

AN EASY AND EFFICIENT MICROWAVE - ASSISTED METHOD TO OBTAIN 1-(4-BROMOPHENACYL)AZOLES IN "DRY MEDIA"

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Abstract- *N*-Alkylation of azoles with 4-bromophenacyl bromide has been carried out under microwave irradiation in solvent-free conditions. The results obtained showed high yields and selectivity. The specific "non-thermal" effect produced by microwave was demonstrated.

INTRODUCTION

"Azole fungicides" represent one of the largest classes of fungicides and antimycotics today acting as sterol biosynthesis inhibitors in fungi.¹⁻⁴ The first reports on 1-substituted azole derivatives and their fungicidal properties were described at the end of the sixties by research groups at Bayer and Janssen.⁵⁻⁷ In the synthesis of *N*-substituted azole fungicides one of the crucial steps is the creation of the C-N bond between a suitable organic substituent and the azole nitrogen in position 1.

The process most frequently used a direct *N*-alkylation of the azole by a suitably functionalized alkyl derivative, in the presence of a base. This method can suffer from some inconvenients due to moderate yields and poor purity of products, possibly connected to low selectivity. On the other hand, *N*-alkylations of azoles with alkyl halides have been performed under solvent free conditions⁸⁻¹⁰ including either a base in a solid-liquid phase transfer catalysis (PTC) system or the absence of base in solid-liquid media. Microwave activation can be eventually coupled with these solvent-free techniques with considerable interest.^{11,12}

We describe here an easy and efficient method to obtain five 1-(4-bromophenacyl)azoles by reacting, in solvent-free conditions and in the absence of base 4-bromophenacyl bromide with pyrazole (**1a**), 3,5-dimethylpyrazole (**1b**), 1,2,4-triazole (**1c**), indazole (**2d**) or benzotriazole (**2e**) under microwave irradiation. In all cases, the *N*-1 alkylated products were mainly obtained as a consequence of the absence of solvent that could avoid tautomeric equilibrium and of the molecular ratio 1:1 that minimizes quaternarization.

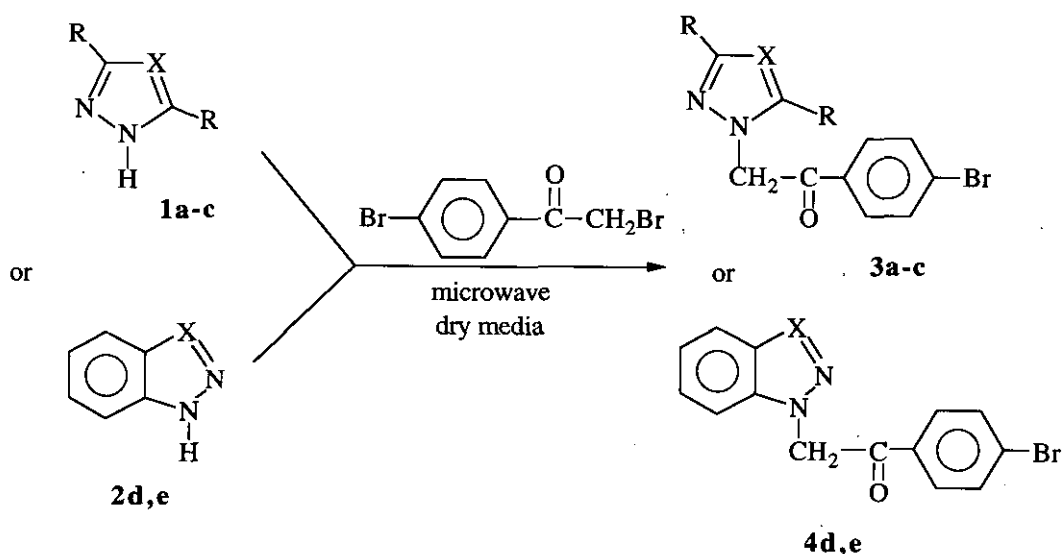
RESULTS AND DISCUSSION

The results obtained in the alkylation of pyrazole (**1a**), 3,5-dimethylpyrazole (**1b**) and 1,2,4-triazole (**1c**) (Table 1) showed very short reaction times (3-6 min) and quantitative yields in the corresponding 1-(4-bromophenacyl) derivatives so that no purification was required afterwards.

