Synthesis of some 1-aryl-3,5-disubstituted-pyrazoles by N-arylation of 3,5-disubstituted-pyrazoles with 4-fluoro and 2-fluoronitrobenzene under microwave irradiation and classical heating

Ibrahim Bouabdallah,[a,*] Rachid Touzani,[a,b] Ismail Zidane,[a] Abdelkrim Ramdani,[a] and Smaail Radi[a]

[a] *Laboratoire de Chimie Organique Physique, Département de Chimie, Faculté des Sciences, Université Mohamed I [er], BP 524, Oujda, Maroc*

[b] *Faculté Pluridisciplinaire de Nador, Université Mohamed I [er] B.P. 300, 62700 Selouane, Nador, Maroc*

E-mail: bouabib2002@yahoo.fr

Abstract

N-Arylation of 3,5-disubstituted-pyrazoles with 4-fluoro and 2-fluoronitrobenzene under microwave irradiation conditions with and without solvent compared to the classical heating afforded, *N*-arylation regioisomers in yields depending on the method used. The structures of compounds : 1-aryl-3,5-disubstituted-pyrazoles were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy, elemental analysis and mass spectrometry.

Keywords: Pyrazole, N-arylation, microwave irradiation, classical heating

Introduction

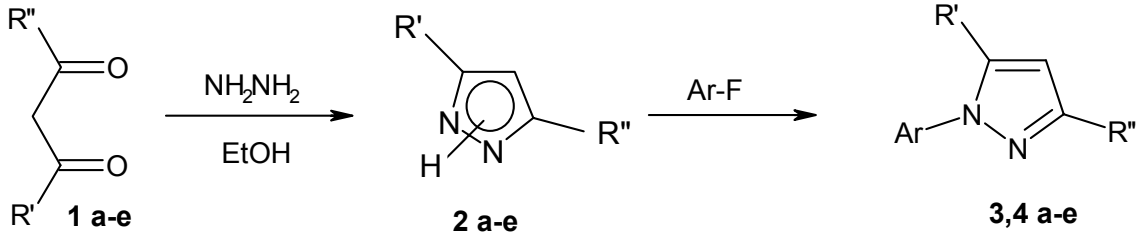
For many years, *N*-arylpyrazoles have been synthesised by condensation of 1,3-diketones with arylhydrazines. Indeed, unsymmetrical 1,3-diketones generally yield a mixture of two regioisomers in a ratio which depends on the nature of 1,3-diketones.[1] Moreover and according to some authors, this condensation leads to the formation of the undesired isomer as a major component.[2-4]

Thereafter, direct substitution of *N*-nonsubstituted pyrazoles under previous reported conditions[5-8] such as K_2CO_3/DMF, K_2CO_3/DMSO, KOH/Bu_4NBr, KOtBu and NaH/THF provide another powerful method for synthesis of *N*-arylpyrazoles. However, the reaction generally gives also a mixture of two regioisomers since pyrazole is an ambident nucleophile. Recently, Wang *et al* reported that direct *N*-arylation of some 3-aryl-5-alkylpyrazoles[9] with 4-fluoronitrobenzene, using potassium *tert*-butoxide as a base in DMSO at 70°C for 1 hour gives regioselectively

compounds in excellent yields, whereas the same reaction with 3,5-dialkylpyrazoles[10] gives a mixture of two regioisomers. In accordance with our recent studies on pyrazoles,[11-17] we are particularly interested now in a practical synthesis of some new *N*-aryl pyrazoles. Thus, in this communication we describe our findings that direct *N*-arylation of 3,5-disubstituted-pyrazoles with 4-fluoronitrobenzene and 2-fluoronitrobenzene in DMSO under microwave irradiation or classical heating conditions, affords the **α** regioisomers in excellent yields. But in solvent-free under microwave irradiation conditions, the reaction gives a mixture of isomers (Table 1).

Results and Discussion

Compounds **3a, 3b, 3c, 4a** and **4e** are already prepared by condensation of arylhydrazine with 1,3-diketones.[18,19] The synthesis of 1-(4-nitro or 2-nitrophenyl)-3,5-disubstituted-pyrazoles **3a-e** and **4a-e** (**Scheme 1**) was first performed using the literature method[9] by the direct *N*-arylation of pyrazoles **2a-e** with 4-fluoronitrobenzene and 2-fluoronitrobenzene using potassium tert-butoxide as a base in DMSO at 70°C for 45 to 120 min. All pyrazole derivatives **3a-e** and **4a-e** were obtained with good yields from 70 to 94 %. The IR spectra of compounds **3a-e** and **4a-e** showed that the absorption peak corresponding to the stretching vibration of the N-H group disappeared, showing that the amino groups in 3,5-disubstituted-pyrazoles **2a-e** had participated completely in the reaction. IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy and mass spectrometry data are consistent with the formulation indicated in Scheme 1.



a : R' = CH_3 ; R" = CH_3
b : R' = CH_3 ; R" = C_6H_5
c : R' = C_6H_5 ; R" = C_6H_5
d : R' = CH_3 ; R" = CO_2CH_3
e : R' = CH_3 ; R" = $CO_2CH_2CH_3$
3 : Ar = p-$NO_2C_6H_4$; **4** : Ar = o-$NO_2C_6H_4$

Scheme 1. *N*-arylation of 3,5-disubstituted pyrazoles with 4- and 2-fluoronitrobenzene.

