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I. Almena [a] , E. Díez-Barra [a] & A. de la Hoz [a]
[a] Facultad de Química., Universidad de Castilla-La Mancha., 13071, Ciudad Real., Spain

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SELECTIVE ALKYLATION OF 2-PYRIDONE IN SOLVENT-FREE CONDITIONS

I. Almena, E. Díez-Barra, A. de la Hoz*

Facultad de Química. Universidad de Castilla-La Mancha.
13071 Ciudad Real. Spain

Abstract.

Alkylation of 2-pyridone has been performed in solvent-free conditions. The effect of base, phase transfer agent, and alkylation agent has been discussed.

Introduction

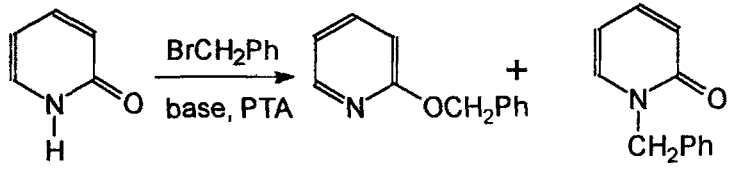
Phase Transfer Catalysis in the absence of solvent have showed to be a useful technique for the anionic activation of several substrates[1,2].

Higher yields in milder conditions[3] and a particular mono[4], regio[2] and stereoselectivity[5], in addition to an easy work-up are the most important advantages of the technique.

In order to check the ability of this technique in the alkylation of heterocyclic ambident nucleophiles we have performed the alkylation of 2-pyridone, considered to be a very important example of N/O-selectivity[6].

Previous results on the application of this technique to the alkylation of tautomeric heterocyclic[7], carbocyclic[8] and non cyclic systems[9] showed the potential of this technique.

Results and Discussion



Reactions were performed by stirring for 3 min a mixture of 2-pyridone and a finely ground base in a 1:2 molar ratio. Addition of the benzyl halide and stirring for the time indicated in table 1, afforded the crude product which was analysed by ^{1}H-NMR.

There are not great differences in transformation in the absence of Phase Transfer Agent. This result indicates that the reaction takes place in the interphase in a great extent, in agreement with the interfacial mechanism proposed for PTC in the absence of solvent. In these conditions the nature of the cation may influence the selectivity.

However, the length of the alkyl chain of the Phase Transfer Agent have a small influence on the selectivity. O-Alkylation (**1**) is favored with long chain alkyl groups due to the increased steric size and charge dispersion on the alkyl group.

The use of mild bases, favors the thermodinamically controlled product producing the exclusive N-alkylation (**2**), in contrast to strongest bases that increases the proportion of the kinetically favored O-alkylation product.

Selectivities observed with some leaving groups are difficult to rationalize. The effect of the alkyl halide in PTC in the absence of solvent is always very complex because in additon to its reactivity it behaves as the organic phase at the beginning of the reaction.

The nature of the alkyl group is the factor the most important that influence the N/O-ratio. In comparison with benzyl groups,

Table 1

Entry	Base	Mole ratio[a]	PTA (10%)	Time (h)	1 : 2	Yield (%)
1	KOH	1:2:1	—	1	90 : 10	77
2	KOH	1:2:1	TBAB (1%)	1	90 : 10	71
3	KOH	1:2:1	Aliquat (1%)	1	81 : 19	88
4	K2CO3	1:2:1	TBAB	24	100 : 0	91
5	LiOH	1:2:1	TBAB	120	100 : 0	51
6	KF	1:2:1	TBAB	70	100 : 0	65
7	Li^{t}BuO	1:1:1	TBAB	48	91 : 9	75
8	KOH/K_2CO_3	1:2:1	TBAB	24	91 : 9	84
9	KOH	1:2:1	Aliquat	1	91 : 9	65
10	KOH	1:2:1	Aliquat	1	84 : 16	38

[a] 2-pyridone : benzyl bromide : base ratio

harder alkyl groups, as ethyl groups, or more sterically demanding, as the butyl group, favor O-alkylation. Using these alkyl halides the exclusive N-alkylation is not observed.

In conclusion, PTC in the absence of solvent is a useful method for the N-alkylation of 2-pyridone. Results are at least comparable to the obtained by classical methods while the experimental procedure and work-up is very simple.

Experimental

All compounds were of commercial quality from freshly opened containers. ^{1}H-NMR spectra were recorder on a VARIAN UNITY 300 at 300 MHz in $CDCl_3$ solutions.

