Quaternization and Dequaternization of Pyrazoles in Solvent-Free Conditions: Conventional Heating *versus* Microwave Irradiation

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We report a study on the quaternization and dequaternization of pyrazoles by conventional heating and microwave irradiation in solvent-free conditions. Microwave irradiation produces an acceleration in the quaternization rate and a rapid equilibration between quaternized and non quaternized products. Dequaternization is also more rapid and a change on the selectivity is observed using symmetric pyrazolium salts.

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Pyrazoles are a representative class of heterocyclic compounds having many derivatives with a wide range of interesting properties, such as drugs, pesticides and new materials, amongst others [1-4].

N-alkylation of pyrazoles is usually carried out in basic conditions [5,6]. This prevents protonation of the pyrazole by X-H (the pyrazolium cation lacking the lone pair on N2 cannot react) and reduces significantly the chances of subsequent quaternization. On the other hand, some undesirable reactions, such as elimination or basic catalysed rearrangements, may occur. We have previously described the alkylation of azoles with allyl and propargyl bromide using phase transfer catalysis in solvent-free conditions. Using hydroxides as bases, rearrangement of the double and triple bond occurs and 1-propenyl and 1-allenylpyrazoles are respectively obtained [7]. However, due to the lowering of the activation energy in solvent-free conditions, a mild base can be used avoiding these rearrangements [7]. An alternative method to prevent them requires palladium(0)-catalyzed reactions [8,9]. Moreover, the rapid first alkylation of neutral azoles which happens under microwaves usually prevents quaternization of the monoalkylated species [10].

Microwave irradiation has been previously used to alkylate pyrazoles. Thus, Bogdal reported the *N*-alkylation of pyrazole itself with benzyl chloride, 1-chlorodecane and 1-bromopentane [11]. Claramunt has studied the adamantylation of pyrazole itself by 1-bromoadamantane obtaining *N*-adamantyl [12] and *C*-adamantyl derivatives [13]. Other NH-azoles have been alkylated under microwave irradiation, for instance propargylation of imidazole in the presence of magnesium oxide [14]. We have reported the alkylation of 1,2,4-triazole and benzotriazole without base [15]. The most relevant results were the modification in the regioselectivity and the absence of quaternary salts formation [16].

We have recently shown that *N*-alkylation of pyrazoles in solvent-free neutral (or mildly basic) conditions reduces the chances of elimination and controls the quaternization.

Quaternization in pyrazoles and indazoles occurs under strong conditions in comparison with imidazoles and benzimidazoles. The basicity of pyrazoles markedly diminishes once the substrate has undergone *N*-substitution [17], steric crowding of the adjacent nucleophilic nitrogen substantially reduces the rate and facility of quaternary alkylation. The reaction is usually performed by heating a mixture of an *N*-alkyl or *N*-arylpyrazole with an alkyl halide at high temperatures and for long reaction times [18]. Under these conditions a possible dequaternization can lead to complications in rationalizing product ratios when asymmetric pyrazoles are used.

In the present paper, we report a comparative study of the quaternization and dequaternization of pyrazoles in solvent-free neutral or basic conditions under microwave irradiation and conventional heating in order to show the influence of microwave irradiation on the extent of quaternization and on the selectivity.

Results and Discussion.

Reactions were conducted in a commercial microwave oven [19] in open vessels (Pyrex flask, 25 ml) in order to avoid effects derived from the pressure developed in closed systems and in a focused microwave reactor that was modified to measure and to control the reaction temperature [20]. All reactions were performed in the absence of solvent and using 10 mmoles of pyrazole, in a smaller scale the volume is not large enough to absorb the microwave radiation efficiently. Product ratios were determined by ^{1}H-nmr.

Quaternization.

In the alkylation of pyrazole, quaternization is a side reaction when the reaction is conducted at high tempera-

tures [18]. With these results in mind we first tried the alkylation of pyrazole with benzyl bromide in order to obtain directly the quaternized product.

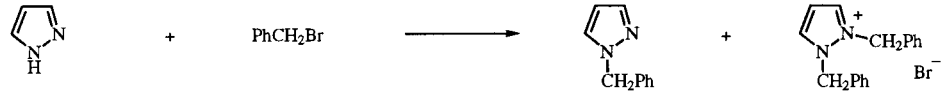
In the absence of base (Table 1, entry 1) the reaction does not produce the complete quaternization (**3**:**4**, 70:30), because the hydrogen bromide produced in the alkylation protonates the benzylpyrazole. However the starting pyrazole **1** is completely consumed within 5 minutes.

