Ionic Liquids as Solvents for the Regioselective O-Alkylation of C/O Ambident Nucleophiles.

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A bstract: The reaction of sodium β -naphthoxide with benzyl halides in molten tetraalkylammonium or phosphonium halides (at 110°C or below) leads to a highly regioselective O-alkylation. These new solvents, which can be quantitatively recovered at the end of the reaction, mimic the behaviour of dipolar aprotic solvents.

A great deal of interest has been devoted to the chemical, electrochemical and physicochemical properties of molten salts and melts. ¹⁻⁴ However, only few studies deal with their use in organic chemistry and most of the data in this area are concerned with molten salts as reagents rather than as solvents.⁵ This observation is rather surprising in view of the fact that some of them are low melting, and, owing to their ionic character, may exhibit unique solvation properties. For example, tetraalkylphosphonium (or ammonium) salts are expected to have very low solvating abilities towards anions since the positive charge is in a core surrounded by large aliphatic groups. From that point of view, their behaviour may approach that of dipolar aprotic solvents. To the best of our knowledge, only the special case of *n*-hexyltriethylammonium *n*-hexyltriethylboride has been examined, and it has indeed been shown that its behaviour more closely approximates that of DMF than methanol.⁶ Unfortunately, this molten salt cannot be considered as a solvent since the boride moiety functions as a hydride donor.⁷

In order to examine the behaviour of simple molten phosphonium and ammonium halides we have considered some of them as possible solvents for the C vs O-alkylation of an ambident nucleophile, a reaction which appeared well suited to compare their properties with those of organic solvents.⁸



Indeed, it is well known that the regioselectivity of the alkylation of β -naphthol salts with benzyl bromide strongly depends upon the nature of both the counter ion and the solvent.^{8,9} Broadly speaking, the freer the nucleophile, the higher the O/C alkylation ratio.¹⁰ For instance, for the reaction of sodium β -naphthoxide with benzyl bromide in protic solvents (alcohols), the distribution varies with the acidity of the solvent (the more acidic the alcohol, the lower the O/C alkylation ratio). In aprotic solvents, the O-alkylation is favoured (e.g. O/C alkylation = 60/36 in THF), and in dipolar aprotic ones (DMF, DMSO), the O-alkylation product is always formed with a high selectivity (> 95%).

The low melting tetra-*n*-butylphosphonium and tetra-*n*-butylammonium bromides and chlorides and 1-methyl 3-ethylimidazolium bromide have thus been tested as solvents for the alkylation of sodium β -naphthoxide with benzyl halides.

Alkylation of sodium β -naphthoxide with benzyl bromide

In a first set of experiments, the alkylation was conducted with benzyl bromide at the lowest possible temperature, that is, just a few degrees after the solid mixture of sodium β -naphthoxide and onium halide has melted and become homogeneous. The main results are reported in Table 1.

run	solvent	temp. (°C)	reaction time (h)	conv. ^{b)} (%)	regioselectivity ^{c)}	
					O-alkylation (%)	C-alkylation(%)
1	<i>n</i> -Bu ₄ PBr	88	2	100	93	7
2	<i>n</i> -Bu ₄ NBr	87	2	100	97	3
3	$C_6H_{11}N_2Br^{d}$	57	2	100	93	7
4	n-Bu ₄ PCl	77	72	100	95	5

Table 1: Alkylation of sodium β -naphthoxide with benzyl bromide^{a)}

a) sodium β -naphthoxide: 5 mmol; benzyl bromide: 5 mmol; solvent: 50 mmol

b) determined by GLC analysis with anisole (2.5 mmol) as internal standard

c) determined by ¹H NMR (Bruker WH90) on the benzylic CH₂ signals

d) 1-methyl-3-ethylimidazolium bromide

As may be seen, the four molten salts induce a high regioselectivity for the O-alkylation product. In the case of tetra-*n*-butylphosphonium chloride (run 4), a halogen exchange has been evidenced, leading to large amounts of benzyl chloride which, as expected, reacts much more slowly than benzyl bromide. After complete conversion

of benzyl bromide (GLC), the reaction medium was cooled to room temperature and extracted with diethylether which is not a solvent for these ammonium or phosphonium salts. The latter could thus be quantitatively separated and proved to be unaffected (³¹P and/or ¹H NMR). They could be used as such in a subsequent experiment to give exactly the same result, although they obviously were contaminated with sodium bromide produced in the previous run. Alternatively, dissolution in toluene allows for separation of sodium bromide by filtration.

Alkylation of sodium β -naphthoxide with benzyl chloride

The alkylation of sodium β -naphthoxide with benzyl chloride was also examined. As expected from run 4 (Table 1), this reaction proved to occur more slowly than with benzyl bromide and was thus conducted at 110°C. Some representative results are given in Table 2. As may be seen, the regioselectivity for the O-alkylation product is always very high. The best "solvent" appears to be tetra-*n*-butylammonium bromide (run 6) which is even more efficient than DMF (run 8) with respect to the reaction rate and the regioselectivity. The interest of these onium salts for the isolation of the reaction products is emphasized by run 6 (97% isolated yield). As for reactions reported in Table 1, the phosphonium or ammonium halides could be recovered quantitatively.

run	solvent	temp. (°C)	reaction time (h)	conv. ^{b)} (%)	regioselectivity ^{c)}	
					O-alkylation (%)	C-alkylation (%)
5	<i>n</i> -Bu ₄ PBr	110	48	80	92	8
6	<i>n</i> -Bu ₄ NBr	110	24	100	99 (97) ^{d)}	traces
7	<i>n</i> -Bu ₄ PCl	110	48	89	93	7
8	DMF	110	24	92	95	5

Table 2: Alkylation of sodium β -naphthoxide with benzyl chloride^{a)}

a) sodium β -naphthoxide: 5 mmol; benzyl chloride: 5 mmol; solvent: 50 mmol

b) determined by GLC analysis with anisole (2.5 mmol) as internal standard

c) determined by ¹H NMR (Bruker WH90) on the benzylic CH₂ signals

d) isolated yield

Results from Tables 1 and 2 thus show that the alkylation of sodium β -naphthoxide with benzyl bromide or chloride always leads to a highly regioselective O-alkylation. In that sense, the molten phosphonium or ammonium halides mimic the properties of dipolar aprotic solvents.

The properties of dipolar aprotic organic solvents are due to their specific solvating properties (basicity) towards alkali cations, thus promoting the disruption of associated ion pair and/or aggregates into solvated cations and highly reactive "free" anions.¹⁰ The onium salts examined in this study are obviously aprotic but cannot promote the separation of sodium β -naphthoxide into free ions otherwise than through an ion pairs exchange. By this process, the hard sodium cation is replaced by the large, poorly complexing onium cation. This salt effect¹¹ thus generates the more reactive "free" β -naphthoxide ions which behave as they do in an aprotic dipolar solvent, and the overall result is a highly selective O-alkylation.

Last, it must be emphasized that the onium salts tested in this study exhibit interesting properties as compared to reaction media allowing to obtain similar regioselectivities, *i.e.* classical dipolar aprotic solvents, either pure or in mixture with THF or DME. Indeed, onium salts are non-volatile, easy to dry and, as shown above, can be *quantitatively* recovered at the end of the reaction. They thus appear as non-dangerous, non-polluting and inexpensive reaction medium.

Work is in progress to show whether these new solvents may find interesting applications in organic synthesis.

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