# Alkylation and Arylation of Pyrazoles Under Solvent-Free Conditions: Conventional Heating *versus* Microwave Irradiation



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The use of sodium hydrogen carbonate under solvent-free conditions and microwave irradiation is by far the best method for *N*-alkylating pyrazoles. The yields are good and the method is devoid of side reactions (quaternization, isomerization, hydrogen halide elimination). Solvent-free conditions are the only ones that allow us to prepare 1-substituted pyrazoles from secondary halides. The procedure using quaternary salts in one-pot provides an interesting alternative for the preparation of 1-heteroarylpyrazoles.

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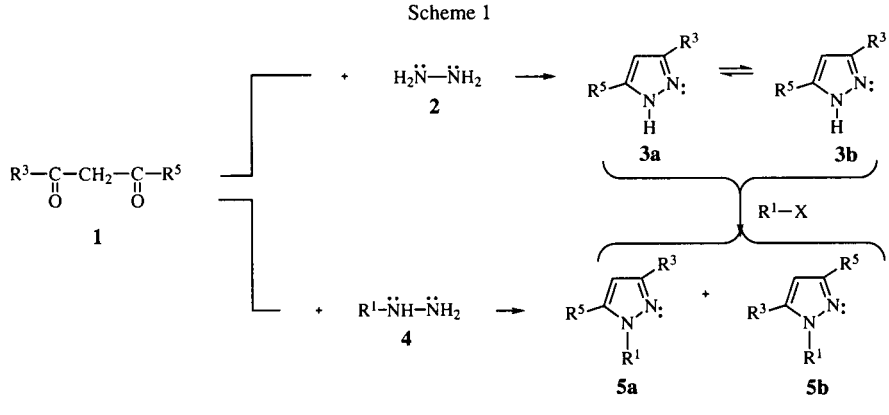
Pyrazoles are a representative class of heterocyclic compounds having many derivatives with a wide range of interesting properties, such as drugs, pesticides and new materials, amongst others [1-4]. In general, these useful pyrazole derivatives are 1-substituted compounds **5** (Scheme 1). In some cases, these alkyl or aryl substituents serve as protecting groups in derivatization reactions involving organometallic reagents [5]. Probably the most employed synthetic procedures use the reaction of hydrazines with a great variety of β-difunctional compounds [1-4], illustrated in Scheme 1 with a β-diketone **1**. Their preparation can be achieved in two ways: the first one consists in the reaction with hydrazine (**2**) to obtain NH-pyrazoles **3**, (existing in two tautomeric forms) followed by reaction with an alkylating or arylating agent, $R^1$-X [6], to prepare the mixture of isomers **5a** and **5b**. The second possibility is to use a monosubstituted hydrazine **4** which yields directly the mixture of isomers **5a** and **5b**, although in general the proportion of **5a/5b** differs in the two procedures. If the second method is limited by the synthetic accessibility of the substituted hydrazine and by the nucleophilicity of the NH nitrogen atom, the first one is generally limited to primary halides and to aromatic or heteroaromatic halides. The reason is that the alkylation reaction is carried out in basic media (on the conjugated pyrazolate anion, an $S_E2cB$ process [6,7]) and under these conditions, elimination occurs with secondary halides; this is why a compound so common as 1-cyclohexylpyrazole is not known.

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 with yields between 60 and 90% using microwave irradiation in dry media but in the presence of tetrabutylammonium bromide and potassium carbonate (or a mixture of potassium carbonate and potassium hydroxide) [8]. These conditions, very similar to those used in phase transfer catalysis [9], being strongly basic, have a number of inconveniences that will be discussed later. Claramunt has studied the adamantylation of pyrazole itself by 1-bromoadamantane obtaining *N*-adamantyl [10] and *C*-adamantyl derivatives [11] but

Scheme 1



the reaction only works with tertiary halides. Other NH-azoles have been alkylated under microwave irradiation, for instance propargylation of imidazole in the presence of magnesium oxide [12]. We have reported the alkylation of 1,2,4-triazole and benzotriazole without base [13]. The most relevant results were the modification in the regioselectivity and the absence of quaternary salts formation. In the present paper we will describe the *N*-alkylation of pyrazoles under solvent-free, neutral (or mildly basic) conditions and present one example of *N*-heteroarylation.

