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Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:

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SYNTHESIS OF 1-(*p*-NITROBENZYL)AZOLES AND 1-(*p*-NITROBENZYL)BENZAZOLES

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To cite this Article Pardo, Carmen , Graf, Sabine , Ramos, Mar , Sesmilo, Esther and Elguero, José(2000) 'SYNTHESIS OF 1-(*p*-NITROBENZYL)AZOLES AND 1-(*p*-NITROBENZYL)BENZAZOLES', *Organic Preparations and Procedures International*, 32: 4, 385 – 390

To link to this Article: DOI: 10.1080/00304940009355941

URL: <http://dx.doi.org/10.1080/00304940009355941>

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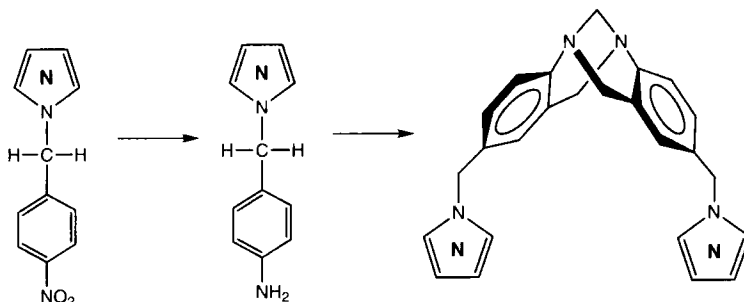
Submitted by
(03/27/00)

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In order to prepare Tröger's bases¹⁻⁵ bearing azolylmethylene substituents (*Scheme 1*), we needed a simple access to *p*-nitrobenzylazoles (*Scheme 1*). Besides our own interest, these compounds, or more precisely, the corresponding amines, are starting materials for Fisher indole synthesis of pharmaceutical and agrochemical interest.⁶

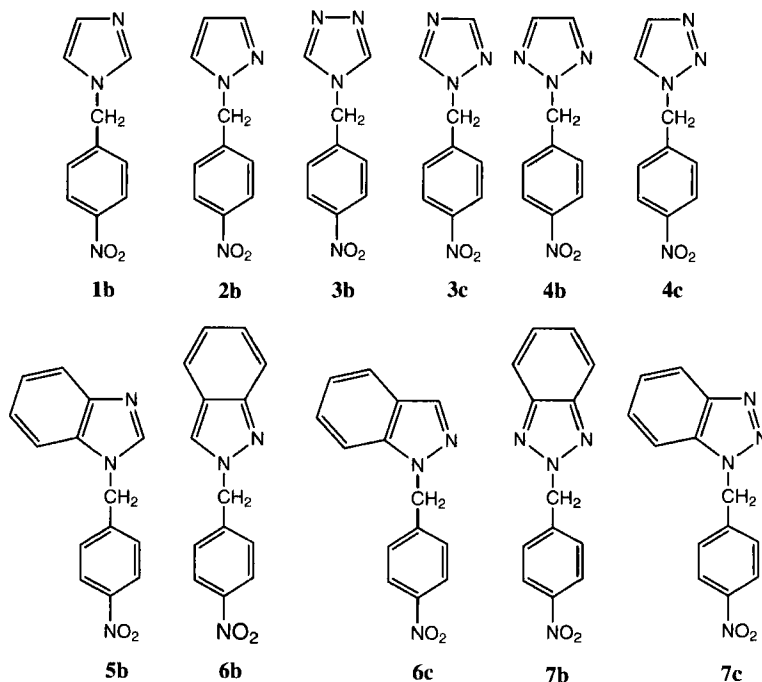


Scheme 1

Therefore, we now describe the eleven *p*-nitrobenzylazoles shown in *Scheme 2*. Since those which were already known were insufficiently characterized, this paper will also report the complete assignment of their NMR (¹H and ¹³C) spectra.

