Pergamon

Tetrahedron 57 (2001) 6147–6153

TETRAHEDRON

Unexpected formation of bis-pyrazolyl derivatives by solid support coupled with microwave irradiation

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Received 24 October 2000; accepted 29 May 2001

Abstract—Starting from 1,3-dimethyl-5-aminopyrazole **1** and *p*-substituted benzaldehydes **2** (R=H, CH_3, NO_2), four different compounds have been obtained: the Schiff bases **4**, a bis-pyrazolyl Schiff base **6a** (R=H), the expected bispyrazolo[3,4-*b*;4′,3′-*e*]pyridine **7b** (R=CH_3) and the carbinol derived from the Schiff base **8c** (R=NO_2). The products have been characterised by MS, NMR (^1H and ^{13}C) and X-ray crystallography (in the case of **6a**). A proposal for the relationships between the different compounds and a possible mechanism is presented.

1. Introduction

Organic synthesis in dry media, eventually under microwave (MW) irradiation is presently under extensive examination.[1–4] The relatively low cost of modern domestic microwave ovens makes them readily available to academic and industrial chemists, and the use of such non-conventional reaction conditions reveals several features such as: a short reaction time compared to conventional heating, reduction of the usual thermal degradation and better selectivity.[5–7] An attractive synthetic methodology is the possibility of performing reactions in solvent-free conditions or on solid inorganic supports. Indeed, in several cases, a solid-state organic reaction occurs more efficiently and more selectively than does its solution counterpart, since molecules in a crystal are arranged tightly and regularly.[8–12] Mineral oxides are very often poor conductors of heat but behave as very efficient MW absorbents.[11] This results in a very rapid and homogeneous heating and, consequently, reactions in solid supports under microwaves show strong MW effects.[12] Furthermore, solid-state reactions are very convenient from a practical viewpoint since the reagents and solid support are efficiently mixed in an appropriate solvent which is then evaporated. After microwave irradiation the products are simply extracted from the support by washing and filtration. The absence of solvent coupled with the high yields and short reaction times are very attractive for organic chemists.

Pyrazoles are a class of heterocyclic compounds having many derivatives with a wide range of interesting properties, such as drugs, pesticides, and new materials, amongst others.[13,14] Our interest in condensation reactions involving pyrazole derivatives led us to apply MW assisted methodology because several condensation reactions in solid support and microwave conditions have been successfully reported in the literature.[15–17] Knowing that aminopyrazoles condense with aromatic aldehydes to yield aldimines (Schiff-bases),[18,19] in the present work we describe the reactivity of 1,3-dimethyl-5-aminopyrazole **1** towards three 4-substituted benzaldehydes (**a** R=H, **b** R=CH_3, **c** R=NO_2) involving solid supports in dry conditions assisted by MW irradiation. Two are the products expected from this reaction. The most obvious are the Schiff-bases **4**, but another well documented reaction is the formation of bispyrazolo[3,4-*b*;4′,3′-*e*]pyridines **7** which implies an oxidation step.[20–29]

2. Results and discussion

2.1. Synthesis

With the intention to prepare 1,3-dimethyl-5-(benzylideneamine)-pyrazoles **4**, we applied initially a standard procedure[30] we had successfully used for Schiff bases derived from piperonal.[31] The method, described for benzylideneaniline, consists in mixing equimolar amounts of aniline and

Keywords: pyrazoles; imines; X-ray crystal structure; microwave irradiation; solid support.