In order to improve the quaternization process the presence of a base is necessary. Although potassium carbonate or hydroxide are strong enough to deprotonate the pyrazolium salt **3**, the use of potassium carbonate do not improve the **3**:**4** ratio (Table 1, entries 4-6) and with potassium hydroxide product **4** increases to 64% (Table 1, entry 8). In an open vessel and without temperature control it is not possible to extend the reaction time due to evaporation of the benzyl halide.

We studied then the alkylation of benzylpyrazole **3** with benzyl bromide (Table 2).

Table 1

Reactions of Pyrazole **1** with Benzyl Bromide **2**



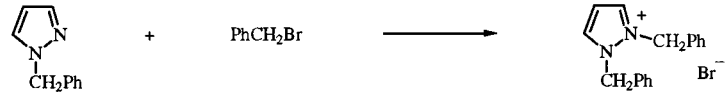
1 **2** **3** **4**

Entry	Base	Molar Ratio [a]	Power (W)	Time (minutes)	Temperature (°C)	**3**/**4** Ratio
1	—	1:2	150	5	140 [b]	70/30
2	— [c]	1:2	CH	5	140	77/23
3	— [d]	1:2	CH	60	120	81/19
4	K_2CO_3	1:2:1.2	150	5	155 [b]	69/31
5	K_2CO_3	1:2:1.2	CH	5	155	65/35
6	K_2CO_3	1:2:1.2	450	2	162 [b]	63/37
7	KOH	1:2:1.1	150	2	157 [b]	63/37
8	KOH	1:2:1.1	80	5	122 [b]	36/64
9	KOH	1:2:1.1	CH	5	120	50/50
10	KOH	1:2:1.1	CH	60	120	40/60
11	KOH	1:2.5:1.1	80	5	107 [b]	32/68

[a] **1**:**2**:base, molar ratio; [b] Determined once the irradiation is completed; [c] **1**, 29%; [d] **1**, 11%.

Table 2

Reactions of Benzylpyrazole **3** with Benzyl Bromide **2**



3 **2** **4**

Entry	Molar Ratio [a]	Power (W)	Time (minutes)	Temperature (°C)	**3** (%)	**4** (%)
1	1:1	780	10	191 [b]	14	86
2	1:1	780	15	200 [b]	27	73
3	1:1	CH	10	200	7	93
4	1:1	CH	60	120	7	93

[a] **1**:**2**, molar ratio; [b] Determined once the irradiation is completed.

Reaction of 1-benzylpyrazole with benzyl bromide always produces a mixture of **3** and **4**. Extending the reaction to 15 minutes the ratio of **3** increases from 14 to 27% but the benzyl pyrazole is never consumed (Table 2, entries 1,2). These results indicate that dequaternization of **4** by nucleophilic attack of the bromide ion is possible under these conditions and an equilibrium between **3** and **4** is reached and that microwave irradiation enhance the nucleophilic character of the bromide ion [19]. By classical heating quaternization is always complete in 10 minutes at 200° (Table 2, entry 3). In the quaternization of pyrazoles under strong conditions, dequaternization is always a side reaction and in the reaction of unsymmetrical pyrazoles can lead to complications in rationalizing product ratios.

In order to confirm the dequaternization process, the reaction of benzylpyrazole with butyl halides were performed (Table 3).

Using butyl bromide only 20% of the reaction is observed under microwaves but some dequaternization is observed as the presence of **6** and **4** confirms (Table 3, entry 1). With butyl iodide the reaction occurs in a high extension and complex mixtures of alkylated and quaternized products were observed. When the reaction is prolonged for 12 minutes an increase of the quaternized products **7**, **4** and **8** is the result, while benzylpyrazole **3** decreases to 35% (Table 3, entry 4). Product distributions indicate that debenzylation is favored over debutylation.

Dequaternization is also observed by conventional heating and product distributions are similar to that observed under microwaves, however reaction times must be extended to 1 hour to observe a similar conversion (Table 3, entry 5).

