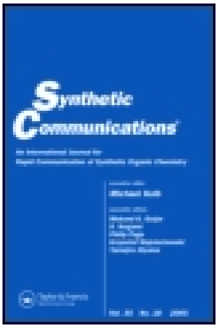

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Alkylation of Imidazole by Solid-Liquid Phase Transfer Catalysis in the Absence of Solvent

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ALKYLATION OF IMIDAZOLE BY SOLID-LIQUID PHASE TRANSFER CATALYSIS IN THE ABSENCE OF SOLVENT.

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ABSTRACT: Phase Transfer Catalysis in the absence of solvent is described as a useful and general method for the selective N-alkylation of imidazole. In all cases high yields are obtained while quaternization is avoided.

Alkylation of imidazole have been performed by reaction of imidazole or more commonly its anion with alkyl halides[1,2]. In both cases is difficult to avoid the formation of imidazolium salts due to the basicity of the N-alkyl derivatives, higher than imidazole itself (N-methylimidazole, pK_a=7.33, imidazole pK_a=6.95)[3]. In order to minimize the quaternization, the use of low temperatures or alkyl halides in stoichiometric amounts and the addition of filters, as trialkylamines have been reported[4]. Classical PTC methods have been used with good results, but they are limited by the poor yields obtained whit long chain halides[5].

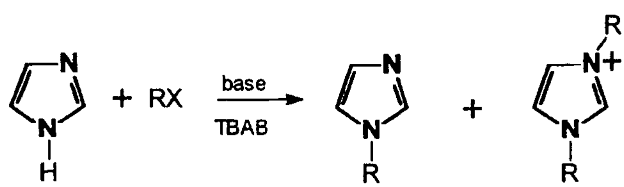
Table 1. Alkylation of imidazole by solid-liquid PTC in the absence of solvent.

entry	RX	base	mole ratio	T(°C)	t(h)	**2 / 3** ratio	**2** yield (%)[a]
1	EtI	KOH	1: 2: 1	0	3	90 / 10	34
2	EtI	KOH	1: 2: 1	25	3	62 / 38	--
3	EtI	KOH	1: 2: 1	40	1	29 / 71	--
4	n-BuBr	KOH	1: 2: 1	25	8	91 / 9	--
5	n-BuBr	KOH	1: 2: 1	80	8	100 / 0	70
6	n-BuBr	KOH	1: 1.2: 1	80	8	91 / 9	78
7	BnBr	KOH	1: 2: 1	25	3	0 / 100	--
8	BnCl	KOH	1: 2: 1	80	6	100 / 0	29
9	BnCl	KOH	1: 1.2: 1	80	0.5	82 / 18	42
10	BnCl	KOBu^t	1: 1.5: 1	25	1	100 / 0	49
11	BnCl	KOBu^t	1: 1.1: 1	25	1	100 / 0	85
12	BnCl	KOBu^t	1: 1: 1	25	0.25	73 / 27	39

a) isolated

Results and discussion

We have tested the alkylation of imidazole by solid-liquid PTC in the absence of solvent[6]. The influence of several factors are gathered in Table 1.



1 **2** **3**

The more reactive halides produce an important proportion of imidazolium salts (entry 3 vs 5), being the only product when benzyl bromide is used (entry 7).

An excess of base must be used to avoid quaternization. This excess has a double positive effect on the monoalkylation, displacement of the equilibrium to the formation of the anion and removal of the water formed during the deprotonation avoiding the solvatation of the imidazole anion (entry 5 vs 6, 8 vs 9, 11 vs 12)[7]. The same effect is observed using a stronger base, potassium *tert*butoxide

Table 2. Selected conditions to alkylation of imidazole.

compound	base	RX	mole ratio	T(°C)	t(h)	2 yield (%)[a]
2a	KOBu^t	EtI	1: 1.1: 1	0	3	77
2b	KOH	n-BuBr	1: 2: 1	80	6	70
2c	KOH	n-OctBr	1: 2: 1	80	6	90
2d	KOH	n-HexadecBr	1: 2: 1	80	6	70
2e	KOBu^t	BnCl	1: 1.1: 1	25	1	85