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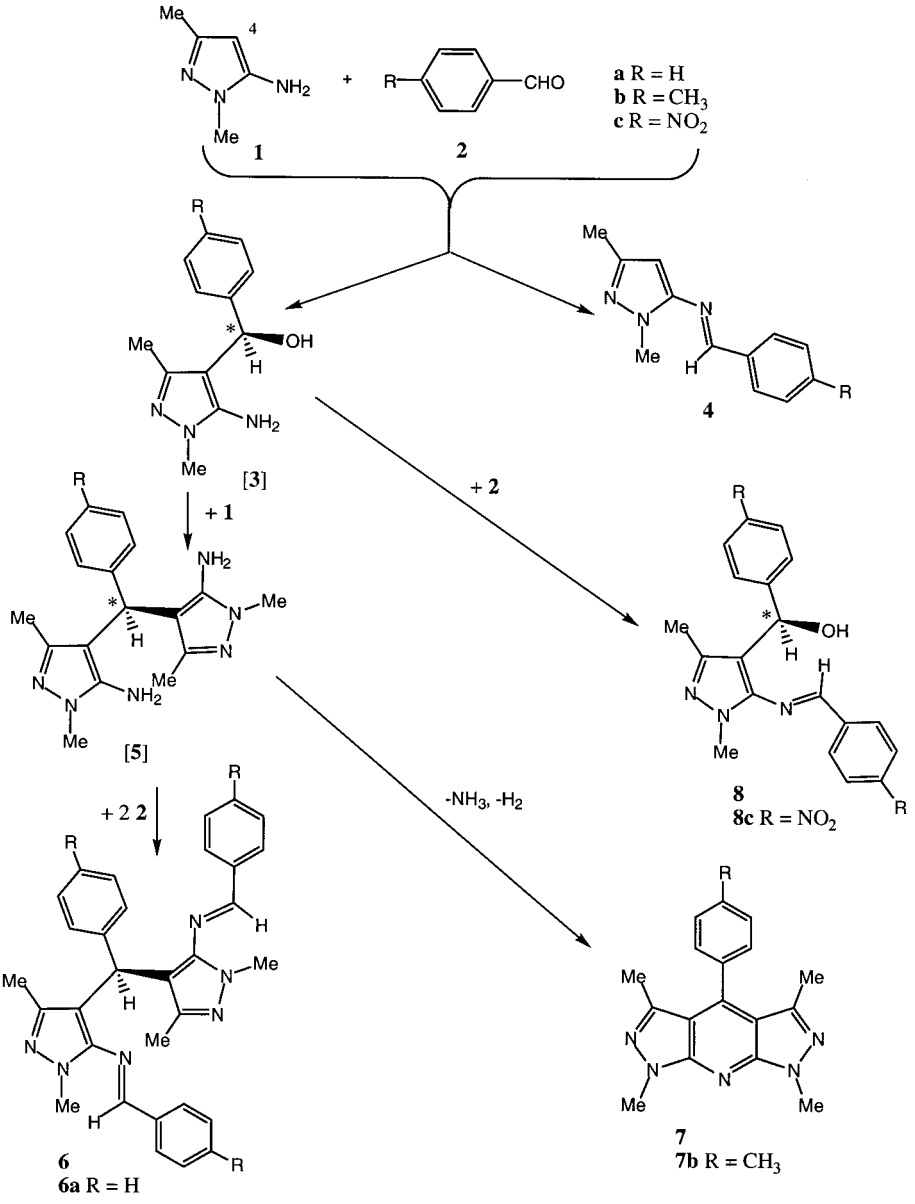
PII: S0040-4020(01)00604-4



Scheme 1.

benzaldehyde without solvent.[30] However, when we applied this procedure to **1** and **2a**, we obtained the desired product **4a**, but in very low yield (10%). Therefore, we decided, in order to improve the yield and make the synthetic procedure easier, to perform the reaction of benzaldehyde **2a** and 1,3-dimethyl-5-aminopyrazole **1** under different conditions.

The first method involved the reaction in solid state at room temperature with silica gel 60 as catalyst, reaction that under stirring conditions for 120 min, furnished compound **6a** in 12% yield. Further experiments were carried out in solid state conditions using silica or sand as dry support assisted by MW irradiation. The experimental procedure was particularly simple: 1,3-dimethyl-5-aminopyrazole **1** was mixed with benzaldehyde itself, **2a**, the mixture adsorbed on the solid support (silica or sand) and submitted to irradiation in a domestic MW oven.[32] The reactions were run in closed Petri plates and the resulting products were treated with methanol/dichloromethane (1:1), filtered and, after subsequent evaporation, purified. The reactions in the presence of silica or sand as solid support provided the same yield (85% of **6a**), but the use of sand is preferable because it makes possible a very easy isolation with a lower quantity of solvent and a high purity of the product. In the same way, we studied the reactivity of *p*-nitro and *p*-methylbenzaldehyde (*p*-toluylaldehyde) (**2b**, **2c**) that afforded compounds **7b** and **8c** instead of the Schiff bases **4b** and **4c** (Scheme 1). Consistently which what happens with **2a**, when reagents **1** and **2b**,**c** were refluxed in ethanol during 5 h, the Schiff bases **4b**,**c** were obtained in 30 and 10% yield, respectively. Furthermore, we have checked that heating **6a** in ethanol during 10 h resulted in the tricyclic structure **7a** in 67% yield. Compound **7a** has been obtained (mp 158–159°C, yield 35%)[18] by heating directly **1** and **2a** in a 2:1 molar ratio without solvent at 200–240°C.[21,28]

