Selective Alkylation of Pyrrole by Phase Transfer Catalysis in the Absence of Solvent

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Received February 28, 1994

Selective *N*-alkylation of pyrrole is performed, in good yield and by a very simple method, using Phase Transfer Catalysis in the absence of solvent.

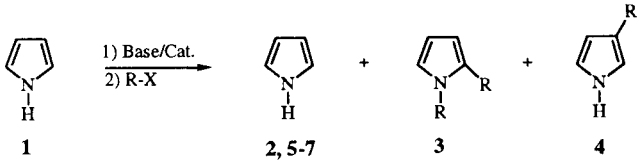
J. Heterocyclic Chem., **31**, 1715 (1994).

Pyrrole salts are classical ambident nucleophiles, the alkylation taking place at the nitrogen or carbon sites [1]. Generally, *C*-alkylation at C-2 is favored rather than C-3 due to the formation of a cyclic transition state [2]. The selectivity is governed by: i) The Hard and Soft Acids and Bases principle (HSAB) and ii) the importance of ionic aggregates. Charge controlled conditions favors *N*-alkylation while *C*-alkylation is predominant under orbital controlled conditions [3]. Thus, polar aprotic solvents, large counterions or hard electrophiles favors *N*-alkylation [3].

Selective *N*-alkylation is observed using potassium hydroxide in DMSO [4], Tin or Stannil [5], or thallium [6] derivatives of pyrrole or phosphonates as alkylating agents [7]. PTC also produces *N*-alkylation but *C*-alkylation is always observed unless toxic and expensive crown ethers [8] or polyethyleneglycols [9] are used.

The objective of this paper is to study the alkylation of pyrrole by PTC in the absence of solvent [10]. This technique has been sucessfully used in the alkylation of other tautomeric heterocyclic compounds [11] or in the propargylation of pyrrole [12].

Results and Discussion.



1 **2, 5-7** **3** **4**

2,3,4: R = Bu
5; R = Me
6; R = Et
7; R = CH_2Ph

Reactions were performed in two steps, base deprotonation of pyrrole catalyzed by a phase transfer agent, followed by addition of the electrophile. The first step was performed in an ultrasonic cleaning bath.

The influence of various factors has been studied using the butylation reaction. Yields and selectivities were determined by gas chromatography. Reaction takes place in the interphase as the reaction in the absence of catalyst confirms, but the use of phase transfer agent (Table 1) is essential to obtain good yields. The N/C ratio is not affected by the presence or the nature of the catalyst. However, the use of tetra-*n*-butylammonium hydrogensulfate (TBAHS), that favors the extraction mechanism produces a slight increase in the N/C ratio.

Table 1
Effect of Catalyst

entry [a]	catalyst (10%)	**2** (%)	**3** (%)	**4** (%)	N:C ratio	Yield (%)
1	none	13	4	0	76:24	17
2	TBAB	61	18	4	74:26	75
3	TBAHS	63	9	traces	85:15	74
4	Aliquat	53	19	4	70:30	76

[a] Pyrrole: potassium hydroxide: butyl bromide 1:2:1, rt, 16 hours.

Table 2
Influence of the Base

entry [a]	base	mole ratio [b]	**2** (%)	**3** (%)	**4** (%)	N:C ratio	yield (%)
1	K_2CO_3	1:2:1	22	6	traces	73:27	30
2	NaOH	1:2:1	61	11	traces	81:19	75
3	KOH	1:2:1	75	4	0	95:5	79
4	KOBu^t	1:1.1:1.1	60	10	traces	82:18	73
5	LiOBu^t	1:1.1:1.1	traces	5	0	17:83	6

[a] T = 80°, t = 16 hours, TBAB (10%). [b] Pyrrole:base:butyl bromide.

Satisfactory yields are obtained with most bases (Table 2) unless mild bases or bases with high lattice energy are used. Differences observed in selectivity, *C*-alkylation increases in the sequence $Li^+ > Na^+ > K^+$, confirm that small cations favor orbital control and thus *C*-alkylation. The fact that the nature of the cation has a strong influence on the selectivity confirms the interfacial mechanism, because only in this case reaction at the interphase is also possible.

The nature of the leaving group has a significant influence in the selectivity (Table 3). *N*-Alkylation increases in the sequence, I < Br < Cl < OTs and confirms the general trend, *N*-alkylation (charge controlled reaction) is favored with hard leaving groups as the energy level in LUMO σ* orbital proved [13]. Using an excess of alkyl halide, quantitative yields are observed.

Table 3

Influence of the Alkylating Agent

entry [a]	X	mole ratio [b]	**2** (%)	**3** (%)	**4** (%)	N:C ratio	yield (%)
1	OTs	1:2:1	79	traces	0	97:3	81
2	Cl	1:2:1	91	traces	0	99:1	92
3	Br	1:2:1	71	8	0	90:10	79
4	I	1:2:1	40	22	5	60:40	67
5	OTs	1:2:1.5	91	0	0	100:0	91
6	Cl	1:2:1.5	96	0	0	100:0	96

[a] t = 80°, t = 16 hours, TBAB (10%). [b] Pyrrole:base:electrophile.

Increasing the temperature (Table 4) *N*-alkylation is favored. This result is similar to the previously reported [14], but is not in agreement with the general assumption that temperature favors aggregation, and, as a consequence, alkylation in the soft center. However, in this kind of reaction the situation is complicated by the presence of various reactive species with different degrees of association. Each one of these species reacts with different rate constants and selectivity. The structure of the anion, the type of counterion, and the temperature exert a strong influence on the position of the equilibrium, and the kinetic may vary in the most unexpected manner when the temperature changes [3].