## Results and Discussion.

### Reaction with Alkyl Halides.

As explained in the introduction, *N*-alkylation of pyrazoles is usually carried out under basic conditions [6,7]. 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 of **5a** and **5b**. On the other hand, some undesirable reactions, such as elimination or basic catalyzed rearrangements, may occur. We have previously described the alkylation of azoles with allyl and propargyl bromide using phase transfer catalysis under solvent-free conditions. Using hydroxides as bases, rearrangement of the double and triple bond occurs and 1-propenyl and 1-allenylpyrazoles are obtained respectively [9]. However, due to the lowering of the activation energy under solvent-free conditions, a mild base can be used avoiding these rearrangements [9]. An alternative method to prevent them requires palladium(0)-catalyzed reactions [14,15]. Moreover, the rapid first alkylation of neutral azoles which happens under microwave conditions usually prevents quaternization of the monoalkylated species [13].

### Reaction of Pyrazole **3**, ($R^3$ = $R^5$ = H) and 3(5)-methylpyrazole **3**, ($R^3$ = methyl, $R^5$ = H) with Phenethyl Bromide.

Alkylation of pyrazole with phenethyl bromide under basic conditions produces styrene by elimination of hydrogen bromide. By using liquid-liquid phase transfer conditions, the elimination is considerably reduced and 70% of 1-phenethylpyrazole (**5**, $R^1$ = phenethyl, $R^3$ = $R^5$ = H) was obtained [16]. An alternative route is to use the very reactive *N*-tributylstannylpyrazole to avoid basic conditions [17]. Under solvent-free phase transfer conditions using potassium hydroxide as the base, 1-phenethylpyrazole was obtained in 61-64% yield both by classical heating or under microwave irradiation (Table 1, entries 1, 2).

Table 1

Reactions of Pyrazole with Phenethyl Bromide

| Entry | Heating method [a] | Molar ratio [b] | Base | Time | Temperature (°C) | **5** (%) [c] |
|---|---|---|---|---|---|---|
| 1 | CH | 1:1:1 | KOH | 8 minutes | 145 | 61 |
| 2 | MW (150 W) | 1:1:1 | KOH | 8 minutes | 145 [d] | 64 |
| 3 | CH | 1:1:0 | ------ | 48 hours | 120 | 69 [e] |
| 4 | MW (150 W) | 1:1:0 | ------ | 8 minutes | 136 [d] | 51 |
| 5 | MW (150 W) | 1:1:1 | $NaHCO_3$ | 12 minutes | [f] | 80 |
| 6 | CH | 1:1:1 | $NaHCO_3$ | 12 minutes | 124 | 36 [g] |

[a] CH: conventional heating, MW: microwave irradiation. [b] Pyrazole:phenethyl bromide:base (molar ratio). [c] Determined by gas chromatography. [d] Final temperature. [e] Quaternization 13%. [f] Performed in a closed Teflon vessel. [g] Quaternization 45%.

When the reaction was carried out in the absence of base, the yield was reduced to 51% under microwave conditions while by conventional heating quaternization (13%) is also observed (Table 1, entries 3, 4). The use of a base, such as sodium hydrogen carbonate, strong enough to neutralize the acid formed during the alkylation but admittedly too weak to promote elimination results in 80% yield of 1-phenethylpyrazole under microwaves (Table 1, entry 5). With conventional heating however, quaternization is even more important than without base (compare entries 3 and 6).

Table 2

Reactions of 3(5)-Methylpyrazole with Phenethyl Bromide

| Entry | Heating method [a] | Molar ratio [b] | Base | Time | Temperature (°C) | **5a** (%) [c] | **5b** (%) [c] | **5a/5b** | **(5a+5b)** % |
|---|---|---|---|---|---|---|---|---|---|
| 1 | CH | 1:1:1 | KOH | 24 hours | 120 | 53 | 20 | 2.6 | 73 |
| 2 | CH | 1:1:1 | $NaHCO_3$ | 24 hours | 120 | 75 | 23 | 3.3 | 98 |
| 3 | CH | 1:1:0 | ------ | 24 hours | 120 | 41 | 11 | 3.7 | 52 |
| 4 | MW (150 W) | 1:1:1 | KOH | 12 minutes | 145 [d] | 38 | 18 | 2.1 | 56 |
| 5 | MW (150 W) | 1:1:1 | $NaHCO_3$ | 12 minutes | [e] | 57 | 23 | 2.5 | 80 |
| 6 | MW (150 W) | 1:1:0 | ------ | 12 minutes | 162 [d] | 22 | 9 | 2.4 | 31 |

[a] CH: conventional heating, MW: microwave irradiation. [b] 3(5)-Methylpyrazole:phenethyl bromide:base (molar ratio). [c] Determined by gas chromatography. [d] Final temperature. [e] Performed in a closed Teflon vessel.