Reaction of 3-methylpyrazole with benzyl bromide produces a mixture of 1-benzyl-3-methyl and 1-benzyl-5-methylpyrazole **10** and **11** respectively without traces of quaternization, 1,2-dibenzyl-3-methylpyrazolium bromide **12** (Table 4).

Although 3-methylpyrazole is consumed more rapidly under microwaves, the **10/11** ratio depends exclusively on the presence or absence of a base and not on the heating technique.

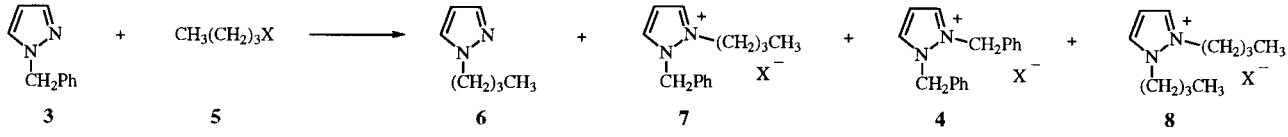
When considering the alkylation of the free base, the orientation of products may result from reaction of the major and/or the minor tautomer, depending on the reactivity of each towards the electrophile.

In unsymmetrical azoles the orientation of reaction products is potentially dependent on numerous factors: i) the reaction conditions, and hence reaction mechanism; ii) the steric and electronic effects of ring substituents; iii) the structure of the alkylating agent; iv) the tautomeric nature of the azole; and v) the effects of quaternary salts formation and decomposition [21-23].

Steric effects are significant. Such effects are largest at the α-position and in consequence alkylation is directed towards the formation of the sterically less-hindered iso-

Table 3

Reactions of Benzylpyrazole **3** with Butyl Halides **5**



a, X = Br; b, X = I

Entry	5	Molar Ratio [a]	Power (W)	Time (minutes)	Temperature (°C)	3 (%)	6 (%)	7 (%)	4 (%)	8 (%)
1	**5a**	1:1	780	15	181 [b]	81	15		4	
2	**5a**	1:1	CH	60	120	97	3			
3	**5b**	1:1	450	10	130 [b]	67	18	7	5	3
4	**5b**	1:1	450	12	169 [b]	35	16	24	21	4
5	**5b**	1:1	CH	60	120	30	10	27	22	10

[a] **1**:**5**, molar ratio; [b] Determined once the irradiation is completed.

mer. Steric and electronic effects are additive when the substituent is electron-withdrawing, and opposing when it is electron-releasing.

Results collected in Table 4 (entries 1,2) show that alkylation on the remote nitrogen is favored in the absence of base. Considering that electron releasing groups activate the azole to electrophilic attack and enhance the nucleophilicity of the vicinal nitrogen, it should be considered that steric effects may play the predominant role.

Under basic conditions the **10/11** ratio is close to 50/50 (Table 4, entries 3,4) due to the increase in the reactivity of **9** produced by formation of the pyrazolate anion that minimize the steric effects. This effect can be confirmed when the temperature decreases to 20°; the **10/11** ratio increases again to 64/36 (Table 4, entry 5).

Dequaternization.

Microwave irradiation coupled with phase transfer catalysis under solvent-free conditions is an excellent method for anionic activation [24].

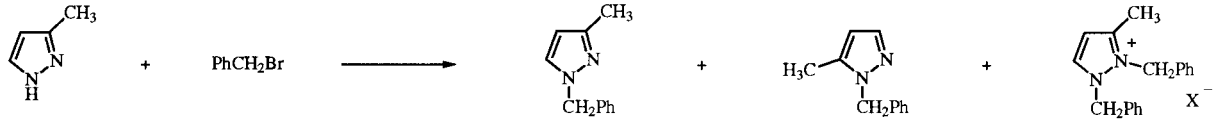
We have tested this methodology in the dequaternization of pyrazolium salts and compared the results with conventional heating, to show the effect of microwave irradiation on the reactivity and selectivity.

Several nucleophiles were tried but potassium bromide always gave the best results. Reaction of 1,2-bibenzylpyrazolium bromide **4** shows a rapid dequaternization under microwave irradiation as in 3 minutes almost 50% of **4** was dequaternized (Table 5, entry 1).

