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Electrophilic catalysis in nucleophilic substitution reactions in ionic liquids

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Abstract—2-Chlorotropone was obtained from 2-tosyloxytropone in 88% yield in the recyclable ionic medium $BMIMBF_4$/LiCl. That Li^+ acts as a Lewis acid was proven by the lack of reactivity of 2-tosyloxytropone, under the above conditions, on replacing LiCl with NaCl or BMIMCl, or using BMIMCl alone, or a $BMIMBF_4$/MeCN/KCl mixture. 2-Bromo- and 2-iodotropone were obtained along similar lines from LiBr or LiI, respectively, whereas LiF proved unreactive.

The fine chemical industry faces major obstacles to the production of pharmaceuticals and commodities from strict environmental regulations in developed countries. On the other hand, circumventing the problem by moving polluting technologies to emerging countries cannot continue endlessly. Therefore, industry sees 'green chemistry' with increasing interest. Ionic solvents, which practically do not evaporate and can be recycled,[1] are being intensely considered to this regard. Although very expensive, ionic solvents may be a solution for industrial products of very high added value, such as certain perfumes and drugs. Reaction types,[2] and specifically organometallic processes,[3] in ionic solvents have been reviewed, with an accumulation of practical recipes for a variety of processes.[2,3] A systematization of these processes is also being sought through mechanistic studies, in particular for S_N2 reactions with methyl *p*-nitrobenzenesulfonate[4,5] or 2-(3-methanesulfonyloxypropyl)naphthalene.[6,7]

We report here our results for a model system, that is, the replacement of the tosyloxy group by halogen from the α-position of the cycloheptatrienone (tropone) nucleus in ionic solvents. These experiments with sensitive and typically bioactive substrates broaden the view on nucleophilic substitution reactions at the unsaturated carbon. Notably, these are of a special type, requiring peculiar conditions, for example, the presence of a Lewis acid,[8] in order to proceed, in contrast with the above processes,[4–7] which are of the standard S_N2 type.

Our general recipe (Table 1, 2nd column) involved adding LiX (1.5×10^{-3}–2×10^{-3} mol) to 1-butyl-3-methylimidazolium tetrafluoroborate ($BMIMBF_4$) (2 mL), heating the resulting solution to 80 °C and further adding 2-tosyloxytropone (**1**, 0.053 g, 1.92×10^{-4} mol), always under N_2 and stirring. The resulting solution was held at 80 °C for 60 min (X = Cl) or 30 min (X = Br or I), then Et_2O extracted (Kutscher–Steudel apparatus) and evaporated to get a residue that was subjected to silica-gel TLC with THF–petroleum ether 2:3. This led to recover, according to LiX used, 2-chlorotropone (**2**, $R_f = 0.53$, 0.024 g, 88%), 2-bromotropone (**3**, $R_f = 0.54$, 0.013 g, 36%) and 2-iodotropone (**4**, $R_f = 0.57$, 0.017 g, 38%). Using LiF or NaCl in place of the other lithium halogenides, or 1-butyl-3-methylimidazolium chloride (BMIMCl) or 1-butyl-3-methylimidazolium bromide (BMIMBr) in place of $BMIMBF_4$, **1** was recovered unchanged; in particular, in case of LiF, no trace of 2-fluorotropone[9] was detected. Using a mixture $BMIMBF_4$–MeCN–H_2O–KCl—which worked well in the case of 2-(3-methanesulfonyloxypropyl)naphthalene[6]—formation of 2-chlorotropone (**2**) was detected in only trace amounts. The same result was obtained using either DMSO or DMF in place of $BMIMBF_4$.

That these processes can be recycled was shown by heating the above $BMIMBF_4$–LiCl mixture to 80 °C

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Table 1. Synthesis of 2-halotropones[a]

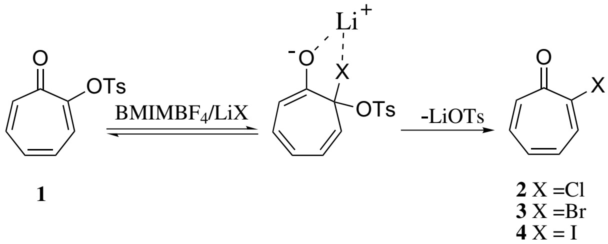
2-X-tropone	$BMIMBF_4/LiX$	$MeOH/BF_3{\cdot}Et_2O/LiX$[b]	von E. Doering conditions[c]	von E. Doering conditions,[c] in our hands[d]
X = Cl (**1**)	88 (79)%	60 (54)%	90%	65 (65)%
X = Br (**2**)	36 (32)%	32 (29)%	75%	44 (29)%
X = I (**3**)	38 (34)%	30 (27)%	54%	33 (21)%

[a] Percent yields on reacted material, in parentheses calculated yields starting from commercially available 2-hydroxytropone.

[b] See Ref. 8.

[c] Starting from 2-hydroxytropone in the X = Cl case, starting from 2-chlorotropone in the X = Br and X = I cases, see note Ref. 10.

[d] During many years of use, see Refs. 8, 9.



Scheme 1.

under vacuum for ca. 1 h, then adding, under N_2 and stirring, **1** (0.045 g, 1.4×10^{-4} mol) and maintaining the mixture under these conditions for 1 h. On cooling and Et_2O extracting as above, **2** was recovered in high yield (0.14 g, 60%). Practical limits to the number of cycles that can be carried out are only posed by the accumulation of moisture during work up.

That these processes are efficient and can be recycled was expected from the use of an ionic solvent.[1–3] But that no catalyst needs to be added, in contrast with previous methodologies,[8,10] is entirely novel and very significant. The catalytic role is exerted here by the reagent itself. This may be rationalized in terms of coordination of lithium ion with both the carbonyl oxygen and the leaving group (Scheme 1).

References and notes

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