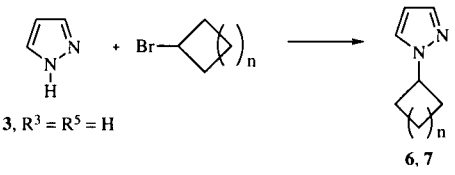
It remains to be established whether the reaction in the presence of sodium hydrogen carbonate (Table 1, entries 5,6) takes place on the neutral pyrazole or in its conjugated base, the pyrazolate anion, *i.e.*, if the reaction proceeds by an $S_E2'$ or an $S_E2cB$ mechanism. Usually, the transition between these two mechanisms occurs at *p*H = p$K_a$ -3; since sodium hydrogen carbonate (p$K_a$ = 10.3 [18]) is not basic enough to deprotonate pyrazole (p$K_a$ = 12.9 [18]), the mechanism should be the $S_E2'$ one.

To verify this conclusion, the reaction of 3(5)-methylpyrazole and phenethyl bromide was studied. Considering all the information gathered for both mechanisms [19-22], it is expected that the **5a/5b** ratio would be different if the reaction takes place on the mixture of tautomers **3a/3b** than if the reactive species is the 3-methylpyrazolate anion **3**$^-$. The results reported in Table 2 show that in both cases, conventional heating and microwave irradiation, the **5a/5b** ratios using sodium hydrogen carbonate (3.3 and 2.5, entries 2,5) are closer to those obtained under neutral conditions (3.7 and 2.4, entries 3,6) than to those obtained in strong basic conditions (2.6 and 2.1, entries 1,4), although with conventional heating there may be a participation of the $S_E2cB$ mechanism.

Reaction of Pyrazole with Cyclopentyl and Cyclohexyl Bromide.

The reaction of pyrazole with cycloalkyl halides was selected to test our solvent-free mildly basic conditions for the alkylation of pyrazoles because 1-cycloalkylpyrazoles cannot be prepared with conventional procedures, both 1-cyclopentyl- (**6**) and 1-cyclohexylpyrazole (**7**) being compounds not yet described (Scheme 2 and Table 3). As expected, the reaction of pyrazole with cyclopentyl or cyclohexyl bromide under basic medium results in very low yields of **6** and **7**.

Scheme 2




**3**, $R^3 = R^5 = H$ **6, 7**

with microwave irradiation lead to elimination (formation of cycloalkenes) due to the activation of the hydroxide (entries 5,6). The use of cycloalkyl chlorides lowered the yields because although the chloride is a less good leaving group, the alkylation reaction requires more drastic conditions. The alkylation under neutral conditions occurs again in low yield due to the protonation of the parent pyrazole; the alkylation rate of pyrazole is notably reduced, therefore favoring the quaternization of 1-cycloalkylpyrazole, more nucleophilic than pyrazole itself (entries 1,2,7,8). The results obtained under the conditions described in Table 3 (entries 3,9) are the only ones that allow us to obtain 1-cycloakylpyrazoles, and probably other pyrazoles bearing secondary alkyls at position 1, in good to moderate yields.

Reaction of Pyrazole with 1,2-Dibromoethane.

Bisazolylalkanes have been prepared by alkylation of azoles with α,ω-dihaloalkanes by liquid-liquid and solid-liquid Phase Transfer Catalysis [23], for instance, symmetrical bisazolylethanes were obtained using xylene or toluene as the solvent. In most cases, elimination of hydrogen bromide from the β-bromoethylazole or of azole from the bisazolylethane with concomitant formation of 1-vinylazoles was observed as a side reaction [23]. These elimination reactions are greatly favored in solvent-free Phase Transfer Catalysis conditions [24,25]. Thus, the reaction of pyrazole (**3**) (Scheme 3) with 1,2-dibromoethane in sol-