An examination of the literature concerning *p*-nitrobenzylazoles shows that some of these compounds were synthesized for a study their photochemical behavior. Thus, Beugelmans *et al.* described that **1b**, **2b** and **5b** are formed with excellent yields (> 90%) by reaction of the azole with *p*-nitrobenzyl chloride in acetonitrile and potassium carbonate upon irradiation and noted that in the dark, the reaction gave yields lower than 10%.⁷ However, other authors have reported that the photochemical reaction of azoles with *p*-nitrobenzyl chloride in DMSO or HMPA in the presence of tBuOK affords *p*-nitrobenzyl derivatives of nitroimidazoles, nitrobenzimidazoles and nitroindazoles but failed with imidazole and benzimidazole themselves.^{8,9}

Reaction of 1,2,4-triazole (**3a**) with *p*-nitrobenzyl chloride in EtONa/EtOH afforded 1-*p*-nitrobenzyl-1,2,4-triazole (**3c**) in 71% yield as the only product.^{10,11} A very recent paper describes again this reaction and the authors report that both isomers, **3b** and **3c**, were actually formed in a 10:90 ratio.¹² 1-*p*-nitrobenzyl-1,2,3-triazole **4c** has been prepared by 1,3-dipolar cycloaddition of



Scheme 2

1-*p*-nitrobenzyl azide and vinyl acetate.^{13,14} Both compounds, by manipulation of the nitro substituent, were starting materials for the synthesis of 1-(*p*-substituted-benzyl)-triazoles which are inhibitors of the arachidonic acid induced malonaldehyde production in human platelets and are also inhibitors of prostaglandin synthesis *in vitro*. In general, *p*-nitrobenzyl azoles are useful intermediates in the synthesis of antifungal agents.¹⁵ The present paper describes the synthesis of *p*-nitrobenzylazoles **1-7** by direct alkylation of the parent *NH*-compounds with *p*-nitrobenzyl bromide in the presence of potassium carbonate by two simple and general methods in solution of DMF (method 1) or by phase transfer catalysis without solvent in an ultrasound bath, using tetrabutylammonium bromide (TBAB) as catalyst (method 2).¹⁶ The experimental conditions are given in Table 1 and the purification procedures and melting points in Table 2.

EXPERIMENTAL SECTION

Mps were obtained on a Gallenkamp apparatus and are uncorrected. ¹H NMR spectra were recorded at 200 MHz on a Bruker AC-200 spectrometer or a 300 MHz on a Varian VXR-300S spectrometer. ¹³C NMR spectra were recorded at 50 MHz on a Bruker AC-250 spectrometer. Elemental analyses were carried out at the 'Servicio de Microanálisis (UCM)'. Aldrich supplied azoles **1a-7a**, *p*-nitrobenzylbromide and TBAB. DMF and the solvents used in chromatography were of Multisolvant quality supplied by Scharlau. Silica gel Merck (230-400 mesh) was used for flash chromatography and Silica gel Merck 60 F254 sheets was used for TLC.

General Procedure. Method 1.- A mixture of 10 mmol of the azole, 1 mmol of TBAB and 20 mmol of anhydrous potassium carbonate, or potassium hydrogen carbonate, in dimethylformamide (Table 1),

was stirred at room temperature for the time required in each case (Table 1, t_1). Then a slight excess of *p*-nitrobenzyl bromide (11 mmol, Table 1) was added and the mixture was stirred at the temperature and for the time indicated in each case (Table 1, T °C and t_2). The reaction mixture was poured into water and the crude product precipitated. If the *p*-nitrobenzyl derivative did not precipitate, the mixture was extracted with dichloromethane and the organic extracts were washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The final crude product obtained was purified by crystallization or by flash chromatography (FC, Table 2).

Method 2.- A mixture of 10 mmol of the azole, 1 mmol of TBAB and 20 mmol of anhydrous potassium carbonate, or potassium hydrogen carbonate (Table 1), was placed in an ultrasound bath at room temperature for the time required in each case (Table 1, t_1). Then, a little excess of *p*-nitrobenzyl bromide (11 mmol, Table 1) was added and the mixture maintained in the sonication bath at room temperature for the time indicated in each case (Table 1, t_2). The crude mixture was extracted with dichloromethane and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the compound was crystallized or chromatographed (FC, Table 2).