In MW assisted organic transformations, the effect of the MW is mainly due to dielectric polarisation, although

Table 1. Dry condensation reactions of **1** with *p*-substituted benzaldehydes under microwave irradiation

Compound	Reaction conditions	Time (min)	Yield (%)	Mp (°C)
6a	Silica/room temperature	120	12	182–184
6a	Silica/MW	15	85	182–184
6a	Sand/MW	15	85	182–184
7b	Sand/MW	15	62	190–193
8c	Sand/MW	15	99	184–186

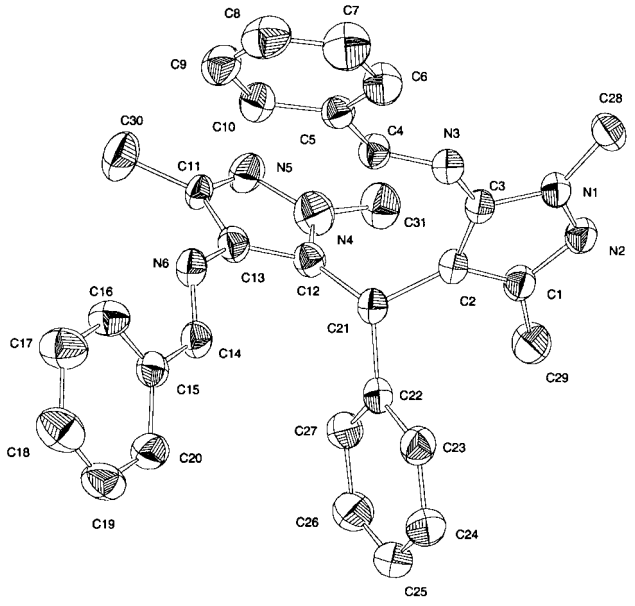


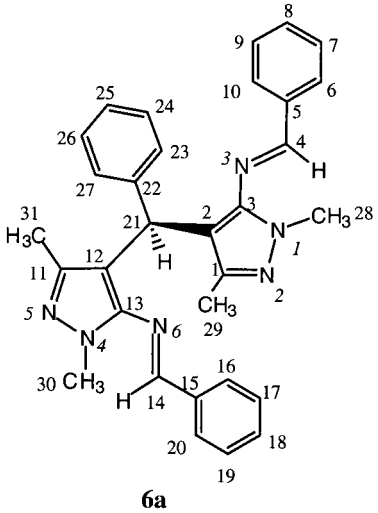
Figure 1. A ZORTEP plot of bis-[5-(benzylideneamine)-1,3-dimethyl-4-pyrazolyl]-phenylmethane **6a**, showing the atoms labelling scheme.

conduction losses can also be important, particularly at higher temperatures.[7] Furthermore, the reactions performed using MW heating in sand or silica, possibly imply the reactants adsorbed on the surface of the solid support, which absorb the microwaves whereas the support does not. Consequently, such supported reagents efficiently induce reactions under safe and simple conditions affording the desired products in high yields. In this manner, not only are the yields better, indicative of a specific MW effect, but also experiments are considerably easier to perform with a very simplified work-up. Table 1 shows the results obtained.

2.2. Identification of the resulting compounds (6a, 7b, 8c)

Although mass spectrometry provided the first indication that the compounds were not the expected Schiff bases **4**, NMR spectroscopy (^{1}H and ^{13}C) proved the simplest way to identify the compounds of Table 1 (for NMR spectroscopy of Schiff bases related to **4**, see Ref. 15 and for those of bispyrazolo[3,4-*b*;4′,3′-*e*]pyridines related to **7**, see Ref. 26). The unexpected structure of **6a** was established definitely by X-ray crystallography. Thus, a single crystal obtained by slow evaporation of an ethanol solution of **6a** was submitted to X-ray crystallography. Fig. 1 shows the ZORTEP view of **6a**.[33]

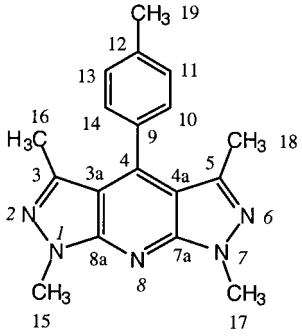
Bis-[5-(benzylideneamine)-1,3-dimethyl-4-pyrazolyl]-phenylmethane (**6a**).