Table 3

Reactions of Pyrazole with Cyclohexyl and Cyclopentyl Bromide

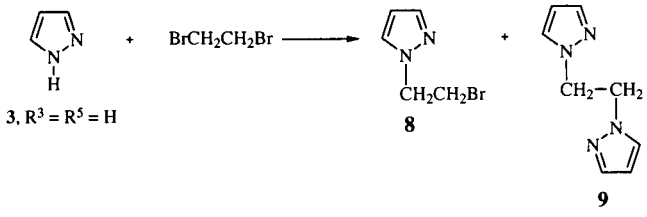
| Entry | Heating method [a] | Cycloalkyl bromide | Molar ratio [b] | Base | Time | Temperature (C) | Yield (%) [c] |
|---|---|---|---|---|---|---|---|
| 1 | CH | cyclopentyl | 1:1:0 | ------ | 12 hours | 120 | 38 (**6**) |
| 2 | MW (150 W) | cyclopentyl | 1:1:0 | ------ | 10 minutes | e | 26 (**6**) |
| 3 | CH | cyclopentyl | 1:2:2 | $NaHCO_3$ | 12 hours | 120 | 99 (**6**) |
| 4 | MW (150 W) | cyclopentyl | 1:1:1 | $NaHCO_3$ | 15 minutes | 87 | 8 (**6**) |
| 5 | CH | cyclohexyl | 1:1:1 | KOH | 48 hours | 20 | --- (**7**) |
| 6 | MW (150 W) | cyclohexyl | 1:1:1 | KOH | 0.5 minutes | 100 [d] | 4 (**7**) |
| 7 | CH | cyclohexyl | 1:1:0 | ------ | 24 hours | 120 | 3 (**7**) |
| 8 | MW (150 W) | cyclohexyl | 1:1:0 | ------ | 3 minutes | 136 [d] | 2 (**7**) |
| 9 | CH | cyclohexyl | 1:2:2 | $NaHCO_3$ | 96 hours | 120 | 53 (**7**) |
| 10 | MW (150 W) | cyclohexyl | 1:1:1 | $NaHCO_3$ | 7 minutes | 120 | 1 (**7**) |

[a] CH: conventional heating, MW: microwave irradiation. [b] Pyrazole:cycloalkyl halide:base (molar ratio). [c] Determined by gas chromatography. [d] Final temperature. [e] Performed in a closed Teflon vessel.

Solvent-free Phase Transfer Catalysis in the presence of sodium hydroxide with conventional heating or coupled

vent-free Phase Transfer Catalysis produces only 18% of the desired 1,2-bispyrazolylethane (**9**) [23].

Scheme 3



3, $R^3 = R^5 = H$

**8**

**9**

thesis of these compounds. The following example will show the use of quaternary salts for the synthesis of 1-heteroarylpyrazoles.

We were interested in the preparation of tris-2,4,6-(pyrazol-1-yl)-1,3,5-triazine (**10**) as a ligand in coordination chemistry [26]. These compounds are usually prepared by reaction of sodium pyrazolate with cyanuryl chloride in toluene [27] (Scheme 4) although, due to the good leaving properties of pyrazole, pyrazole substituents are progressively replaced by hydroxy groups, **11**, if the reaction is not carried out under drastic anhydrous conditions.

Table 4

Reactions of Pyrazole with 1,2-Dibromoethane

| Entry | Heating method [a] | Molar ratio [b] | Base | Time | Temperature (C) | **8** (%) [c] | **9** (%) [c] | **9/8** |
|---|---|---|---|---|---|---|---|---|
| 1 | CH | 2:1:2 | KOH | 48 hours | 20 | 13 | 28 | 2.2 |
| 2 | MW (150 W) | 2:1:2 | KOH | 10 minutes | 103 [d] | --- | 19 | ---- |
| 3 | CH | 1:1:1 | KOH | 48 hours | 20 | 20 | 10 | 0.5 |
| 4 | CH | 1:1:2 | KOH | 48 hours | 20 | --- | 18 | ---- |
| 5 | CH | 2:1:0 | ------ | 24 hours | 130 | 1 | 56 | 56 |
| 6 | MW (150 W) | 2:1:0 | ------ | 10 min | 172 [d] | --- | 21 | ---- |
| 7 | CH | 2:1:2 | $NaHCO_3$ | 24 hours | 130 | --- | 70 | ---- |

[a] CH: conventional heating, MW: microwave irradiation. [b] Pyrazole:1,2-dibromoethane:base (molar ratio). [c] Determined by gas chromatography. [d] Final temperature.

