Tetrahedron Vol. 41, No. 24, pp. 5955 to 5963, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00

REACTIVITY OF AZOLES TOWARDS BENZALDEHYDE AND ITS DIMETHYLACETAL. SYNTHESIS OF N,N'-DIAZOLYLPHENYLMETHANES

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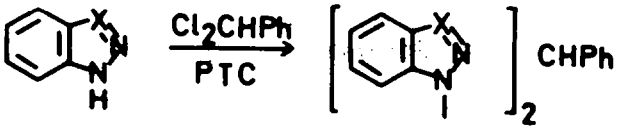
(*Received in UK* 28 *June* 1985)

Abstract - Some 1,1'-diindazolylphenylmethanes have been prepared from indazoles and benzaldehyde in presence of zinc chloride as catalyst. The reaction was strongly dependent on the basic pK_a's of azoles and only few pyrazolyl derivatives could be prepared by this procedure. Extension of this method to other azoles was accomplished by using benzaldehyde dimethylacetal.

Only few N,N'-diazolylphenylmethanes have been described in the literature. Pyrazolyl and imidazolyl derivatives were prepared either by alkylation with benzal chloride using phase transfer catalysis techniques (1) or from N,N'-carbonyldiazoles (2,3).

Due to their interest as antifungal agents similar to chlotrimazol (4) we have tried to find a simple and more general procedure to prepare this type of compounds not only from azoles but also from their benzoderivatives. Attempts to get them by alkylation with benzal chloride under the same conditions previously described for pyrazole (1) gave poor results in the case of indazole and benzotriazole. Reaction products were difficult to isolate and purify, and no improvement could be reached even by using different conditions (Table 1).

Table 1. Reaction of indazole and benzotriazole with benzalchloride under phase transfer catalysis (PTC).



1 X = CH
2 X = N

3 X = CH
4 X = N

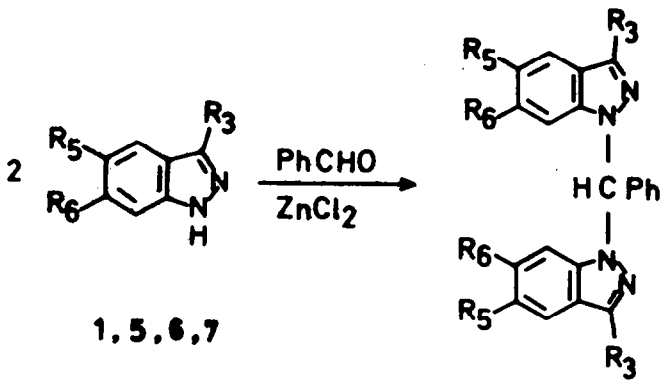
X	PTC	Product	Yield (%)[a]
CH	sol-liq	3	15
CH	liq-liq[b]	3	47[c]
N	sol-liq	4	5
N	liq-liq[b]	4	27

[a]Yield in pure isolated compound. [b]According to reference 1. [c]Crude compound difficult to purify.

These results promted us to focus our attention on the reaction of azoles with benzaldehyde. The reactivity of azoles towards aldehydes and ketones has hardly been studied. Isolated examples have been reported which mainly deal with paraformaldehyde to give either carbinols or Mannich bases (5-7). Similar behaviour has been observed for acetaldehyde (8).

It is not known if azoles could react with aldehydes to give N,N'-diazolylalkanes. The only reaction found in the literature of direct condensation with aldehydes is that reported by Fischer (9) for indazole and benzaldehyde in presence of zinc chloride to give 3,3'-diindazolylphenylmethane. We reproduced this reaction and identified the single compound formed as the 1,1'-diindazolylphenylmethane 3 (Table 2). Substitution on the nitrogen atom has been confirmed not only by the absence of N-H stretching bands in the infrared spectrum but also by the presence of the proton at the 3-position which gives a doublet at 8.10 ppm. The carbon atom at the 3-position appears at 134.8 ppm which is in agreement with values reported for other N_1-substituted indazoles (10) (Tables 3 and 4).

Similarly, 3-methyl, 5-nitro and 6-nitroindazole derivatives 8-10 have been obtained by this procedure.