Table 3. Alkylimidazoles. ^{1}H-NMR δ(ppm) (J,Hz)

	H-2	H-4	H-5	N-CH_2	Others
2a	7.5 (bs)	6.9 (d,1.2)	6.9 (d,1.2)	4.0 (q,7.2)	1.4 (t)
2b	7.5 (bs)	7.0 (d,0.9)	6.9 (t,1)	3.9 (t,7.4)	0.9(t),1.3(sext), 1.7(quint)
2c	7.4 (bs)	7.0 (bs)	6.9 (t,1.2)	3.9 (t,7.2)	0.9(t),1.3(m), 1.8(quint)
2d	7.5 (bs)	7.0 (d,1)	6.9 (d,1)	3.9 (t,7.2)	0.9(t),1.3(m), 1.8(quint)
2e	7.5 (bs)	7.1 (d,1.2)	6.8 (d,1.2)	5.1 (s)	7.1-7.4(m)

(entry11). However, the formation of *tert*butylbenzylether is detected when an excess of base is used (entry 10). Temperature has not an important influence in the alkylation/quaternization ratio (entry 4 vs 5, 8 vs 9), except when more reactive halides are used (entries 1, 2 and 3). Considering the effect of the studied factors the selective preparation of N-alkylimidazoles requires low temperatures (0-25°C) and strong base (PTB) in a slight excess with reactive alkyl halides or higher temperatures (80°C) and mild base (KOH) in a 2 mole excess with the low reactive halides (Table 2).

In conclussion solid-liquid PTC in the absence of solvent is an easy and useful method for the preparation of N-alkylimidazoles. Yields are satisfactories, even when long chain alkyl halides are used and quaternization is avoided.

Experimental

IR spectra were recorded with a Philips PU 9500 spectrophotometer. ^{1}H-NMR spectra ($CDCl_3$) were recorded on a Varian Unity (300MHz) using TMS as internal standard. Microanalysis were peformed at the Centro Nacional de Química Orgánica, C.S.I.C., Madrid, Spain.

General procedure: Imidazole (10 mmol) and the required proportions of base and the catalyst (2%) were mixed and submerged in an ultrasonic cleaning bath (50 w, 200MHz) for 15 minutes. The halide was added at 0°C and the reaction was stirred at the temperature and during the time indicated in tables 1 and 2. Distillation or column chromatography afforded the pure products.

1-Ethylimidazole (**2a**): b.p.: 200°C / 710 mmHg (lit[8] 40-41°C / 0.5 mmHg). IR(neat) ν_{max}(cm^{-1}): 1508, 1463, 1446. 1-Butylimidazole (**2b**): b.p.: 120°C / 11 mmHg (lit[4b] 111-115°C / 15 mmHg). IR(neat) ν_{max}(cm^{-1}): 1507, 1463. 1-Octylimidazole (**2c**): b.p.: 115°C / 0.02 mmHg). IR(neat) ν_{max}(cm^{-1}): 1506, 1465, 732. Anal. Calc. for $C_{11}H_{20}N_2$: C:73.28, H: 11.18, N: 15.54. Found C: 73.44, H: 10.89, N: 15.46. 1-Hexadecylimidazole (**2d**): b.p.: 210°C / 0.11 mmHg). IR(KBr) ν_{max}(cm^{-1}): 1507, 1464, 725. Anal. Calc. for $C_{19}H_{36}N_2$: C:78.08 H: 12.33, N: 9.59. Found C: 78.03, H: 11.98, N: 9.54. 1-Benzylimidazole (**2e**): b.p.: 145°C / 0.02 mmHg) (lit[5a] m.p.:72°C). IR(KBr) ν_{max} (cm^{-1}): 1600, 1506, 1448.

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