6a

We have used the atom numbering of the crystal structure (Fig. 1) although it is not systematic. The NMR results are reported in Table 2.

1,3,5,7-Tetramethyl-bispyrazolo-[3,4-*b*;4′,3′-*e*]-4-(*p*-methylphenyl)pyridine (**7b**).



7b

Table 2. ^{1}H and ^{13}C NMR parameters of compound **6a**. Chemical shifts in ppm. Solvent DMSO-d_6

NMe (28,30)	CMe (29,31)	CHsp^3 (21)	CHsp^2 (4,14)	CHsp^2 (Ph)	CHsp^2 (Ph)		
3.58	1.66	5.36	7.96	7.12 (*o*)	7.57 (*o*)		
				7.25 (*m*)	7.41 (*m*)		
				7.14 (*p*)	7.47 (*p*)		
$C_{28,30}$ 34.72	$C_{29,31}$ 13.17	$C_{1,11}$ 145.08	$C_{2,12}$ 107.73	$C_{3,13}$ 142.50	C_{21} 37.31	C_{22} 145.56	$C_{23,27}$ 128.37
$C_{24,26}$ 128.53	C_{25} 126.34	$C_{4,14}$ 162.00	$C_{5,15}$ 135.39	$C_{6,10,16,20}$ 128.70	$C_{7,9,17,19}$ 128.30	$C_{8,18}$ 131.86	

The spectra shows the characteristic patterns of two identical pyrazole Schiff bases,[18] as well as the presence of a CHsp^3 group at position 21.

Table 3. ^{1}H and ^{13}C NMR parameters of compound **7b**. Chemical shifts in ppm. Solvent DMSO-d_6

NMe (15,17)	CMe (16,18)	$CHsp^2$ (Ph)	CMe (19)	$C_{3,5}$	$C_{3a,4a}$	$C_{7a,8a}$	
3.90	1.86	7.29 (10,14) 7.32 (11,13)	2.39	140.94[a]	110.85	151.22	
C_4 140.90[a]	C_9 131.07	$C_{10,14}$ 128.75	$C_{11,13}$ 128.42	C_{12} 138.20	$C_{15,17}$ 33.12	$C_{16,18}$ 14.98	C_{19} 20.89

[a] The ^{1}H and ^{13}C NMR spectra of **7b** are characterised by their simplicity and also by the quaternary carbons C_{3a} and C_{4a} near 110 ppm.[21,26] Otherwise, the spectra are very similar to those reported in Ref. 21 (NMe) and Ref. 26 (NPh).

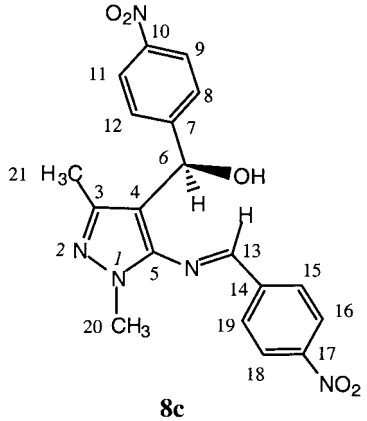
Table 4. ^{1}H and ^{13}C NMR parameters of compound **8c**. Chemical shifts in ppm. Solvent DMSO-d_6

NMe (20)	Cme (21)	$CHsp^3$ (6)	$CHsp^2$ (13)	$CHsp^2$ (Ph-8,9)	$CHsp^2$ (Ph-15,16)		
3.74	2.07	5.94 6.36 (OH) $J_{H6/OH}$=4.0 Hz	8.80	7.55 (8,12) 8.07 (9,11)	8.03 (15,19) 8.28 (16,18)		
C_3 145.64 C_{13} 160.64	C_4 110.48 C_{14} 145.75	C_5 140.96 $C_{15,19}$ 129.48	C_6 64.58 $C_{16,18}$ 124.01	C_7 148.99 C_{17} 148.99	$C_{8,12}$ 126.95 C_{20} 34.96	$C_{9,11}$ 122.90 C_{21} 12.61	C_{10} 146.10

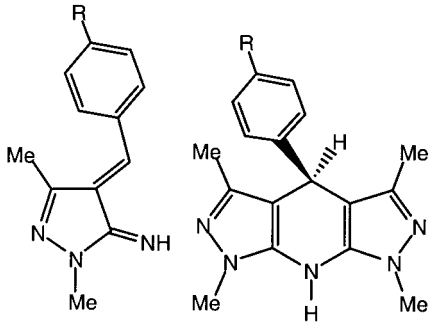
The NMR data corresponding to **7b** are reported in Table 3.