1, 5, 6, 7

3, 8, 9, 10

	R_3	R_5	R_6
1, 3 :	H	H	H
5, 8 :	H	NO_2	H
6, 9 :	H	H	NO_2
7, 10 :	Me	H	H

Scheme 1

Especial mention should be made in relation to the regiospecificity of this reaction. Only one isomer is obtained with absence of the N_2 derivative. The same isomer was also produced in low yield by alkylation of indazole with benzal chloride.

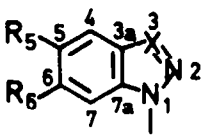
Surprisingly the reaction failed when it was tried out on pyrazole ot benzotriazole, the starting materials were recovered in the case of pyrazole and a $ZnCl_2$-complex in the case of benzotriazole (11). To explain this behaviour, the basic pK_a's of a series of azoles were checked and those with pK_a's similar to the ones of indazoles where the reaction took place satisfactorily were selected (see table 2). Thus, 4-bromopyrazole yielded the compound 13 and 3-methyl-4-bromopyrazole gave a mixture of isomers 15 and 16. However the reaction failed with 1,2,4-triazole and 2-methyl-4-nitroimidazole although their basic pK_a's are within the adequate range. These evidences suggested that this reaction is specific for indazoles and pyrazoles with basic pK_a's in the

Table 2. Results obtained from the reaction of azoles and benzazoles with benzaldehyde and its dimethylacetal

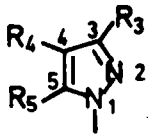
Starting product	pK_a [a]	Procedure	Reaction time (h)	Reaction product	Yield (%) [b]	m.p. (°C)	R_f (CH_2Cl_2)
Indazole 1	1.31	A	16	1,1'-diindazolylphenylmethane 3	44 [c] 62 [d]	136-8 Lit (9):	0.30
		B	22		64 [e]	138-9	
5-Nitroindazole 5	-0.68	A	30	1,1'-di(5-nitroindazolyl) phenylmethane 8	8 [d] 43 [f]	218-20	0.27
		B	22				
6-Nitroindazole 6	-0.70	A	18	1,1'-di(6-nitroindazolyl) phenylmethane 9	16 [g]	195-6	0.38
3-Methylindazole 7	2.17	A	1	1,1'-di(3-methylindazolyl) phenylmethane 10	77 [h]	193-5	0.22
		B	3		66 [h]		
Pyrazole 11	2.52	A	17	N.R.	--	---	---
		B	3-22	1-α-methoxybenzylpyrazole 20	i	---	---
		C	6.5	1,1'-dipyrazolylphenylmethane 23	58 [d]	58-61 Lit (1): 62-63	0.07
4-Bromopyrazole 12	0.68	A	16	1,1'-di(4-bromopyrazolyl) phenylmethane 13	49 [d]	122-125	0.31
3-Methyl-4-bromopyrazole 14	1.46	A	15	3,3'-dimethyl-4,4'-dibromo-1,1'-dipyrazolylphenylmethane 15	30 [d]	99-101	0.19
				3,5'-dimethyl-4,4'-dibromo-1,1'-dipyrazolylphenylmethane 16	16 [d]	98-100	0.36
4-Nitropyrazole 17	-2.00	A	16	N.R.	--	---	---
1,2,4-Triazole 15	2.19	A	16	N.R.	--	---	---
		B	23	1-α-methoxybenzyl-1,2,4-triazole 21	i	---	---
		C	22		i	---	---
Benzotriazole 2	Unknown	A	23	N.R.	--	---	---
		B	7-22	1-α-methoxybenzylbenzotriazole 22	i	---	---
		C	7	1,1'-dibenzotriazolylphenylmethane 4	32	135-7	0.12
2-Methyl-4-nitroimidazole 19		A	17	N.R.	--	---	---
		C	23	1-α-methoxybenzyl-2-methyl-4-nitroimidazole 24	i	---	---

[a] Data from references 14 and 15; [b] Yields in pure isolated compound; [c] Isolated according to reference 9; [d] Column chromatography isolation on silicagel and CH_2Cl_2 as eluent. In the case of compound 23 elution was accomplished with CH_2Cl_2/EtOH (98:2); [e] Crystallization from the cold hexane solution; [f] Crystallization from the hot reaction medium; [g] Column chromatography isolation on silicagel and $CHCl_3$ as eluent. [h] Crystallization from the reaction medium and purification by washing with cold ethanol and water; [i] Quantitative yield respect to the benzaldehyde dimethylacetal. In the case of compound 24 yield was only 50%.