In order to test if microwave irradiation produces any change in the selectivity we studied the dequaternization of 1,2-dibenzyl-3-methylpyrazoliumbromide **12**.

Table 4

Reactions of 3(5)-Methylpyrazole **9** with Benzyl Bromide **2**



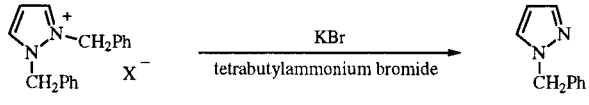
9 **10** **11** **12**

Entry	Base	Molar Ratio [a]	Power (W)	Time (minutes)	Temperature (°C)	**10/11** Ratio
1	— [b]	1:2	150	5	170	67/33
2	— [c]	1:2	CH	5	170	71/29
3	KOH	1:2:2	80	5	100 [d]	52/48
4	KOH [e]	1:2:2	CH	5	100	55/45
5	KOH	1:2:2	CH	24 hours	20	64/36

[a] **9**:**2**: base, molar ratio; [b] Performed in a monomode reactor; [c] **9**, 20%; [d] Determined once the irradiation is completed; [e] **9**, 44%.

Table 5

Dequaternization of 1,2-Dibenzylpyrazolium Bromide **4**



4 **3**

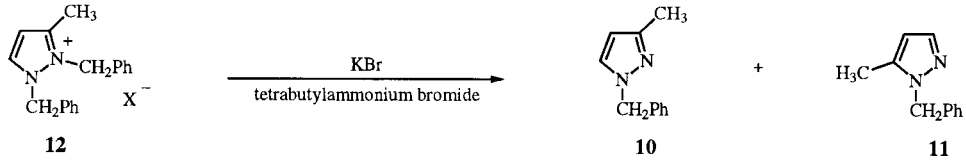
Entry	Molar Ratio [a]	Power (W)	Time (minutes)	Temperature (°C) [b]	**3** (%)	**4** (%)
1	1:2:2	780	3	177	46	54
2	1:2:2	CH	15	180	38	61

[a] Pyrazole:potassium bromide:water molar ratio; [b] Determined once the irradiation is completed.

Results collected in Table 6 shows that removal of the 2-benzyl group is favored by conventional heating or microwave irradiation but the **10/11** ratio increased under microwaves as a result of the activation of the nucleophile under microwave irradiation.

Table 6

Dequaternization of 1,2-Dibenzyl-3-methylpyrazolium Bromide **12**



12 **10** **11**

Entry	Molar Ratio [a]	Power (W)	Time (minutes)	Temperature (°C)	**10** (%)	**11** (%)	**12** (%)	**10/11**
1	1:2:2	780	5	180 [b]	42	12	45	78/22
2	1:2:2	CH	5	180	36	18	46	66/33
3	1:2:2	CH	30	180	23	34	43	60/40
4	1:2:2	CH	60	180	27	37	35	58/42
5	1:2:2	CH	5 hours	180	31	40	28	56/44

[a] Pyrazole:potassium bromide:water molar ratio; [b] Determined once the irradiation is completed.

Conclusion.

Microwave irradiation produces an acceleration in the quaternization rate and a rapid equilibration between quaternized and non quaternized products when compared with conventional heating. Dequaternization is also more rapid and a change on the selectivity is observed using symmetric pyrazolium salts. These effects can be justified by the enhancement of the nucleophilic character of the bromide ion as a counterion in the quaternized products and in potassium bromide in the dequaternization reactions.

EXPERIMENTAL

The nmr spectra were recorded in deuteriochloroform with tetramethylsilane as the internal standard on a Varian Unity-300 spectrometer at 299.890 MHz for ^{1}H and 75.414 MHz for ^{13}C. Commercially available reagents and compounds were purchased from Acros chemical company and were used without further purification.

Reactions under classical heating were performed in round bottom flasks (25 ml) submerged in an oil bath and with magnetic stirring. Microwave alkylations were performed on a Miele M-720 oven working at 780 W and on a modified Prolabo Maxidigest MX-350 microwave reactor working at 300 W. In the first case, reactions were performed in cylindrical Pyrex flasks (25 ml) and the temperature was measured at the end of the irradiation with a thermocouple probe. In the second case, reactions were performed in specially designed glassware of cyclindrical shape. The reaction temperature was measured by an ir pyrometer and controlled within ±1° by reducing the incident power to 30 W.