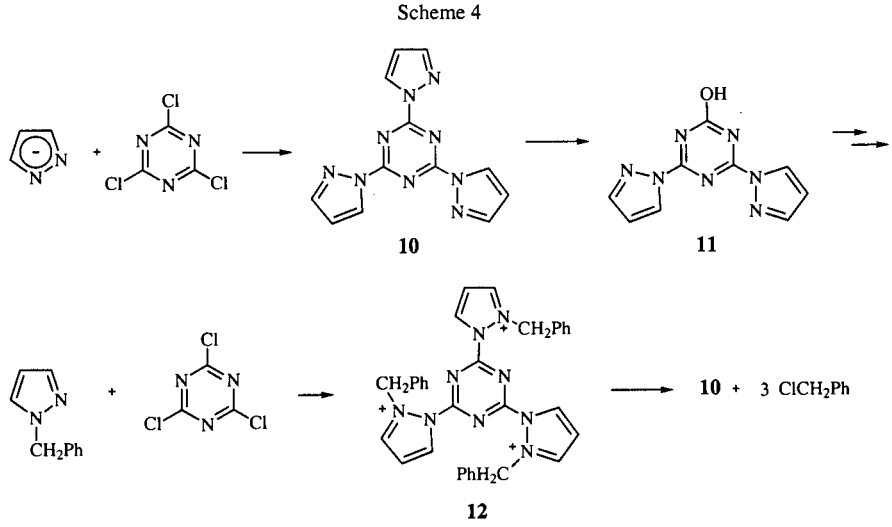
Using basic conditions with conventional heating or microwave irradiation (Table 4, entries 1-4) the elimination is still the prevalent reaction and only 10-28% of the desired bispyrazolylethane (**9**) was obtained, in most cases as a mixture with the monoalkylated β-bromoethylpyrazole (**8**). Under neutral conditions, monoalkylation is greatly reduced and yields are improved specially in classical conditions (Table 4, entries 5,6) but again the use of a mild base (sodium hydrogen carbonate) produces the best results by far (entry 7).

Reaction with Heteroaryl Halides.

Up to now, we have shown the problems that unwanted quaternization of *N*-alkylpyrazoles produces in the synthesis of these compounds. The following example will show the use of quaternary salts for the synthesis of 1-heteroarylpyrazoles.

This problem can be overcome by using a quaternization-dequaternization procedure. Thus, reaction of 1-benzylpyrazole with cyanuryl chloride under solvent-free conditions and under microwave irradiation afforded compound **10** within 10 minutes. The intermediate tris-quaternary salt **12** is not isolated. Pure **10** is obtained without traces of hydrolysis after washing with hexane to remove the benzyl chloride formed in the reaction. The absence of any solvent and basic medium helps to eliminate the side reactions.

Scheme 4



**10**

**11**

**12**

## 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 $^1H$ and 75.414 MHz for $^{13}C$. Analysis by gas chromatography were performed in a Fisons GC 9000 instrument. Distillations and sublimations were performed ball-to-ball in a Büchi GKR-51 apparatus. Commercially available reagents and compounds were purchased from Acros chemical company and were used without further purification. Reactions under classical heating were performed in an oil bath with magnetic stirring. Microwave alkylations were performed on a Miele M-720 oven in a cylindrical Pyrex flask (25 ml) or in a screw-cap closed Teflon vessel (25 ml) (Tables 1-4). Reactions with cyanuric chloride under microwave conditions were performed on a modified Prolabo Maxidigest MX-350 microwave reactor with temperature measurement by an ir pyrometer.

Alkylation Reactions. General Procedure.

Reactions were performed with 10 mmoles of pyrazole or 3(5)methylpyrazole. Molar ratios, reaction times and temperatures for each single reaction are collected in Tables 1-4. The crude products were extracted with dichloromethane (4 x 10 ml) and analyzed by gas chromatography and $^1H$-nmr.

In the reactions by Phase Transfer Catalysis the mixture of pyrazole, potassium hydroxide and *tetra-n*-butylammonium bromide (5%) was sonicated for 10 minutes in an ultrasonic cleaning bath before addition of the alkyl halide. The ammonium salt was removed by filtering the crude product through Florisil.

1-Phenethylpyrazole (**5**, $R^1$ = phenethyl, $R^3 = R^5 = H$).

