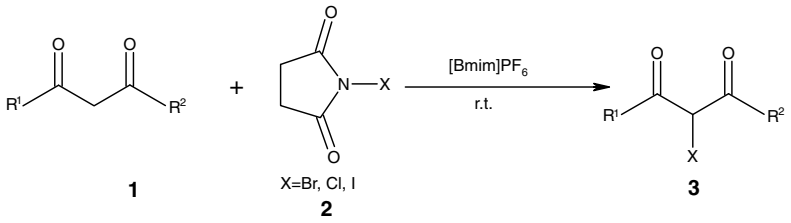


Scheme 1.

catalyze many transformations of commercial importance under mild conditions without the need for any additional acid catalyst.[16,17] We report here the use of an ionic liquid for the halogenation of a wide range of functionalized ketones using *N*-halosuccinimides without the requirement for catalyst, and under mild conditions.

The reaction was initially carried out by treating ethyl benzoylacetate **1a** ($R^1 = Ph$, $R^2 = Et$) with 1.05 equiv of NBS in 2 mL of ionic liquid, [Bmim]PF_6 at ambient temperature affording the α-brominated product in 95% yield (Scheme 1). Next we tested the possibility of chlorination and iodination of compound **1** with NCS or NIS under the same conditions and the 2-chloro- and 2-iodo-1,3-keto-esters were obtained in 93% and 89% yields, respectively. A variety of 2-unsubstituted and 2-substituted 1,3-keto-esters and 1,3-diketones reacted well under these conditions to give the corresponding α-halogenated products in high yields. The results are summarized in Table 1.

Both α-bromination and α-chlorination were accomplished equally well along with somewhat reduced yields in the case of α-iodination. In some cases α,α-dihalo products were formed but as minor products only. Longer reaction times were necessary for aliphatic acyclic keto-esters.

Table 1. 2-Halogenation of various 1,3-keto-esters with *N*-halosuccinimides

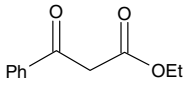
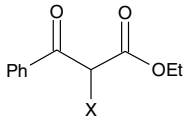
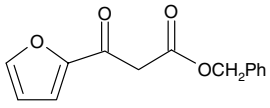
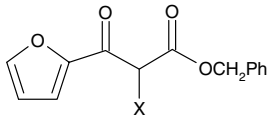
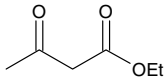
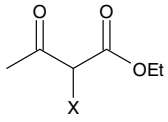
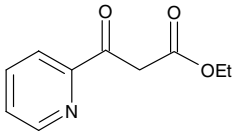
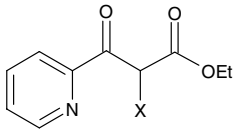
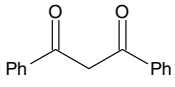
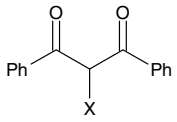
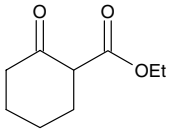
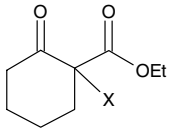
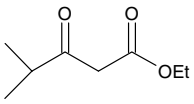
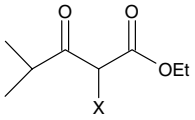
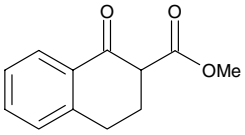
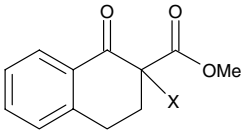
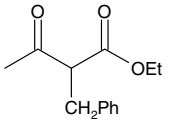
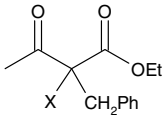
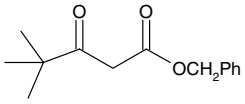
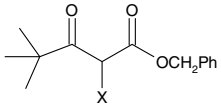
Entry	1,3-Keto-esters **1**	Product[a] X = **3** Br, **3′** = Cl, **3″** = I	X	Time (min)	Yield (%)[b]
a			Br Cl I	20 20 25	95 93 89
b			Br Cl I	30 35 30	92 88 86
c			Br Cl I	50 45 50	89 85 86
d			Br Cl I	15 20 35	90 87 78
e			Br Cl I	10 10 20	90 92 87
f			Br Cl I	20 30 30	94 89 82

Table 1 (*continued*)

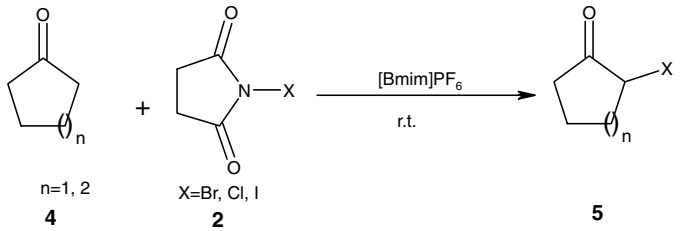
Entry	1,3-Keto-esters **1**	Product[a] X = **3** Br, **3′** = Cl, **3″** = I	X	Time (min)	Yield (%)[b]
g			Br	55	92
			Cl	60	92
			I	60	90
h			Br	20	90
			Cl	20	88
			I	40	85
i			Br	45	82
			Cl	60	80
			I	75	76
j			Br	60	88
			Cl	75	85
			I	75	87

[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Isolated and unoptimized yield.

