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A study of the regioisomerism in pyrazole alkylation using environmental friendly microwave irradiation

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Abstract. Pyrazole alkylation by benzyl, diphenylmethyl and trityl halides (chlorides and bromides) has been achieved by means of microwave irradiation. The structures and percentages of the different derivatives obtained have been determined by analytical methods: NMR spectroscopy plus gas chromatography coupled to mass spectrometry.

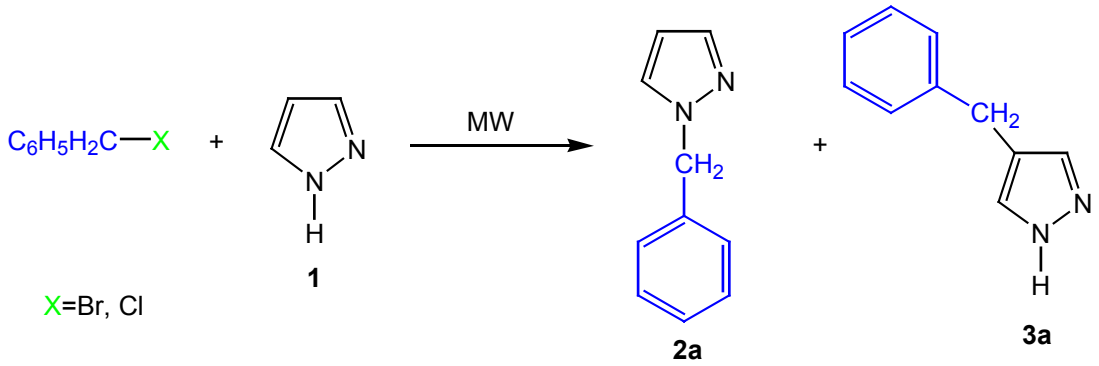
Introduction

Pyrazoles monosubstituted at position 4 are inhibitors and deactivators of liver alcohol dehydrogenase and one of them, 4-methylpyrazole, has been developed into a drug for the treatment of alcoholism and could also be used as an antidote in methanol and ethylene glycol intoxication [1-6]. The main problem is that they are difficult to prepare [7].

In this work, we have studied the alkylation reaction of pyrazole under microwave irradiation in absence of solvent expecting to obtain 4-substituted in addition to 1-substituted derivatives [8,9]. Some reaction parameters, such as irradiation power and time and type of halogen derivative have been studied in order to know their influence on the activity and selectivity of the reaction.

Results and Discussion

Reactions were carried out with pyrazole/halogen derivative in a 1/1 ratio and the relative amounts of the reaction products were determined by mass spectrometry/gas chromatography in wt %. Treatment of pyrazole **1** with benzyl bromide in different conditions affords a mixture of compounds **2a** and **3a** in the tested conditions (Scheme 1 and Table 1). The same reaction with benzyl chloride yields the product **2a** and traces of disubstituted derivatives.



1 **2a** **3a**

Scheme 1

Table 1. Experimental conditions for the reaction of **1** with benzyl halides.

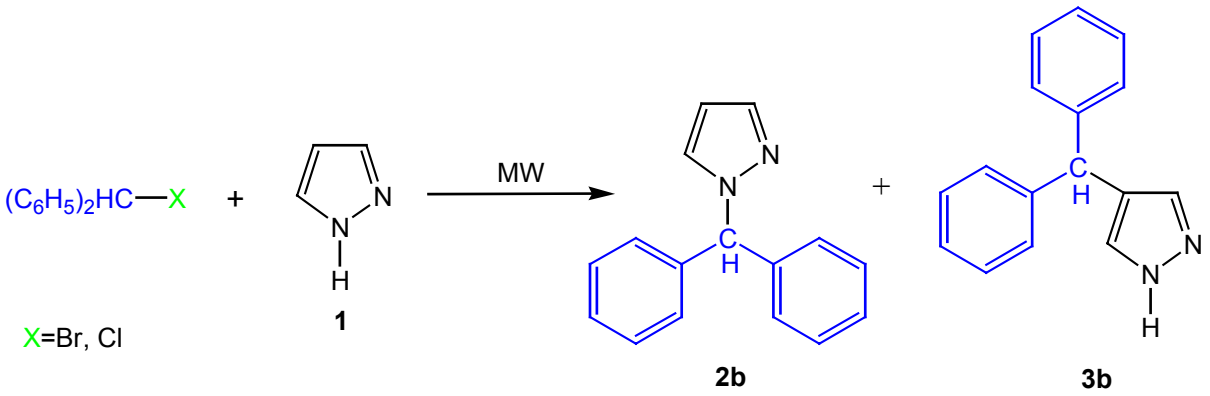
					Compounds (%)	
			Power (W)	Time (min)	2a	3a
a Series	Pyrazole 1	$C_6H_5CH_2Br$	600	5	21.3	**35.3**
			600	10	**48.2**	23.9
			900	5	**41.9**	19.8
		$C_6H_5CH_2Cl$	600	5	**86.1**	-

The ^{1}H NMR chemical shifts are gathered in Table 2 and they are in agreement with the values described in the literature [7,10-12].

Table 2. ^{1}H NMR chemical shifts, δ in ppm relative to external TMS, in $CDCl_3$.

	CH_2	C_6H_5	H_3/H_5	H_4	NH
2a	5.32 (s)	7.05-7.29	7.56 (dd)/7.38 (dd)	6.28 (dd)	-
3a	3.82 (s)	7.28-7.19	7.35 (s)	-	9.90 (br)

The reacción between pyrazole **1** and diphenylmethyl bromide at different conditions (Table 3) affords compound **3b** and traces of **2b** (Scheme 2). The N-substituted **2b** is obtained exclusively in the reaction with diphenylmethyl chloride. The ^{1}H NMR results are reported in Table 4.