This compound had bp 80°/0.15 mm Hg (lit [16] 99°/1 mm Hg); ir (liquid): $\nu_{max}$ ($cm^{-1}$) 1510, 1494, 1452, 1394; $^1H$-nmr: δ (ppm) 3.2 (t, J = 7.3, 2H, $CH_2Ph$), 4.4 (t, J = 7.3, 2H, $NCH_2$), 6.2 (t, J = 1.9, 1H, H-4), 7.0-7.3 (m, 6H, Ph and H-5), 7.5 (d, J = 1.9, H-3); $^{13}C$-nmr: δ (ppm) 36.7 ($CH_2Ph$), 53.2 ($NCH_2$), 104.8 (C-4), 126.3 (C-4'), 128.3 and 128.4 (C-2' and C-3'), 129.0 (C-5), 137.9 (C-1'), 139.1 (C-3).

1-Phenethyl-3-methylpyrazole (**5a**, $R^1$ = phenethyl, $R^3 = CH_3$, $R^5 = H$).

This compound had bp 150°/8.5 mm Hg (lit [28] 117-120°/10 mm Hg); ir (liquid) $\nu_{max}$ ($cm^{-1}$) 1519, 1515, 1494, 1451, 1052; $^1H$-nmr: δ (ppm) 2.3 (s, 3H, $CH_3$), 3.1 (t, J = 7.4, 2H, $CH_2Ph$), 4.3 (t, J = 7.4, 2H, $NCH_2$), 5.9 (t, J = 1.9, 1H, H-4), 7.0-7.3 (m, 6H, Ph and H-5); $^{13}C$-nmr: δ (ppm) 14.1 ($CH_3$), 37.6 ($CH_2Ph$), 53.9 ($NCH_2$), 105.0 (C-4), 127.0 (C-4'), 129.0 and 129.2 (C-2' and C-3'), 130.5 (C-5), 138.8 (C-1'), 149.1 (C-3).

1-Phenethyl-5-methylpyrazole (**5b**, $R^1$ = phenethyl, $R^3 = CH_3$, $R^5 = H$).

This compound had bp 150°/3 mm Hg; ir (liquid) $\nu_{max}$ ($cm^{-1}$) 1540, 1452, 1403, 1072; $^1H$-nmr: δ (ppm) 1.9 (s, 3H, $CH_3$), 3.1 (t, J = 7.2, 2H, $CH_2Ph$), 4.2 (t, J = 7.2, 2H, $NCH_2$), 5.9 (t, J = 1.8, 1H, H-4), 7.0-7.3 (m, 5H, Ph), 7.4 (d, J = 1.8, 1H, H-3); $^{13}C$-nmr: δ (ppm) 10.7 ($CH_3$), 36.9 ($CH_2Ph$), 50.3 ($NCH_2$), 104.8 (C-4), 126.6 (C-4'), 128.5 and 128.8 (C-2' and C-3'), 138.4 and 138.5 (C-3, C-5 and C-1').

*Anal.* Calcd. for $C_{12}H_{14}N_2$: C, 77.38; H, 7.57; N, 15.04. Found: C, 77.12; H, 7.30; N, 14.77.

1-Cyclopentylpyrazole (**6**).

This compound had bp 100°/9 mm Hg; ir (liquid): $\nu_{max}$ ($cm^{-1}$) 1507, 1440, 1089, 1044; $^1H$-nmr: δ (ppm) 1.7-2.2 (m, 8H, H-2', H-3', H-4' and H-5'), 4.67 (quint, J = 7.0, 1H, NCH), 6.23 (dd, J = 2.1, 1.4, 1H, H-4), 7.42 (d, J = 2.1, 1H, H-5), 7.50 (d, J = 1.4, 1H, H-3); $^{13}C$-nmr: δ (ppm) 24.1 (C-3' and C-4'), 33.0 (C-2' and C-5'), 62.8 (C-1'), 104.9 (C-4), 127.2 (C-5), 138.7 (C-3).

*Anal.* Calcd. for $C_8H_{12}N_2$: C, 70.55; H, 8.58; N, 20.57. Found: C, 70.87; H, 8.91; N, 20.23.

1-Cyclohexylpyrazole (**7**).