Table 1. Benzoylation of Azoles

Starting Azole	Product	M ^a	Solvent	t ₁ (h)	t ₂ (h)	temp. (°C)	Yield (%) ^b
Imidazole (1a)	1b	1	(DMF (15 mL))	1	24	50	53
Imidazole (1a)	1b	2	-----	1	24	rt	40
Pyrazole (2a)	2b	1	DMF (10 mL)	1	24	40-60	70
Pyrazole (2a)	2b	2	-----	1	24	rt	76
1,2,4-Triazole (3a)	3b/3c^c (20/80)	1	DMF (20 mL) (NaHCO ₃)	1	72	40	60
1,2,3-Triazole (4a)	4b/4c^c (40/60)	1	DMF (20 mL)	1	48	rt	65 ^d
1,2,3-Triazole (4a)	4b/4c^c (40/60)	2	-----	1	48	rt	60 ^d
Benzimidazole (5a)	5b	1	DMF (20 mL) (NaHCO ₃) ^e	1	72	rt	50
Indazole (6a)	6b/6c (80/20)	1	DMF (20 mL) (NaHCO ₃)	1	72	rt	50
Indazole (6a)	6b/6c (80/20)	2	-----	3	72	rt	53
Benzotriazole (7a)	7b/7c (31/69)	1	DMF (20 mL)	1	72	rt	65
Benzotriazole (7a)	7b/7c (20/80)	2	-----	1	48	rt	50

a) M = method b) Yield of pure compound c) Relative amounts determined by ¹H NMR on the mixture d) Yield of crude compound e) Twenty mmol of *p*-NO₂C₆H₄CH₂Br were used.

TABLE 2. Isolation, Purification, Melting Points and Elemental Analysis Data

Cmpd	Purification ^{a,b}	mp. (°C)	lit. mp. (°C)	Elemental Analyses (Found)		
				C	H	N
1b	MeOH	54-55	53 ¹⁰			----
2b	iPrOH ^c	88-89	^d	58.55 (58.68)	4.46 (4.31)	20.68 (20.83)
3b	FC ^e	140-142	143-145 ¹²			----
3c	FC ^e	101-102	100-101 ¹²			----
4b	FC ^f	113-115	----	52.92 (53.08)	3.95 (4.07)	27.44 (27.21)
4c	FC ^f	118-120	110-116 ¹³			----
5b	FC ^g	74-76	^d	66.40 (66.51)	4.38 (4.19)	16.59 (16.77)
6b	FC ^h	94-96	----	66.40 (66.18)	4.38 (4.52)	16.59 (16.63)
6c	FC ^h	116-118	----	66.40 (66.35)	4.38 (4.27)	16.59 (16.48)
7b	FC ^h	153-154	----	61.41 (61.33)	3.96 (3.96)	22.04 (22.24)
7c	FC ^h	132-134	----	61.41 (61.68)	3.96 (3.79)	22.04 (21.77)

a) Crystallization solvent b) FC: Flash chromatography c) Or sublimation d) These compounds are described in reference 7 but their melting points are not reported e) AcOEt/EtOH (9.5/0.5) f) CHCl₃/EtOH (9.5/0.5) g) AcOEt/hexane (7/3) h) Hexane/diethyl ether (7/3).