5-(*p*-Nitrobenzylideneamine)-1,3-dimethyl-4-pyrazolyl-(*p*-nitrophenyl)-6-hydroxymethane (**8c**).

Compound **8c** lacks the symmetry of the previous compounds (**6a** C_s, **7b** C_{2v}). Consequently, it has been a little more complicated to assign the NMR signals and several two-dimensional techniques have been necessary to complete the assignments of Table 4.

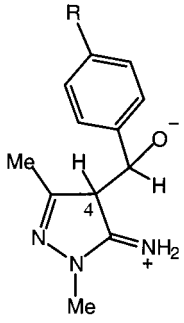


8c

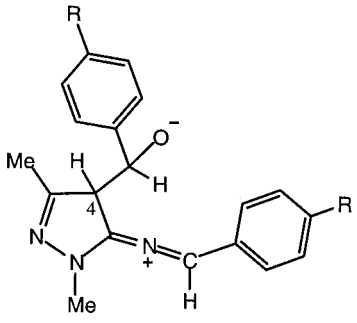


[**8**]

[**9**]



[**10**]



[**11**]

3. Conclusion

Scheme 1 is not intended to be a reaction mechanism but only a table of connectivities. We have selected bimolecular reactions with the only exception of the transformation of the intermediate [**5**] into **6**, where two successive condensations with **2** are necessary. Therefore, the arrows in Scheme 1 only connect direct transformations. We have used brackets for those compounds that have not been isolated, like the carbinol [**3**] and the intermediate [**5**]. Pyrazolylalkanols, related to [**3**] but without the 5-amino group, have been described recently by Soai.[34] The intermediate [**5**] has been proposed by Brack.[20] Some authors, have proposed as intermediates the dehydrated derivative [**8**] and the reduced precursor [**9**].[24]

Our discussion is based on the argument that if the lone pair on the amino group in **1** is able to activate the position 4 (formally an enamine behaviour), the lone pair in the imine **4** is not. The corresponding plausible intermediates, [**10**] and [**11**], illustrate these differences.

We have summarised the experimental observations in Table 5. Only the first one is a simple process, all others involve several intermediates. For instance, it is known that Schiff bases **4** (in general, not only 1,3-dimethyl derivatives, but those derived from *N*-phenyl pyrazoles) can be transformed, on treatment with 5-aminopyrazoles **1**, into the tricyclic structures **7**,[21,24] to account for this reaction an isomerization **4**→**6** has to be assumed (**4**→**1**+**2**→[**3**]→

Table 5. Experimental results related to Scheme 1

General reaction	Specific reaction
1+**2**→**4**	**1**+**2a**→**4a**, **1**+**2b**→**4b**, **1**+**2c**→**4c**
1+**2**→**6**	**1**+**2a**→**6a**
1+**2**→**7**	**1**+**2a**→**7a** (Lit. Refs. 21,28), **1**+**2b**→**7b**
1+**2**→**8**	**1**+**2c**→**8c**
6→**7**	**6a**→**7a**
1+**4**→**7**	(Lit. Refs. 21,24)

[**5**]→**6**). If **4** cannot be the direct precursor of **6**, **7** and **8**, then the reactions starting from **1** and **2**, must go through intermediates like [**3**] and [**5**]. Compound **6a**, isolated as intermediate, under reflux in ethanol furnished also **7a**. This transformation **6**→**7** probably involves the hydrolysis of, at least, one imine, i.e. **6**→[5]→**7**. Finally, the reaction **1**+**4**→**7**, should proceed through **1** and **2**.