This compound had bp 120°/8 mm Hg; ir (liquid): $\nu_{max}$ ($cm^{-1}$) 1450, 1394, 1091; $^1H$-nmr: δ (ppm) 1.1-2.2 (m, 10H, $C_5H_{10}$), 4.1 (tt, J = 11.5, 3.8, 1H, NCH), 6.2 (dd, J = 2.2, 1.6, 1H, H-4), 7.4 (d, J = 2.2, 1H, H-5), 7.5 (d, J = 1.6, 1H, H-3); $^{13}C$-nmr: δ (ppm) 25.4 (C-3' and C-4'), 33.6 (C-2'), 61.1 (C-1'), 104.7 (C-4), 126.3 (C-5), 138.4 (C-3).

*Anal.* Calcd. for $C_9H_{14}N_2$: C, 71.96; H, 9.39; N, 18.65. Found: C, 71.49; H, 8.97; N, 18.36.

1-(2-Bromoethyl)pyrazole (**8**).

This compound had bp 100°/4 mm Hg (lit [29] 65-66°/0.5 mm Hg); ir (liquid): $\nu_{max}$ ($cm^{-1}$) 1511, 1394, 1286, 1079, 1046; $^1H$-nmr: δ (ppm) 3.7 (t, J = 6.1, 2H, $NCH_2$), 4.5 (t, J = 6.1, 2H, $BrCH_2$), 6.2 (t, J = 2.0, 1H, H-4), 7.4 (d, J = 2.0, 1H, H-5), 7.5 (bs, 1H, H-3); $^{13}C$-nmr: δ (ppm) 30.3 ($BrCH_2$), 53.4 ($NCH_2$), 105.5 (C-4), 129.9 (C-5), 140.2 (C-3).

1,2-Bispyrazol-1-yl ethane (**9**).

This compound had bp 105°/$10^{-4}$ mm Hg (lit [23] 184°/40 mm Hg); ir (liquid): $\nu_{max}$ ($cm^{-1}$) 1511, 1435, 1394, 1276, 1089, 1046; $^1H$-nmr: δ (ppm) 4.5 (s, 4H, $CH_2$ $CH_2$), 6.1 (dd, J = 2.6 and 1.6, 1H, H-4), 6.9 (d, J = 2.6, 1H, H-5), 7.5 (d, J = 1.6, 1H, H-3); $^{13}C$-nmr: δ (ppm) 52.3 ($CH_2CH_2$), 105.9 (C-4), 130.8 (C-5), 140.7 (C-3).

2,4,6-Tris(pyrazol-1-yl)-1,3,5-triazine (**10**).

A mixture of cyanuric chloride (0.46 g, 2.5 mmoles) and 1-benzylpyrazole (1.2 g, 7.5 mmoles) was irradiated in a focused microwave reactor at 225 W for 10 minutes (final temperature, 130°). The crude mixture, washed with hexane (3 x 5 ml), afforded the pure product (0.58 g, 84%). This compound had mp 226-227° (lit 208-210° [27,30]; ir (liquid): $\nu_{max}$ ($cm^{-1}$) 1578, 1529, 1459, 1438, 1389, 1077, 1035, 943; $^1H$-nmr: δ (ppm) 6.61 (dd, J = 2.9 and 1.5, 1H, H-4), 7.98 (d, J = 1.4, 1H, H-3), 8.81 (d, J = 2.9, 1H, H-5); $^{13}C$-nmr: δ (ppm) 110.4 (C-4), 130.7 (C-5), 146.1 (C-3), 163.7 (C-triazine).

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## REFERENCES AND NOTES

[1] A. N. Kost and I. I. Grandberg, *Adv. Heterocyclic Chem.*, **6**, 347 (1966).

[2] L. C. Behr, R. Fusco, and C. H. Jarboe. Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings, R. H. Wiley, ed, Interscience, New York, 1967.

[3] K. Schofield, M. R. Grimmett, and B. R. T. Keene, The Azoles, Cambridge University Press, Cambridge, 1976.

[4] J. Elguero, Pyrazoles and their Benzo Derivatives in Comprehensive Heterocyclic Chemistry, A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, **5**, 167 (1984); J. Elguero, Pyrazoles in Comprehensive Heterocyclic Chemistry II, A. R. Katritzky, C. W. Rees, and E. F. Scriven, eds, Pergamon, Oxford, **3**, 1 (1996).

[5] A. R. Katritzky, G. W. Rewcastle and W. Q. Fang, *J. Org. Chem.*, **53**, 5685 (1988).

[6] P. A. Benjes and M. R. Grimmett in *N*-Alkylation of Nitrogen Azoles, Advances in Detailed Reaction Mechanisms, **3**, 199 (1994), JAI Press Inc.: UK.