General procedure

A mixture of 2-pyridone (10 mmol), finely ground base (20 mmol) and the phase transfer agent (10 %) were stirred at room temperature for 30 min. After addition of the alkyl halide (see tables), the mixture was stirred at room temperature for the desired time. The crude product was extracted with dichloromethane and analysed by ^{1}H-NMR.

Pure products were obtained by column chromatography on silica gel (20 g)

Reaction with benzyl bromide (table 1, entry 3). Elution with light petroleum : ethyl acetate 4 : 1 afforded 0.16 g of 2-benzyloxypyridine (9%) Bp, 125°C/0.05 mm Hg. ^{1}H-NMR, 5.38 (s, -CH_2); 6.8 (td, J=0.8.; 8.3, H-3); 6.88 (ddd, J=0.8; 5.5, 7.1, H-5); 7.2-7.5 (m, Ph); 7.59 (ddd, J=1.9, 7.1, 8.3, H-4); 8.18 (ddd, J=0.8, 1.9, 5.5, H-6). and 1.46 g of 1-benzyl-2-pyridone (79%) Bp, 230°C/0.01 mm Hg. ^{1}H-NMR, 5.18 (s, CH_2); 6.14 (td, J=1.4, 6.4, H-5); 6.62 (ddd, J=0.8, 1.4, 9.2, H-3); 7.25 (ddd, J=0.8, 2.1. 6.4, H-6); 7.2-7.4 (m, Ph, H-4).

Reaction with ethyl iodide (table 2, entry 6). Elution with ethyl acetate afforded 0.22 g of 2-ethoxypyridine (18%) Bp, 50°C/0.1 mm Hg, ^{1}H-NMR, 1.4 (t, J=7.2, CH_3); 4.35 (q, J=7.2, CH_2); 6.72 (d, J=8.7, H-3); 6.85 (ddd, J=1, 5.2, 7.1, H-5); 7.56 (ddd, J=1.3, 7.1, 8.7, H-4); 8.15 (dd, J=1.3, 5.2, H-6). and 0.4 g of 1-ethyl-2-pyridone

Table 2

Entry	R-X	Base	ATP (10%)	t (h)	1 : 2	Yield (%)
1	EtI	KOH	BBDECl[a]	72	86 : 14	37
2	BuBr	KOH	BBDECl	42	83 : 17	25
3	BnBr	KOH	BBDECl	1	100 : 0	77
4	BuBr	KOH	Aliquat	20	81 : 19	88
5	BnBr	KOH	Aliquat	1	81 : 19	88
6	EtI	KOH	TBAB	72	78 : 22	86
7	BnBr	KOH	TBAB	1	90 : 10	71
8	BuBr	K_2CO_3	BBDECl	96	88 : 12	76
9	BnBr	K_2CO_3	BBDECl	3	100 : 0	76
10	EtI	K_2CO_3	TBAB	48	91 : 9	100
11	BuBr	K_2CO_3	TBAB	28	76 : 24	82
12	BnBr	K_2CO_3	TBAB	24	100 : 0	100

[a] Ref 10

(33%) Bp, 97°C /0.1 mm Hg. ^{1}H-NMR, 1.35 (t, J=7.2, CH_3); 4 (q, J=7.2, CH_2); 6.19 (td, J=1.5, 6.6, H-5); 6.54 (dd, J=1.5, 9.8, H-3); 7.33 (m, H-4, H-6).

Reaction with butyl bromide (table 2, entry 4). Elution with light petroleum : ethyl acetate 2 : 1 afforded 0.26 g of 2-butoxypyridine (17%) Bp, 103°C /0.1 mm Hg, ^{1}H-NMR, 0.97 (t, J=7.3, CH_3); 1.48 (sext,J=7.3, CH_2-CH_3); 1.76 (quint, J=7.5, CH_2-CH_2); 4.28 (t, J=7.5; OCH_2); 6.72 (dt, J=0.9, 8.3, H-3); 6.82 (ddd, J=1.0, 5.1, 7.1, H-5); 7.53 (ddd, J=2.1, 7.1, 8.4, H-4); 8.14 (ddd, J=0.9, 2.1 5.1, H-6) and 0.77 g of 1-butyl-2-pyridone (51%) Bp, 135°C/0.1 mm Hg, ^{1}H-NMR, 0.95 (t, J=7.5, CH_3); 1.37 (sext, J=7.5, CH_2-CH_3); 1.73 (quint, J=7.5, CH_2-CH_2); 3.93 (t, J=7.5, OCH_2); 6.17 (td, J= 1.6, 6.6 H-5); 6.54 (dd, J=1.6, 9.9, H-3); 7.3 (dd, J=2, 6.6, H-6); 7.32 (ddd, J=1.9, 6.6, 9.9, H-4).

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