A last point that has to be discussed is the effect of the substituent R in benzadehydes **2** on the course of the reactions of Scheme 1. Especially, the fact that when **1** reacts with **2**, besides the imines **4**, three different compounds are obtained depending on the nature of R: R=H **6a**, R=CH_3 **7b** and R=NO_2 **8c**. A possible explanation using the pivotal intermediate [**3**] is that when R=NO_2, its electron withdrawing effect make the carbinol less reactive and only the formation of the imine **8c** occurs. In the two other cases, intermediate [**5**] is formed. When R=CH_3, the methyl group would make [**5b**] more easily oxidized into **7b** than [**5a**] into **7a** (although **6a** can be transformed into **7a**). Finally, when R=H, **6a** is isolated. The role of the silica could be related to its acid catalytic properties, which could prevent the formation of **4**. Another fact that must be considered is that under MW irradiation, the temperature depends on the dielectric constants (relative permittivities ε_r) of the reagents and the values of ε_r for the three benzaldehydes should be different.

In conclusion, this work has shown that solid supported MW irradiation not only affords better yields and cleaner reactions than conventional heating,[35] but even leads to different compounds showing a change not only of reactivity but also of selectivity. This is true, even if probably in all cases mixtures of **4**, **6** (**6a** 85%), **7** (**7b** 91%) and **8** (**8c** 99%) are formed, because the major products are very abundant.

4. Experimental

4.1. General procedures

The microwave assisted organic reactions were performed in a Consul Pratice-Brastemp S.A./Model MU31AO, a domestic oven. Melting points, uncorrected, were taken on Mel-Temp II capillary apparatus. Infrared spectra were obtained on a Perkin–Elmer FT 1640 spectrometer in KBr pellets. Mass spectra were recorded using a MSD Hewlett Packard Series 1100 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity-500 spectrometer operating at 499.88 and 125.71 MHz, respectively, using CD_3OD or DMSO-d_6 as solvents and internal TMS as reference.

Table 6. Crystal data and structure refinement for **6a**

Empirical formula	$C_{31}H_{30}N_6$
Formula weight	486.61
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, *P*-1 (no. 2)
Unit cell dimensions	a=9.727(2) Å α=69.12(3)° b=11.719(2) Å β=76.61(3)° c=13.857(2) Å γ=70.35(3)°
Volume	1375.0(5) Å^3
Z, calculated density	2, 1.175 Mg m^{-3}
Absorption coefficient	0.072 mm^{-1}
F(000)	516
Crystal size	0.56×0.50×0.10 mm
θ range for data collection	2.25–25.00°
Index ranges	$0 \leqq h < 11$, $-12 \leqq k \leqq 13$, $-15 \leqq 1 \leqq 16$
Reflections collected/unique	5101/4801 (R(int)=0.0197)
Completeness to 2θ=25.00	99.0%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4801/0/335
Goodness-of-fit on F^2	1.084
Final R indices ($I > 2\sigma(I)$)	$R1$=0.0629, $wR2$=0.1657
Extinction coefficient	0.045(5)
Largest diff. peak and hole	0.360 and −0.324e Å^{-3}

Monodimensional experiments were performed using standard conditions. 2D Inverse proton detected heteronuclear shift correlation spectra, HMQC and HMBC, were obtained with the following conditions: data were collected in a 4096×128 matrix with a spectral width of 8000 Hz in the proton domain and 25,000 Hz in the carbon domain, and processed in a 4096×512 matrix. The HMQC experiment was optimised for one bond heteronuclear coupling constant of 145 Hz and the HMBC experiment for long range coupling constants of 8 Hz.

4.2. X-ray crystallography (see Table 6)

A yellow crystal was mounted on a glass fiber and used to collect data on a Nonius CAD-4 diffractometer[36] with graphite-monochromated MoKα radiation and ω–2θ scans. The structure was solved by means of direct methods using SHELXS97[37] and refined by full-matrix least-squares techniques using F2 with SHELXL97.[37]

4.3. 5-Benzylideneamine-1,3-dimethyl-aminopyrazoles

Standard procedure: Benzaldehyde **2** (~0.5 mL, 4.5 mmol) and 1,3-dimethyl-5-aminopyrazol **1** (0.5 g, 4.5 mmol) were mixed in the presence of some drops of concentrated HCl in 30 mL of benzene as solvent. The mixture was refluxed during 5 h and the water formed was collected in a Dean–Stark trap. After cooling, the product was filtered and recrystallised from ethanol.

4.3.1. 5-Benzylideneamine-1,3-dimethyl-aminopyrazol (4a). Yellow solid, 10% yield, mp 172–174°C. ^{1}H NMR δ 1.80 (3H, s), 3.70 (3H, s), 7.2 (1H, m), 7.3 (1H, m), 7.6 (1H, m), and 7.8 (1H, s).