Table 3. Proton NMR data of N,N'-diazol- and N,N'-dibenzazolyl-phenylmethanes[a]



X=CH 3,8,9
X=CMe 10
X=N 4



13,15,16,23

26

Product	H_3	H_4	H_5	H_6	H_7	CH (sp^3)	Phenyl and other substituents
3[b]	8.10 (d) $J_{3,7}$= 0.75	7.70 (d) J_o= 8.0	7.08-7.38[c] (m)	7.08-7.38[c] (m)	7.52 (d) J_o= 8.5	8.50 (s)	7.08-7.38 (m), 5H
8[b]	8.27 (bs)	8.71 (d) J_m= 2.2	----	8.23 (d,d) J_o= 9.2 J_m= 2.2	7.60 (d) J_o= 9.2	8.54 (s)	7.07 (m), 2H 7.39-7.47 (m), 3H
9[b]	8.23 (s)	7.86 (d) J_o= 9.0	8.06 (d,d) J_o= 8.9 J_m= 1.8	----	8.46 (bs)	8.63 (s)	7.09 (m), 2H 7.38-7.42 (m), 3H
10[d]	----	6.95-7.70 (m)	6.95-7.70 (m)	6.95-7.70 (m)	6.95-7.70 (m)	8.32 (s)	6.95-7.35 (m), 5H 2.50 (s), CH_3
4[d]	----	8.00-8.15 (m)	7.05-7.70 (m)	7.05-7.70 (m)	7.05-7.70 (m)	9.00 (s)	7.05-7.50 (m), 5H
13[d]	7.55 (d) $J_{3,5}$= 0.9	----	7.47 (d) $J_{3,5}$= 0.9	----	----	7.55 (s)	6.95-7.10 (m), 2H 7.30-7.45 (m), 3H
15[d]	----	----	7.40-7.55[c] (m)	----	----	7.43 (s)	7.05-7.15 (m), 2H 7.40-7.55 (m), 3H; 2.29 (s), CH_3
16[d]	7.50 (m)	----	7.50 (m)	----	----	7.55 (s)	6.90-7.10 (m), 2H; 2.29 (s), CH_3-3 7.35-7.45 (m), 3H 2.39 (s), CH_3-5
23[d]	7.62 (d) $J_{3,4}$= 1.8	6.32 (d,d)	7.51 (d) $J_{4,5}$= 2.5	----	----	7.74 (s)	7.00-7.03 (m), 2H 7.34-7.37 (m), 3H
26[b]	7.52 (bs) (H_2)	7.16 (bs)	6.90 (t) J = 1.4	----	----	7.38 (s)	7.07-7.16 (m), 2H 7.43-7.47 (m), 3H

[a]Attribution of the signals was made on the basis of the previous data obtained for similar structures (see references 1 and 16). Apparent multiplicity is given on the Table: s, singlet; d, doublet; t, triplet; m, multiplet; bs, broad singlet. [b]At 300 MHz; [c]Signal masked by the phenyl group; [d]At 90 MHZ.

Table 4. Carbon-13 NMR data of N,N'-diazolyl- and N,N'-dibenzazolyl-phenylmethanes[a] (See Table 3 for structural formulae numbering).