Scheme 2

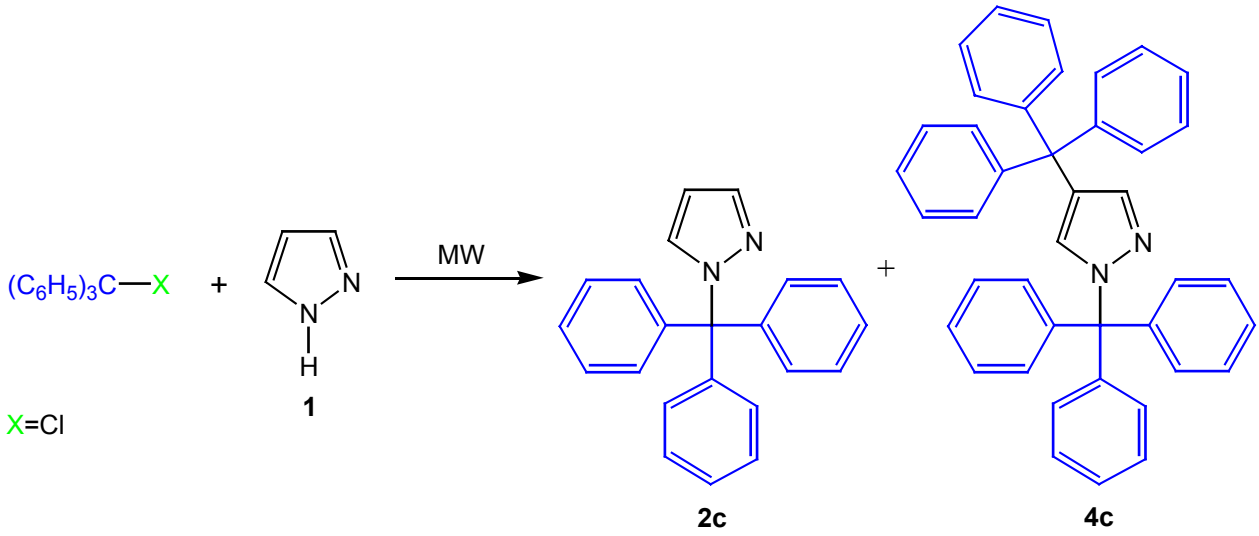
Table 3. Experimental conditions for the reaction of **1** with diphenylmethyl halides.

					Compounds (%)	
			Power (W)	Time (min)	2b	3b
b Series	Pyrazole 1	$(C_6H_5)_2CHBr$	600	5	2.8	**63.0**
			600	10	0.8	**60.3**
			900	5	1.8	**66.5**
		$(C_6H_5)_2CHCl$	600	5	**77.0**	**-**
			600	10	**85.9**	**-**
			900	5	**82.6**	**-**

Table 4. ^{1}H NMR chemical shifts, δ in ppm relative to external TMS, in $CDCl_3$.

	CH	C_6H_5	H_3/H_5	H_4	NH
2b	6.78 (s)	7.05-7.09 (Ho) 7.25-7.34(Hm + Hp)	7.58 (dd)/7.24 (dd)	6.25 (dd)	-
3b	5.40 (s)	7.18-7.34	7.26 (s)	-	8.10 (br)

The last reaction we carried out involves pyrazole **1** and trityl halides. When the reaction was performed using trityl chloride, together with the N-trityl derivative **2c** it was possible to isolate the 1,4-disubstituted compound **4c** (Scheme 3). The molar ratio for **2c**/**4c** is 85/15 as calculated by ^{1}H NMR integration. The ^{1}H NMR results are summarized in Table 5.



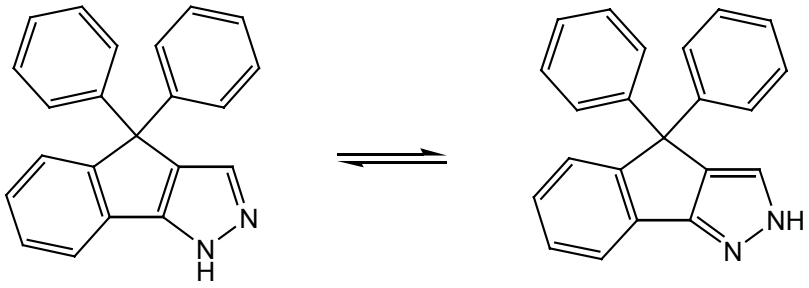
2c **4c**

Scheme 3

Table 5. ^{1}H NMR chemical shifts, δ in ppm relative to external TMS, in $CDCl_3$.

	C_6H_5	H_3/H_5	H_4
2c	7.10-7.18 (Ho) 7.26-7.33(Hm + Hp)	7.66 (dd)/7.37 (dd)	6.23 (dd)
4c	7.09-7.30	7.39 (d)/7.08 (d)	-

However with trityl bromide the reaction was more complex than expected. The main compound is 4,4-diphenyl-1,4-dihydroindeno[1,2-*c*]pyrazole **5c** and its structure is supported by NMR spectroscopic data.



5c

Experimental procedure

A mixture of pyrazole and halogen derivatives in stoichiometric amounts was placed in a tube (“Mini” #7 Ace-Thred). The system was irradiated in a microwave oven (Panasonic NN 5252 B) at different powers and times (Tables 1 and 3). After cooling to room temperature, the reaction crude was dissolved in dichloromethane and chromatographed over silica gel with different eluents. NMR spectra were obtained using a Bruker DRX 400 instrument. The mass spectra were recorded on a Shimadzu QP-5000 spectrometer (EI, 60 eV).

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