The method was applied to cyclic ketones, under the same reaction conditions giving exclusively α-mono halo products with high yields in short reaction times (Scheme 2). In the case of 2-methylcyclohexanone (Table 2, entry c) halogenation occurred predominantly at the more substituted position. The reaction was found to applicable to cyclic 1,3-diketones also, dimedone (Table 2, entry d) furnished the corresponding α-halo product in good yield. Attempts to perform the α-halogenation of lactams under these reaction conditions failed. The scope and generality of this process is illustrated with respect to various cyclic ketones, and the results are presented in Table 2.[18]

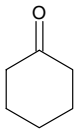
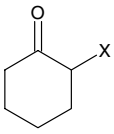
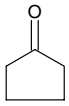
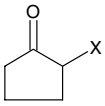
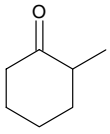
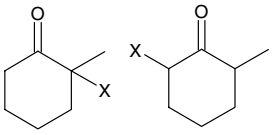
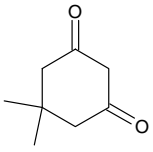
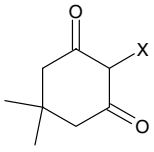
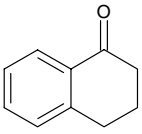
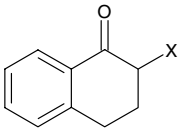
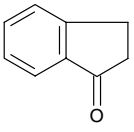
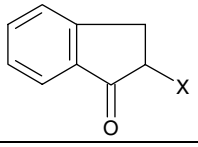
N-Halosuccinimides show enhanced reactivity in the presence of ionic liquids thereby reducing the reaction times, and improving the yields. The rate enhancement in an ionic liquid is probably due to increased polarization of the N–X bond in the polar ionic medium and also to stabilization of the charged ionic intermediates. In an ionic liquid polarization of carbonyl compound is increased significantly compared to organic solvents. The halo cation generated from *N*-halosuccinimide reacted with enol form of carbonyl compound to give the α-halogenated products. Since the products were weakly soluble in the hydrophobic ionic liquid [Bmim]PF_6, they could be easily separated by simple extraction with ether, then the ionic liquid was thoroughly washed with water to remove the water-soluble succinimide. The recovered ionic liquid was activated at 80 °C under reduced pressure and reused without any significant loss of activity. For example, reaction of tetralone (Table 2, entry e) with *N*-bromosuccinimide gave 2-bromotetralone in 92%, 90%, 85% and 80% yields over four cycles. The reaction was also studied in the hydrophilic ionic liquid [bmim]BF_4 and similar results were found. However, removal of succinimide is simple from [Bmim]PF_6 in comparison to [Bmim]BF_4 due to its hydrophobic nature.

In summary, an ionic liquid was shown to be an effective and useful polar alternative reaction medium for the 2-halogenation of 1,3-keto-esters, 1,3-diketones and for α-halogenation of cyclic ketones with *N*-halosuccinimides by playing the dual role of solvent as well as promoter. This procedure offers several unique features,



Scheme 2.

Table 2. α-Halogenation of various cyclic ketones using *N*-halosuccinimides

Entry	Cyclic ketones	Product[a] X = **5** Br, **5′** = Cl, **5″** = I	X	Time (min)	Yield (%)[b]
a			Br	15	94
			Cl	25	90
			I	40	87
b			Br	20	93
			Cl	30	91
			I	40	82
c			Br	20	89
			Cl	30	79
			I	40	74
d			Br	30	81
			Cl	30	86
			I	45	79
e			Br	20	92
			Cl	30	84
			I	30	86
f			Br	30	88
			Cl	30	79
			I	40	86

[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Isolated and unoptimized yield.

providing enhanced yields, shorter reaction times, operational simplicity, mild reaction conditions, ease of isolation of products and a greener aspect by avoiding the need for a catalyst.

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18. *General procedure*: A mixture of 1,3-keto-ester or cyclic ketone (1 mmol), *N*-halosuccinimide (1.05 mmol) in [bmim]PF_6 (2 mL) was stirred at room temperature for the appropriate time (see Tables 1 and 2). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with diethyl ether (3×10 mL). The combined organic extracts were concentrated under vacuum and the resulting product was directly charged on a silica gel (Merck, 60–120 mesh) column and eluted with a mixture of ethyl acetate/*n*-hexane (1:9) to afford the corresponding pure product. The residual ionic liquid was washed with water to remove the succinimide. The ionic liquid was reactivated at 80 °C under reduced pressure and recycled in subsequent runs without any loss of activity. Compound **3b**: IR (KBr): *v* 2963, 1759, 1678, 1461, 1273, 1017, 758, 698, 592 cm^{-1}. ^1H NMR (300 Hz, $CDCl_3$): δ 5.23 (s, 2H), 5.45 (s, 1H), 6.54 (d, 1H, $J = 2.2$ Hz), 7.23–7.34 (m, 6H), 7.51 (s, 1H). EIMS Mass: *m*/*z*: 325 ($M^{81}Br+1$, 11), 323 ($M^{79}Br+1$, 10), 308 (9), 283 (12), 245 (59), 181 (15), 135 (23), 91 (100). Compound **3′g**: IR (KBr): *v* 2979, 1761, 1728, 1466, 1299, 1179, 1023 cm^{-1}. ^1H NMR (300 Hz, $CDCl_3$): δ 1.18 (t, 6H, $J = 7.5$ Hz), 1.33 (t, 3H, $J = 7.5$ Hz), 3.10 (h, 1H, $J = 7.5$ Hz), 4.28 (q, 2H, $J = 7.5$ Hz), 4.83 (s, 1H). EIMS Mass: *m*/*z*: 195 ($M^{37}Cl+1$, 12), 193 ($M^{35}Cl+1$, 10), 144 (9), 139 (11), 118 (17), 102 (100).