Considering the factors studied, the specific *N*-butylation of pyrrole is achieved using an excess of *n*-butyl chloride, and potassium hydroxide at a temperature of 80°. Extending these conditions to other alkyl halides the exclusive *N*-alkylation is always observed (Table 5).

Table 4

Effect of Temperature

entry [a]	mole ratio [b]	T (°C)	**2** (%)	**3** (%)	**4** (%)	N:C ratio	yield (%)
1	1:2:1	25	61	18	4	73:26	83
2	1:2:1	80	71	8	0	90:10	79
3	1:2:1.5	25	75	5	0	94:6	80
4	1:2:1.5	80	96	0	0	100:0	96

[a] T = 16 hours. [b] Pyrrole: potassium hydroxide: butyl bromide.

Comparison with classical methods (see references [4,6,8,9,16]) shows that our method without solvent provides similar or better results and avoids the use of toxic catalysts or solvents. In conclusion, Phase Transfer Catalysis in the absence of solvent produces *N*-alkylpyrroles without *C*-alkyl derivatives. This, together with the high yields observed and the simple experimental procedure makes PTC in the absence of solvent a method of choice for the preparation of *N*-alkylpyrroles.

Table 5

Selected Conditions for the Exclusive *N*-Alkylation of Pyrrole [a]

Compound	R-X	T (°C)	t (h)	yield (%)
5	MeI	25	24	91
6	EtI	25	24	85
2	BuCl	80	16	96
7	BnBr	25	24	80

[a] Pyrrole: potassium hydroxide: RX, 1:2:1.5, TBAB (10%).

EXPERIMENTAL

Pyrrole and alkyl halides were of commercial quality from freshly opened containers. *n*-Butyl tosylate was prepared from *n*-butanol by a literature procedure [15]. The ir spectra were recorded with a Philips PU 9500 spectrophotometer. The ^{1}H-nmr spectra (deuteriochloroform) were recorded on a Varian Unity 300 using TMS as the internal standard. J-Values are given in Hz.

General Procedure.

A round bottom flask containing the appropriate quantities of pyrrole, base and phase transfer agent (see Tables) was submerged in an ultrasonic cleaning bath (50 KHz, 200 w) for 15 minutes. Then, without sonication, the halide was added and the reaction mixture was allowed to react at the required temperature for the indicated time (Tables). The crude products were extracted with dichloromethane and filtered through Florisil. Removal of the solvent and vacuum distillation or column chromatography (1-benzylpyrrole) afforded the pure products.

1-Butylpyrrole (**2**).

This compound had bp 65°/2 mm Hg (lit [16] 171°/760 mm Hg); ir (liquid): ν max (cm^{-1}) 1542, 1499, 1458, 1088, 1061; ^{1}H-nmr: δ (ppm) 0.6-1.8 (m, 7H, C_3H_7), 3.8 (t, J = 6.8, 2H, N-CH_2), 6.1 (t, J = 2, 2H, H-3 and H-4), 6.6 (t, J = 2, 2H, H-2 and H-5).

2-Butylpyrrole (**3**).

This compound had bp 60°/1 mm Hg (lit [17] 90-91/24 mm); ir (liquid): ν max (cm^{-1}) 3384, 1565, 1465, 1117, 1095; ^{1}H-nmr: δ (ppm) 0.6-1.8 (m, 7H, C_3H_7), 2.6 (t, J = 6.7, 2H, CH_2), 5.9 (m, 1H, H-3), 6.1 (q, J = 2.7, 1H, H-4), 6.6 (dt, J = 2.4, 1.6, 1H, H-5); ms: m/z (%) 123 (M^+, 22), 80 (100), 53 (12).

1-Methylpyrrole (**5**).

This compound had bp 125° (lit [18] 113-114°); ir (liquid): ν max (cm^{-1}) 1506, 1286, 1088; ^{1}H-nmr: δ (ppm) 3.6 (s, 3H, N-

CH_3), 6.1 (t, J = 1.9, 2H, H-3 and H-4), 6.6 (t, J = 2, 2H, H-2 and H-5).

1-Ethylpyrrole (**6**).

This compound had bp 155° (lit [18] 129-130°); ir (liquid): ν max (cm^{-1}) 1500, 1279, 1088; ^{1}H-nmr: δ (ppm) 1.4 (t, J = 7.2, 3H, CH_3), 3.9 (q, J = 7.2, 2H, N-CH_2), 6.2 (t, J = 1.8, 2H, H-3 and H-4), 6.6 (t, J = 1.8, 2H, H-2 and H-5).

1-Benzylpyrrole (**7**).

Isolation by column chromatography (silica gel, *n*-hexane:ethyl acetate, 97:3) provided **7**, bp 72-74°/0.2 mm Hg (lit [18] 88-90°/0.8-0.9 mm Hg); ir (liquid): ν max (cm^{-1}) 1495, 1452, 1087, 1066; ^{1}H-nmr: δ (ppm) 5.0 (s, 2H, N-CH_2), 6.2 (t, J = 1.6, 2H, H-3 and H-4), 6.6 (t, J = 1.6, 2H, H-2 and H-5), 7.0-7.4 (m, 5H, arom).

Acknowledgements.

Financial support from Spanish CICYT (PB91-0310) is gratefully acknowledged.

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