The structures of all compounds were established by ¹H and ¹³C NMR (Tables 3-6) by comparison with the *N*-benzyl analogues.^{17,18}

TABLE 3. Proton NMR Data *N*-(*p*-Nitrobenzyl)azoles in CDCl₃

Azole	H-2	H-3	H-4	H-5	CH ₂	H-2'	H-3'
1b	7.633	---	7.156	6.918	5.262	7.275	8.216
2b	---	7.648 <i>J</i> _{3,4} =1.7	6.393	7.610 <i>J</i> _{4,5} =2.2	5.541	7.385	8.195
3b^a	---	8.665	---	8.665	5.467	7.523	8.241
3c	---	8.196	---	8.028	5.484	7.410	8.193
4b	---	---	7.670	7.670	5.713	7.479	8.178
4c	---	---	7.749 <i>J</i> _{4,5} =1.0	7.613	5.693	7.382	8.187

a) In DMSO-d₆.

TABLE 4. Proton NMR Chemical Shifts (δ) and Coupling Constants (Hz) in CDCl₃ of *N*-(*p*-nitrobenzyl)benzazoles

Benzazole	H-2	H-3	H-4	H-5	H-6	H-7	CH ₂	H-2'	H-3'
5b	8.002	-	7.837	"7.25"	"7.30"	7.186	5.474	7.278	8.154
6b	-	7.981	7.656 <i>J</i> _{4,5} =8.3	7.100 <i>J</i> _{5,6} =6.6 <i>J</i> _{5,7} =1.0	"7.30"	7.711 <i>J</i> _{6,7} =8.6	5.665	7.316	8.131

TABLE 4. Continued...

Benzazole	H-2	H-3	H-4	H-5	H-6	H-7	CH ₂	H-2'	H-3'
6c	-	8.091	7.783	7.188	7.387	~7.30	5.697	7.296	8.150
		$J_{3,7}=1.0$	$J_{4,5}=8.1$	$J_{5,6}=6.5$	$J_{6,7}=8.5$				
			$J_{4,6}=1.2$	$J_{5,7}=1.5$					
7b	-	-	7.882	7.424	7.424	7.882	5.995	7.548	8.227
7c	-	-	8.120	7.3-7.6	7.3-7.6	7.3-7.6	5.968	7.3-7.6	8.209
			$J_{4,5}=8.2$						

TABLE 5. Carbon-13 NMR Chemical Shifts (δ) in CDCl₃ of *N*-(*p*-nitrobenzyl)azoles

Compound	C-2	C-3	C-4	C-5	CH ₂	C-1'	C-2'	C-3'	C-4'
1b	137.55	-	130.50	119.25	49.87	143.48	127.70	124.22	147.76
2b	-	140.32	106.58	129.71	54.89	144.06	127.95	123.97	147.58
3b^a	-	143.42	-	143.42	46.77	144.14	128.80	123.98	147.16
3c	-	152.75	-	143.51	52.46	141.77	128.50	124.25	148.14
4b	-	-	135.05	135.05	57.45	142.17	128.62	123.96	147.81
4c	-	-	134.51	123.71	52.78	141.79	128.43	124.15	147.90

a) In DMSO-d₆.TABLE 6. Carbon-13 NMR Chemical Shifts (δ) in CDCl₃ of *N*-(*p*-nitrobenzyl)benzazoles

Compound	C-2	C-3	C-3a	C-4	C-5	C-6	
5b	143.08	-	143.94	120.73	122.75	123.58	
6b	-	123.31	"123"	120.10	122.12	126.34	
6c	-	134.22	124.00	121.42	121.11	126.90	
7b	-	-	144.78	118.12	126.90	126.90	
7c	-	-	146.32	120.43	124.34	128.01	
Compound	C-7	C-7a	CH ₂	C-1'	C-2'	C-3'	C-4'
5b	109.68	133.51	48.02	142.76	127.55	124.29	147.78
6b	117.44	149.23	56.27	143.03	128.12	123.90	147.58
6c	108.73	139.61	52.02	144.12	127.81	124.00	-
7b	118.12	144.78	59.22	141.48	129.06	124.12	148.01
7c	109.05	136.75	51.13	141.80	128.23	124.29	147.80

Acknowledgement.- Financial support from DGES of Spain (Project PB96-0001-C03-03) is greatly acknowledged.

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