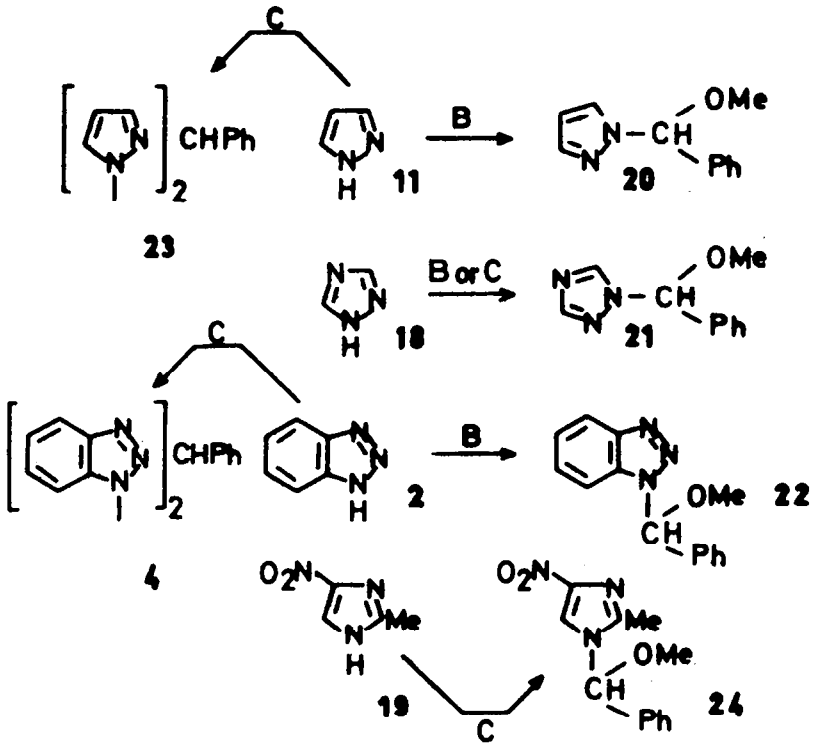
Product	C_3	C_{3a}	C_4	C_5	C_6	C_7	C_{7a}	CH (sp^3)	Phenyl and other substituents
3	134.8	124.9	121.5	121.0	126.8	110.9	139.9	74.8	135.2 (C_i); 128.5 (C_o); 127.5 (C_m); 128.8 (C_p)
8[b]	137.5	124.3	118.2	143.4	122.2	111.4	141.8	75.3	133.5 (C_i); 129.2 (C_o); 127.2 (C_m); 129.8 (C_p)
9	135.5	128.0	122.1	116.7	147.0	107.6	138.7	75.2	133.6 (C_i); 129.2 (C_o); 127.1 (C_m); 129.8 (C_p)
10	142.5	124.4	120.6	120.2	126.5	111.1	140.8	74.5	136.0 (C_i); 128.5 (C_o and C_p); 127.5 (C_m); 12.0 (CH_3)
4	---	146.2	120.3	124.8	127.0	110.8	132.4	72.4	132.3 (C_i); 129.1 (C_o); 128.6 (C_m); 129.9 (C_p)
13	141.7	---	94.9	129.9	---	---	---	78.6	134.8 (C_i); 129.1 (C_o); 127.0 (C_m); 129.9 (C_p)
15	149.2	---	95.5	129.9	---	---	---	78.3	135.0 (C_i); 129.0 (C_o); 127.0 (C_m); 129.6 (C_p); 12.1 (CH_3)
16	148.4 140.7 (CH)	---	95.0 95.7	130.3 (CH) 135.3	---	---	---	75.6	138.3 (C_i); 128.9 (C_o); 126.9 (C_m); 129.4 (C_p); 12.0 (CH_3-3); 9.8 (CH_3-5)
23	140.7	---	106.5	129.6	---	---	---	77.7	136.1 (C_i); 128.8 (C_o); 126.9 (C_m); 129.2 (C_p)
26	C_2: 136.5	---	126.7	118.0	---	---	---	70.5	134.8 (C_i); 129.4 (C_o); 130.7 (C_m); 130.3 (C_p)

[a]Attribution of the several signals to the corresponding carbons were made on the basis of the previous data obtained for similar structures (see references 10 and 17); [b]The following coupling constants confirm the assignment of the signals: $J(C_3H_3)$ = 193.2; $J(C_3H_4)$ = 2.8; $J(C_4H_4)$ = 170; $J(C_4H_6)$ = 4.4; $J(C_5H_7)$ = 3.7; $J(C_6H_6)$ = 169.8; $J(C_6H_4)$ = 4.4; $J(C_7H_7)$ = 170.7; $J(C_{7a}H_6)$ = 6.9; $J(C_{7a}H_4)$ = 6.9; $J(C_{7a}H_7)$ = 3.4; $J(CH_{sp}3)$ = 216.7 Hz.

interval from -0.7 to 2.2.