4.3.2. 5-(*p*-Methyl-benzilideneamine)-1,3-dimethylaminopyrazol (4b). White solid, 10% yield, mp 184–186°C. ^{1}H NMR δ 2.18 (3H, s), 2.63 (3H, s), 3.96 (3H, s), 7.28–7.76 (1H, m), and 8.07 (1H, s).

4.3.3. 5-(*p*-Nitro-benzilideneamine)-1,3-dimethylamino-pyrazol (4c). Yellow solid, 30% yield, mp 185–188°C. ^{1}H NMR δ 1.75 (3H, s), 1.97 (3H, s), 5.96 (1H, s), 7.38 (1H, d, J=8.68 Hz), 8.19 (1H, d, J=8.68 Hz), and 8.40 (1H, s).

4.3.4. Bis-[5-(benzylideneamine)-1,3-dimethyl-4-pyrazolyl]-phenyl-methane (6a). *Method A: Using silica at ambient temperature.* The mixture benzaldehyde (0.5 mL, 4.5 mmol), 1,3-dimethyl-5-aminopyrazole (0.5 g, 4.5 mmol) and silica gel 60 (2 g) were stirred at room temperature for 120 min. The product was extracted with methanol/dichloromethane 1:1 (50 mL) after the excess of solvent was evaporated and the product filtered. The recrystallisation from hot ethanol gave 90 mg (12%) as a yellow solid with mp 182–184°C; ν_{max} 3059 (C–H_{arom}), 2927 (CH_3), 1617 (C=N), 1515 (C=C_{arom}); MS, *m/z* (%): 486 (M^+, 33).

Method B: Using silica and microwave irradiation. Benzaldehyde (0.5 mL, 4.5 mmol), and 1,3-dimethyl-5-aminopyrazole (0.5 g, 4.5 mmol) in dried silica gel (2 g) were submitted to microwave irradiation for 15 min. The product was extracted with methanol/dichloromethane 1:1 (50 mL) and after evaporation the product was filtered. The recrystallisation from hot ethanol gave 625 mg (85% yield).

Method C: Using sand microwave irradiation. Benzaldehyde (0.5 mL, 4.5 mmol) and 1,3-dimethyl-5-amino-pyrazole (0.5 g, 4.5 mmol) in dry sand (5 g, Angra dos Reis, RJ, Brazil) were submitted to microwave irradiation for 15 min. The product was extracted (using 30 mL of solvent mixture), isolated and purified in the same way above to afford 625 mg (85%) of **6a**.

4.3.5. 1,3,5,7-Tetramethyl-bispyrazolo-[3,4-*b*;4′,3′-*e*]-4-(*p*-methylphenyl)pyridine (7b). *p*-Tolualdehyde (0.53 mL, 4.5 mmol), 1,3-dimethyl-5-aminopirazole (0.5 g, 4.5 mmol) were added to dry sand (5 g), and submitted to microwave irradiation for 15 min. The solid obtained was treated in the same way to afford 425 mg (91%) as a yellow solid with mp 184–186°C. ν_{max} 3040 (C–H_{arom}), 2923–2856 (CH_3), 1605 (C=N), 1512 (C=C_{arom}); MS, *m/z* (%): 307 (M^+, 57).

4.3.6. 5-(*p*-Nitrobenzylideneamine)-1,3-dimethyl-4-pyrazolyl-(*p*-nitrophenyl)-6-hydroxymethane (8c). A mixture of *p*-nitro-benzaldehyde (0.7 g, 5.5 mmol), 1,3-dimethyl-5-aminopirazole (0.5 g, 4.5 mmol) and dry sand (5 g) was submitted to microwave irradiation for 15 min. The product was extracted with methanol/dichloromethane 1:1 (25 mL), filtered and recrystallised from hot ethanol gave 880 mg (99%) of a yellow solid with mp 190–193°C. ν_{max} 3056 (C–H_{arom}), 2931–2838 (CH_3), 1600 (C=N), 1519 (C–NO_2), 1511 (C=C_{arom}); MS, *m/z* (%): 395 (M^+, 100).

Acknowledgements

The authors wish to thank CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) and CAPES (Coordenação de Aperfeiçoamento de Pessoal de Ensino de Nível Superior) for financial support and fellowships, and Professor Maria da Graça Nascimento, from Departamento de Química da Universidade Federal de Santa Catarina, for personal assistance with mass spectra recording.

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