Reactions were performed with 10 mmoles of the azole, by conventional heating or under microwave irradiation. In the reactions in the presence of a base, a mixture of pyrazole, base and tetrabutylammonium bromide was sonicated in an ultrasonic cleaning bath for 15 minutes before addition of the benzyl halide. Molar ratios, reaction times and temperatures were used as indicated in Tables 1-6. The crude products were dissolved in deuteriochloroform (0.6 ml) and product ratios were determined by ^{1}H-nmr.

1-Benzylpyrazole (**3**).

This compound had bp 100°/0.1 mm Hg (lit [25]); ir (liquid): ν max (cm^{-1}) 1511, 1494, 1453; ^{1}H-nmr: δ (ppm) 5.2 (s, 2H, CH_2Ph), 6.2 (t, J = 2.1, 1H, H-4), 7.1-7.4 (m, 6H, H-5, Ph), 7.5 (d, J = 1.8, 1H, H-3); ^{13}C-nmr: δ (ppm) 55.7 (CH_2), 105.8 (C-4), 127.5 (C-2'), 127.8 (C-5), 128.6 (C-3'), 129.1 (C-4'), 136.5 (C-1'), 139.4 (C-3).

1,2-Dibenzylpyrazolium Bromide (**4**).

This compound had mp 188-189° (dichloromethane); ν max (cm^{-1}) 1529, 1497, 1467, 1456; ^{1}H-nmr: δ (ppm) 6.09 (s, 4H, CH_2Ph), 6.65 (t, J = 2.9, 1H, H-4), 7.30-7.42 (s, 10H, Ph), 8.31 (d, J = 2.9, 2H, H-3, H-5); ^{13}C-nmr: δ (ppm) 54.7 (CH_2), 107.3 (C-4), 128.8 (C-2'), 129.6 (C-3'), 129.7 (C-4'), 130.8 (C-1'), 138.0 (C-3, C-5).

Anal. Calcd. for $C_{17}H_{17}N_2Br$: C, 62.02; H, 5.20; N, 8.51. Found: C, 61.98; H, 5.31; N, 8.32.

1-Benzyl-3-methylpyrazole (**10**) and 1-Benzyl-5-methylpyrazole (**11**).

From a 67/33 mixture, the following were obtained; 1-benzyl-3-methylpyrazole (**10**); ^{1}H-nmr: δ (ppm) 2.30 (s, 3H, CH_3), 5.24 (s, 2H, CH_2Ph), 6.04 (d, J = 2.2, 1H, H-4), 7.07-7.33 (m, 6H, Ph and H-5) and 1-benzyl-5-methylpyrazole (**11**); ^{1}H-nmr: δ (ppm) 2.21 (s, 3H, CH_3), 5.29 (s, 2H, CH_2Ph), 6.06 (d, J = 2.2, 1H, H-4), 7.07-7.33 (m, 5H, Ph), 7.45 (d, J = 2.2, 1H, H-3).

1,2-Dibenzyl-3-methylpyrazolium Bromide (**12**).

This compound had mp 172-173° (dichloromethane); ν max (cm^{-1}) 1606, 1536, 1519, 1496, 1471, 1464, 1455; ^{1}H-nmr: δ (ppm) 2.5 (s, 3H, CH_3), 5.96 (s, 4H, CH_2Ph), 6.66 (d, J = 2.9, 1H, H-4), 6.84-6.89 and 7.30-7.32 (m, 10H, Ph), 8.71 (d, J = 2.9, 1H, H-5); ^{13}C-nmr: δ (ppm) 12.6 (CH_3), 51.1 (CH_2-2), 54.6 (CH_2-1), 108.0 (C-4), 125.5 (C-2'-2), 128.6 (C-2'-1), 128.7 (C-4'-2), 129.2 and 129.3 (C-3'-1 and -2), 129.4 (C-4'-1), 130.8 (C-1'-1), 131.4 (C-1'-2), 137.9 (C-5), 148.1 (C-3).

Anal. Calcd. for $C_{18}H_{19}N_2Br$: C, 62.98; H, 5.58; N, 8.16. Found: C, 62.76; H, 5.86; N, 7.98.

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