Alternatively, benzaldehyde was activated as dimethylacetal to prepare N,N'-diazolylphenylmethanes from those azoles which were not able to react with the simple aldehyde. Similarly, some N,N'-dipyrazolylalkanes were previously synthesized using pyrazole and ketone dimethylketals (12). Compounds 3, 8, and 10 were obtained in good yield when the corresponding indazole reacted with benzaldehyde dimethylacetal by refluxing hexane in presence of p-toluene sulfonic acid (Procedure B). Reaction was also regiospecific giving only one isomer which was identical to the one obtained by reaction with benzaldehyde. Conversely, pyrazole, 1,2,4-triazole and benzotriazole gave only monosubstituted intermediates 20, 21 and 23 (13). These intermediates proved to be very unstable decomposing whenever attempts to purify them by either distillation of chromatography were tried. Thus, compound 20 gave benzaldehyde dimethylacetal and 23 when it was distilled under vacuum. Since no isolation could be performed intermediates were identified by ^{1}H NMR spectroscopy as well as by mass spectrometric analysis of the reaction crude (Table 5).

When pyrazole and benzotriazole were heated with the acetal in a higher boiling point solvent such as toluene (Procedure C), compounds 23 and 4 were obtained. Only monosubstituted intermediates were still formed from 1,2,4-triazole and 2-methyl-5-nitroimidazole even using toluene as solvent.

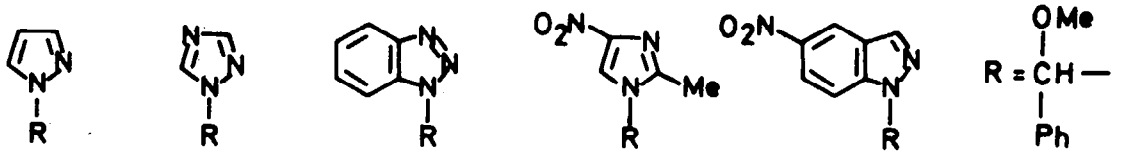


Scheme 2

From all the foregoing results it may be concluded that Fischer's reaction of indazole and benzaldehyde only gives 1,1'-diindazolylphenylmethane instead of the previously quoted 3,3'-diindazolylphenylmethane. The reaction results specific for indazoles and pyrazoles with basic pK_a's in the interval from -0.7 to 2.2. Neither 1,2,4-triazole nor imidazoles are able to react with benzaldehyde under Fischer's reaction conditions although their pK_a's are in the suitable range.

The more reactive benzaldehyde dimethylacetal is a good reagent to prepare N,N'-diazolylphenylmethanes from azoles which do not react with benzaldehyde giving the possibility to obtain intermediates which would be suitable starting materials to synthesize mixed N,N'-diazolylphenylmethanes.

Table 5. Proton NMR data for intermediate α-methoxybenzyl-azoles and -benzazoles.



Product	H_3	H_4	H_5	H_6	H_7	CH (sp^3)	OCH_3	Phenyl and other substituents
20[a]	7.58 (d) $J_{3,4}$=2.6	6.34 (m)	7.43 (d) $J_{4,5}$=1.9	----	----	6.37 (s)	3.42 (s)	7.26-7.37 (m), 5H
21[b]	8.03 (s)	----	8.20 (s)	----	----	6.39 (s)	3.50 (s)	7.39 (s), 5H
22[a]	----	8.05-8.10 (m)	7.22-7.50 (m)	7.22-7.50 (m)	7.22-7.50 (m)	7.10 (s)	3.44 (s)	7.22-7.50 (m), 5H
24[b]	----	----	8.30 (s)	----	----	6.55 (s)	3.80 (s)	7.35 (s), 5H 2.37 (s), CH_3
25[b]	8.25 (d) $J_{3,7}$= 0.9	8.70 (d,d) $J_{4,6}$= 2.1 $J_{4,7}$= 0.9	----	8.10 (d,d) $J_{6,7}$= 9.6	7.35 (d,d)	6.75 (s)	3.42 (s)	7.35 (s), 5H

[a]At 300 MHz; [b]At 90 MHz.

Table 6. Elemental analyses of the new N,N'-diazolylphenylmethanes.