In the alkylation of indazole (**2d**) the yield of the *N*-1 alkylated product (**4d**) was proved to be about 96 % and no other isomer was detected neither by thin layer chromatography (tlc) nor by gas chromatography (gc) techniques (Table 1).

The overall yield in the case of benzotriazole (**2e**) was about 95 % and showed the *N*-1 alkylated (**4e**) isomer yield about 80 % (Table 1). The mass spectrometry data for compound (**4e**) ensured us that no quaternarization occurred.

In order to check the possible intervention of specific (*i.e.*, non-thermal) effects of microwave, we carried out all the solvent-free reactions using the conventional heating mode (oil bath) at the same final temperature and reaction times as measured in the microwave experiments. In all cases no reaction was detected neither by tlc nor gc. In the Table 2 we showed comparative results obtained using microwave irradiation and those under conventional conditions for two products (**3a** and **3c**).



	a	b	c	d	e
X	CH	CH	N	CH	N
R	H	CH ₃	H	-	-

Table 1. Alkylation of azoles(**1a-c**, **2d,e**) with 4-bromophenacyl bromide under microwave irradiation in dry media (power = 385W)

Substrate	Reaction time (min)	Temp (°C) ^a	Product Yield (%) ^b
1a	2	35-40	3a ≥98
1b	4	40-45	3b ≥98
1c	4	35-40	3c ≥98
2d	6	40-50	4d 96
2e	3	40-50	4e 80

^a Measured immediately after the reaction using a glass thermometer.^b Determined by gc**Table 2.** Comparative results obtained for *N*-alkylation of pyrazole (**1a**) and 1,2,4-triazole (**1c**) with 4-bromophenacyl bromide using traditional heating and microwave activation

Method A: Conventional heating

Method B: Microwave activation under solvent-free conditions

Substrate	Method	Molar ratio ^a	Solvent	Reaction time (min)	Temp (°C) ^b	Product Yield (%) ^c
1a	A	1:2	MeOH	180	reflux	3a 37 ^d
1a	A	1:1	none	2	35-40	3a ≤2
1a	B	1:1	none	2	35-40	3a ≥98
1c	A	1:2	MeOH	150	reflux	3c 40 ^d
1c	A	1:1	none	4	35-40	3c ≤2 ^e
1c	B	1:1	none	4	35-40	3c ≥98

^a 4-Bromophenacyl bromide: azole. ^b Final temperature as described above. ^c Determined by gc.^d Complement to 100% is a mixture of decomposition products. ^e Only starting materials are recovered

The results were very satisfactory taking in account the short reaction times, the low reaction cost as azoles are relatively expensive reagents and the increase of the yield on the *N*-1 alkylated products without any further purification procedure.

It is evident here that specific "non-thermal" effect produced by microwaves is of prime importance as:

- i) no reaction occurred under the same conditions (time and temperature) as a conventional heating without irradiation; ii) more pure products were obtained on comparison with classical method in methanol, where decomposition appeared.

EXPERIMENTAL PART

Starting materials came from commercial sources. Melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. The reactions were carried out in a Sanyo domestic microwave oven which allows the selection of output power up to 800 Watts. Tlc analyses were run on 60 F254 silica gel chromatoplates from Merck in a mixture of chloroform:ethyl acetate 8:1 as eluent. Gc analyses were performed on an apparatus from Shimadzu fitted with flame ionization detector. All the solvents employed for chromatographic analyses were hplc grade from BDH. Ir. spectra were recorded on a Philips Analytical PU 9600 FTIR Spectrometer. ^1H -Nmr spectra were recorded on a Bruker AC 250 using TMS as an internal standard and CDCl_3 as solvent. The mass spectrometric analysis for compound (**4e**) was performed on a Delsi / Nermag Spectral 30 by direct inlet.

