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SYNTHESIS OF *p*-NITROPHENYLAZOLES BY PHASE TRANSFER CATALYSIS WITHOUT SOLVENT

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Abstract. Several *N*-*p*-nitrophenylazoles have been synthesized by direct arylation of the corresponding azole with *p*-fluoronitrobenzene (FNB) using phase-transfer catalysis (PTC) without solvent.

Direct *N*-arylation of azoles using di- or tri-nitrophenylhalobenzenes is quite general and occurs with good yields[1], but the direct arylation with *p*-nitrophenylhalobenzenes is more difficult and only take place in good yields with 1,2,4-triazole[1d] (90% yield, 1-aryl to 4-aryl ratio =4/1) using *p*-fluoronitrobenzene (FNB) in the presence of potassium fluoride at 180ºC. In similar experimental conditions, pyrazole[1a],

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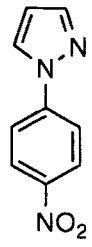
imidazole[2], 1,2,3-triazole[1c] and indazole[3] give poor yields. Benzimidazole[4] reacts with *p*-chloronitrobenzene in the presence of sodium hydride in refluxing glyme but the yield is only moderate (30%) giving the corresponding *N*-*p*-nitrophenylderivative. Arylation under Ullmann conditions[5] allows to obtain *N*-*p*-nitrophenyl-pyrazole, -imidazole, -benzimidazole, -1,2,4-triazole and -indazole but in moderate yields (imidazole, 54%, being the best), and in the two last cases only the 1-substituted isomer was obtained. 1-*p*-Nitrophenylbenzotriazole[6] and 2-*p*-nitrophenylbenzotriazole[7] have been synthesized by indirect methods. All these procedures involve high temperatures and/or long reaction times.

It is well known that phase transfer catalysis (PTC) without solvent gives good results both in the alkylation of the pyrazole anion[8] and in nucleophilic aromatic substitution reactions using carbon and oxygen nucleophiles[9]. In this paper, we describe a simple and general method to prepare *N*-*p*-nitrophenylazoles by direct arylation using FNB and PTC without solvent in an ultrasound bath. The use of sonication gives better yields than magnetic stirring. We have used tetrabutylamonium bromide (TBAB) as catalyst, other catalyst such as TDA-1[9] or BBDE Cl[10] give lower yields and similar isomer ratios. *N*-*p*-nitrophenylazoles **1-9** have been synthesized in this way.

Table 1 shows the optimized reaction times (t_1: formation of azole anion; t_2: substitution reaction) for each azole. In all cases, the FNB/azole ratio is a little more than one and the azole/catalyst ratio is ten to one. Both isomers were isolated when the azole has two different nucleophilic sites, and yields were good except for benzotriazole, but



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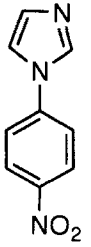

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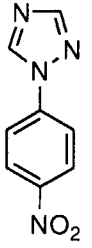

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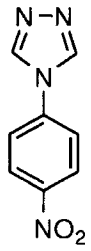

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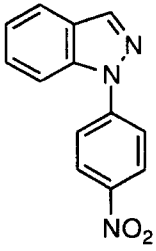

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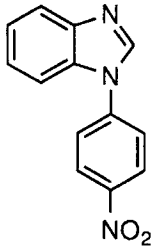

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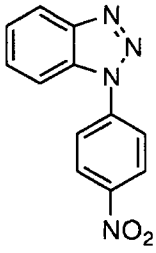

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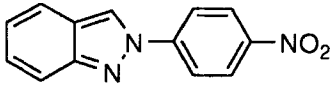

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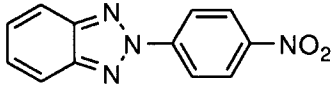

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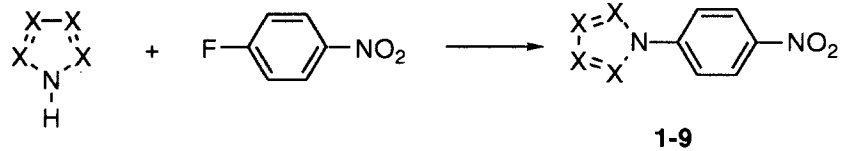
even in this case the advantages over other methods are clear due to the mild and simple reaction conditions and the easy isolation of the pure isomers.

EXPERIMENTAL

GENERAL PROCEDURE.- A mixture of 10 mmol of the azole, 1 mmol of catalyst and 20 mmol of potassium hydroxide was placed in an ultrasound bath for the time required in each case (Table 1, t_1). Then a

TABLE 1 : Experimental Conditions



1-9

Azole	catalyst	t_1 (h)	t_2 (h)	Product	Yield (%)[a]
Pyrazole	TBAB	1.5	24	**1**	80
Pyrazole	TDA-1	1.5	24	**1**	60
Pyrazole	TDA-1	1.0	24	**1**	68
Pyrazole	BBDE Cl	1.5	24	**1**	73
Imidazole	TBAB	3.0	24	**2**	76
1,2,4-Triazole	TBAB	1.0	48	**3/4** : (3/1)[b]	70
1,2,4-Triazole	TDA-1	1.0	48	**3/4** : (4/1)[b]	53
1,2,4-Triazole	BBDE Cl	1.0	48	**3/4** : (4/1)[b]	47
Indazole	TBAB	3.0	72	**5/6** : (2/1)[b]	71
Benzimidazole	TBAB	2.0	24	**7**	77
Benzotriazole	TBAB	1.0	48	**8/9** : (9/1)[c]	30

a) yield in isolated product; b) estimated from ^{1}H-NMR data;

c) determined from isolated isomers

little exces of FNB (about 11 mmol) was added and the mixture maintained in the sonication bath for the time indicated in each case (Table 1, t_2). The reaction was controlled by thin layer chromatography (hexane-ethyl acetate: 1/1). The crude was extracted with methylene chloride, except for benzotriazole where the pure mixture of isomers was extracted from the crude with hot chloroform, and dried over anhydrous

magnesium sulfate. After evaporation of the solvent the product was recrystallized or chromatographed.

1-*p*-Nitrophenylpyrazole **1**: the crude was recrystallized from ethanol, mp 173-175ºC.

1-*p*-Nitrophenylimidazole **2**: the crude was recrystallized from hexane-ethyl acetate, mp 213-215ºC.

N-*p*-nitrophenyl-1,2,4-triazoles **3** and **4**: the crude was chromatographed over silicagel 60 Merck (70-230 mesh) with a mixture of ethanol-chloroform (7/3) as eluent. **3**, mp 197-199ºC and **4**, mp 333-335ºC.

N-*p*-nitrophenylindazoles **5** and **6**: recrystallization of the crude from ethanol yielded **5**, mp 120-122ºC. The insoluble residue was recrystallized from ethyl acetate yilding **6**, mp 224-226ºC.

1-*p*-Nitrophenylimidazole **7**: the crude was recrystallized from ethanol, mp 180-182ºC.

N-*p*-nitrophenylbenzotriazoles **8** and **9**: from the chloroform extract of the crude the mixture of pure isomers crystallized on cooling. This mixture was recrystallized from chloroform yielding **8**, mp 246-248ºC. The residue from the mother liquors was recrystallized three times from dimethylformamide to yield pure **9**, mp 294-296ºC.

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