Compound No.	Calculated values	Found %
8	C = 60.87; H = 3.41; N = 20.28	C = 60.80; H = 3.36; N = 19.96
9	C = 60.87; H = 3.41; N = 20.28	C = 60.88; H = 3.66; N = 19.98
10	C = 78.38; H = 5.72; N = 15.90	C = 78.37; H = 5.64; N = 16.20
13	C = 40.87; H = 2.64; N = 14.67	C = 41.17; H = 2.58; N = 14.50
15	C = 43.93; H = 3.44; N = 13.66	C = 44.27; H = 3.72; N = 13.47
16	C = 43.93; H = 3.44; N = 13.66	C = 44.15; H = 3.62; N = 13.54

EXPERIMENTAL

Melting points are uncorrected. The IR spectra were recorded on a Perkin Elmer model 257 spectrometer in potassium bromide and nujol mulls. The ^{1}H-NMR spectra were performed on a Varian EM 390 (90 MHz) and a varian XL-300 (300 MHz) in $CDCl_3$ using TMS as internal reference. ^{13}C-NMR spectra were recorded on a Varian XL-300 (75.43 MHz) and a Bruker WP 80SY (20.15 MHz). Chemical shifts were measured in ppm (δ) and coupling constants (J) in Hz. Mass spectra were determined with a Hitachi Perkin Elmer RMU-6M mass spectrometer at 75 eV. Analyses (C,H,N) are reported in Table 6.

Anhydrous $ZnCl_2$ was stored in a dessicator over P_2O_5 under vacuum prior to use. p-Toluene sulfonic acid was used as monohydrate. Hexane and toluene were dried over sodium metal. Commercial products were used without further purification and 3-methylindazole was obtained according to reference 18.

Reaction of indazole with benzal chloride a) Solid/liquid phase transfer catalysis: A mixture of indazole (1.1 g. 0.01 mol), KOH (0.6 g. 0.01 mol) and anhydrous K_2CO_3 (1.38 g. 0.01 mol) in toluene (200 ml) was refluxed with stirring for 10 min. Tetrabutylammonium bromide (0.1 g. 0.3 mmol.) and benzal chloride (1.2 g. 0.0075 mol) were added. Reaction was allowed to reflux for 135 hr. Hot solution was filtered and dried (Na_2SO_4). After concentration 2.5 g of residue was obtained. Column chromatography of the crude on silica gel using benzene/chloroform (1:1) as eluent yielded 0.25 g (15%) of 3. b) Liquid/liquid phase transfer catalysis: A mixture of indazole (2.89 g. 0.024 mol), tetrabutylammonium hydrogensulfate (0.41 g. 0.0012 mol.), 40% NaOH (16 ml) and benzal chloride (6.44 g. 0.04 mol) was refluxed with stirring for 17 hr. The cold mixture was extracted with CH_2Cl_2 (30 ml) and dried (Na_2SO_4). After concentration 7 g of residue was obtained. Treatment of the residue with ether/hexane gave 1.85 g (47%) of crude compound 3.

Reaction of benzotriazole with benzal chloride a) Solid/liquid phase transfer catalysis: The same procedure described for indazole was followed with tetrabutylammonium hydrogensulfate as catalyst. Chromatographic purification on silica gel using chloroform as solvent gave 5% of compound 4 together with traces of 2-n-butylbenzotriazole. b) Liquid/liquid phase transfer catalysis: The same procedure described for indazole was followed. Extraction with ether of the reaction mixture gave a crude which was treated with hexane/ether and some drops of ethyl acetate yielding 27% of pure compound 4.

Reaction of azoles with benzaldehyde and $ZnCl_2$ (Procedure A) A mixture of azole or its benzo-derivative, benzaldehyde and anhydrous $ZnCl_2$ (2:1:1/20 molar ratio) was heated in an oil bath at 120-130°C for 15-16 hr. After cooling the residue was purified as indicated in table 2.

Reaction of azoles with benzaldehyde dimethylacetal in hexane (Procedure B) A mixture of azole or its benzoderivative, benzaldehyde dimethylacetal and p-toluene sulfonic acid (2:1:1/10 molar ratio) in dry hexane (50 ml x 1 g. of azole) was refluxed in a Dean Stark apparatus for the time shown in table 2. Hot solution was filtered and products purified after concentration as shown in table 2.

Reaction of azoles with benzaldehyde dimethylacetal in toluene (Procedure C) Reaction conditions were identical to procedure B but using toluene as solvent. After the reaction was completed the solution was allowed to cool at room temperature and filtered. Products were purified after concentration as described in table 2.

ACKNOWLEDGEMENTS

We thank Mrs. M. D. Casado and M. Plaza for recording the ^{1}H and ^{13}C-NMR spectra. One of us (P. B.) is grateful indebted to the Comisión Asesora de Insvestigación en Ciencia y Tecnología of Spain for a grant.

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