General procedure. The equimolar mixture (3 mmol) of 4-bromophenacyl bromide and the corresponding azole was placed into a pyrex-glass open vessel and irradiated in a domestic microwave oven. When the irradiation was stopped, the final temperature was measured by introducing a glass thermometer into the reaction mixture and homogenizing it, in order to obtain a temperature value representative of the whole mass. The reaction mixture was washed with cold water and the products were filtered off and conveniently dried, then recrystallized from absolute ethanol.

1-(4-Bromophenacyl)pyrazole (3a): mp 134-135°C (EtOH) ; ν_{max} (KBr)/ cm^{-1} : 1690, 1580, 1570, 1540, 1450; ^1H nmr (CDCl_3) δ (ppm): 5.5 (s, 2H), 6.3 (t, $J=1.8$ and 2.3 Hz, 1H), 7.2 (d, $J=2.3$ Hz, 1H), 7.5 (d, $J=1.8$ Hz, 1H), 7.6 (d, $J=8.7$ Hz, 2H), 7.8 (d, $J=8.7$ Hz, 2H). Anal. Calcd for $\text{C}_{11}\text{H}_9\text{N}_2\text{OBr}$: C, 49.84; H, 3.39; N, 10.57. Found: C, 50.01; H, 3.36; N, 10.84.

1-(4-Bromophenacyl)3,5-dimethylpyrazole (3b): mp 112-114°C (EtOH) ; ν_{max} (KBr)/ cm^{-1} : 1685, 1590, 1585, 1550, 1460; ^1H nmr (CDCl_3) δ (ppm): 2.1 (s, 3H), 2.2 (s, 3H), 5.4 (s, 2H), 5.9 (s, 1H), 7.6 (d, $J=8.7$ Hz, 2H), 7.83 (d, $J=8.7$ Hz, 2H). Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{OBr}$: C, 53.26; H, 4.42; N, 9.56. Found: C, 53.16; H, 4.30; N, 9.87.

1-(4-Bromophenacyl)1,2,4-triazole (3c): mp 178-180°C (EtOH) ; ν_{max} (KBr)/ cm^{-1} : 1680, 1580, 1533, 1450, 1335; ^1H nmr (CDCl_3) δ (ppm): 5.9 (s, 2H), 7.8 (s, 1H), 7.9 (d, $J=8.6$ Hz, 2H), 8.0 (d, $J=8.6$ Hz, 2H), 8.1 (s, 1H). Anal. Calcd for $\text{C}_{10}\text{H}_8\text{N}_3\text{OBr}$: C, 45.14; H, 3.01; N, 15.79. Found: C, 45.12; H, 2.99; N, 15.91.

1-(4-Bromophenacyl)indazole (4d): mp 150-152°C (EtOH) ; ν_{max} (KBr)/ cm^{-1} : 1690, 1590, 1580, 1460, 1350; ^1H nmr (CDCl_3) δ (ppm): 5.8 (s, 2H), 7.1 (t, $J=7.9$ and 7.2 Hz, 1H), 7.3 (t, $J=7.2$ Hz, 1H), 7.7-7.6 (m, 2H), 7.6 (d, $J=8.6$ Hz, 2H), 7.9 (d, $J=8.6$ Hz, 2H), 8.0 (s, 1H). Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{OBr}$: C, 57.16; H, 3.52; N, 8.89. Found: C, 57.31; H, 3.60; N, 8.98.

1-(4-Bromophenacyl)benzotriazole (4e): mp 159-161°C (EtOH) ; $\nu_{\max}$ (KBr)/cm⁻¹: 1695, 1580, 1533, 1450, 1355; ¹H nmr (CDCl₃) δ (ppm): 6.0 (s, 2H), 7.5-7.3 (m, 3H), 7.7 (d, J=8.6 Hz, 2H), 7.9 (d, J=8.6 Hz, 2H), 8.1 (d, J=9.5 Hz, 1H); ms (m/z): 315/317 M⁺, 289/287, 258/260, 183/185, 169/171, 155/157, 132, 77, 51. Anal. Calcd for C₁₄H₁₀N₃OBr: C, 53.19; H, 3.19; N, 13.29. Found: C, 53.31; H, 3.25; N, 13.32.

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