[7] M. Begtrup and P. Larsen, *Acta Chem. Scand.*, **44**, 1050 (1990).

[8] D. Bogdal, J. Pielichowski, and K. Jaskot, *Heterocycles*, **45**, 715 (1997).

[9] E. Díez-Barra, A. de la Hoz, A. Sánchez-Migallón, and J. Tejeda, *Synth. Commun.*, **20**, 2849 (1990).

[10] I. Forfar, P. Cabildo, R. M. Claramunt, and J. Elguero, *Chem. Letters*, 2079 (1994).

[11] P. Cabildo, R. M. Claramunt, I. Forfar, and J. Elguero, *Tetrahedron Letters*, **35**, 183 (1994).

[12] R. M. Martín Aranda, M. L. Rojas Cervantes, A. J. López Peinado, and J. D. López González, *Catalysis Letters*, **25**, 3 (1994).

[13] D. Abenhaïm, E. Díez-Barra, A. de la Hoz, A. Loupy, and A. Sanchez-Migallón, *Heterocycles*, **38**, 793 (1994). E. Pérez, E. Sotelo, A. Loupy, R. Mocelo, M. Suárez, R. Pérez, and M. Autié, *Heterocycles*, **43**, 539 (1996).

[14] C. Goux, S. Sigismondi, M. Pérez, M. Moreno-Mañas, R. Pleixats, and M. Villarroya, *Tetrahedron*, **52**, 9521 (1996).

[15] M. J. Konkel and R. Vince, *J. Org. Chem.*, **61**, 6199 (1996).

[16] H. J. M. Dou, J. Elguero, M. Espada, and P. Hassanaly, *An. Quím.*, **74**, 1137 (1978).

[17] R. Gassend, J. C. Maire, and H. J. M. Dou, *C. R. Acad. Sci. (Paris)*, **281C**, 945 (1975).

[18] Handbook of Chemists and Physics, 70th Ed., R. C. Weast and D. R. Linde, eds, CRC Press, Boca Raton, 1989-90.

[19] M. R. Haque and M. Rasmussen, *Tetrahedron*, **50**, 535 (1994); M. R. Haque and M. Rasmussen, *Tetrahedron*, **53**, 6937 (1997).

[20] J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, The Tautomerism of Heterocycles, Academic Press, New York, 1976, p 296.

[21] A. Grimison, J. H. Ridd, and V. B. Smith, *J. Chem. Soc.*, 1352 (1960); A. Grimison, J. H. Ridd, and V. B. Smith, *J. Chem. Soc.*, 1357 (1960); J. H. Ridd and V. B. Smith, *J. Chem. Soc.*, 1363 (1960).

[22] J. Elguero, E. Gonzalez, and R. Jacquier, *Bull. Soc. Chim. France*, 5009 (1968); J. Elguero and A. Fruchier, and R. Jacquier, *Bull. Soc. Chim. France*, 207 (1968).

[23] J. Torres, J. L. Lavandera, P. Cabildo, R. M. Claramunt, and J. Elguero, *J. Heterocyclic Chem.*, **25**, 1138 (1988).

[24] J. Barry, G. Bram, G. Decodts, A. Loupy, P. Pigeon, and J. Sansoulet, *J. Org. Chem.*, **49**, 1138 (1984).

[25] P. Vinczer, T. Kovacs, L. Novak, and C. Szantay, *Org. Prep. Proc. Int.*, **21**, 232 (1989).

[26] F. Gómez-de la Torre, A. de la Hoz, F. A. Jalón, B. R. Manzano, A. Otero, A. M. Rodríguez, M. C. Rodríguez-Pérez, A. Echevarría, and J. Elguero, *Inorg. Chem.*, in press.

[27] A. Echevarría, J. Elguero, A. L. Llamas-Saiz, C. Foces-Foces, G. Schultz, and I. Hargittai, *Struct. Chem.*, **5**, 255 (1994).

[28] M. Nazarinia, A. Sarifian, and A. Shafie, *J. Heterocyclic Chem.*, **32**, 223 (1995).

[29] A. J. Canty and R. T. Honeyman, *J. Organomet. Chem.*, **387**, 247 (1990).

[30] H. Reimlinger, A. Noels, J. Jadot, and A. van Overstraeten, *Chem. Ber.*, **103**, 1954 (1970).