Then a similar reaction was repeated, to be performed without or with some drops of solvent, using microwave irradiation, which has recently been used as an efficient technique to increase reaction rates. Thus, we attempted to take advantage of this technique to decrease the reaction time and to improve the regioselectivity of the previous *N*-arylation reaction. The mixture of 3,5-disubstituted pyrazoles **2a-e**, potassium tert-butoxide and 4-fluoronitrobenzene or

2-fluoronitrobenzene was introduced into a Pyrex tube without or with some drops of solvent and was then placed under microwave irradiation. All N-arylation reactions were optimised to obtain the best yield and complete consumption of the starting materials. Then the residues were washed with water and were finally purified by column chromatography wherever necessary, to afford pure products **3a-e** and **4a-e** in excellent yields. The regioselectivity, the yields and the time of reaction are given in Table 1.

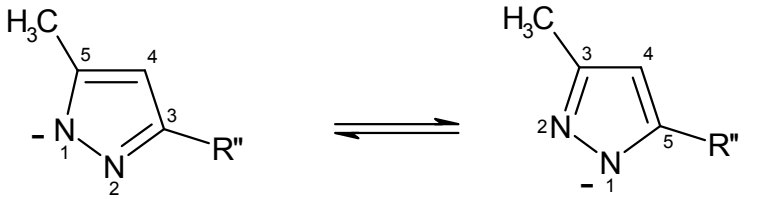
Table 1. Comparison between Classical Heating and Microwave Irradiation with and without solvent of synthesis of 1-(4-nitro and 2-nitrophenyl)-3,5-disubstituted-pyrazoles

Entry	R'	R''	m. p. (°C)	Classical heating			Microwave irradiation without solvent			Microwave irradiation with solvent		
				Time (min)	Yield (%)[f]	Ratio α : β[a]	Time (min)	Yield (%)[f]	Ratio α : β[a]	Time (min)	Yield (%)[f]	Ratio α : β[a]
3a	CH_3	CH_3	100-101	45	83	-	5 [b]	98	-	5 [b]	96	-
3b	CH_3	Ph	124-125	45	86	98 : 2	5 [d]	96	81 : 19	5 [b]	94	97 : 3
3c	Ph	Ph	122-124	120	80	-	5 [e]	0	0	10 [c]	82	-
3d	CH_3	CO_2Me	120-121	60	76	96 : 4	10 [e]	80	57 : 43	5 [b]	88	97 : 3
3e	CH_3	CO_2Et	102-103	50	92	97 : 3	5 [b]	72	78 : 22	5 [b]	98	88 : 12
4a	CH_3	CH_3	98 – 99	60	70	-	5 [b]	88	-	5 [b]	90	-
4b	CH_3	Ph	Viscous	45	90	98 : 2	5 [b]	93	97 : 3	5 [b]	94	100 : 0
4c	Ph	Ph	112-113	120	94	-	10 [d]	98	-	5 [b]	92	-
4d	CH_3	CO_2Me	128-129	45	70	94 : 6	9 [b]	72	71 : 29	5 [b]	87	100 : 0
4e	CH_3	CO_2Et	88-89	60	85	97 : 3	8 [b]	69	35 : 65	5 [b]	90	100 : 0

[a] Determined by ^{1}H NMR of crude products
[b] 30 W; [c] 60W; [d] 90 W; [e] 120 W; [f] Combined yield of **α** and **β**

Results (Table 1) show that for symmetrical products **3 (a, c)** and **4 (a, c)** the microwave irradiation appeared to be rapid and economical. The reaction proceeded smoothly within 5-10 min whereas under classical heating conditions, 45-120 min were required. However, with 3,5-diphenylpyrazole and 4-fluoronitrobenzene we did not observe the *N*-arylation reaction under solvent-free conditions (Entry **3c**). So, some drops of DMSO were necessary and sufficient to change the reactivity.

For unsymmetrical products we notice different results in terms of selectivity between microwave irradiation without solvent and classical heating in DMSO. It can be seen from the data that the selectivity was not preserved and the adduct ratio changed under microwave irradiation. The *N*-arylation reaction is regioselective under classical heating**,** but under microwave irradiation without solvent, the regioselectivity is much affected. For the pyrazole anion, there is equilibrium between two equivalent resonance forms (Scheme 2).



α : 3, 4 (b, d, e) β : 3, 4 (b, d, e)

Scheme 2

Under classical heating conditions the observed regioselectivity of this process may be attributable to the steric hindrance of R'' group, that disfavours the formation of the **β** product. But under microwave irradiation without solvent, *N*-arylation reaction was dramatically controlled by **β** pyrazol anion. So the effect of microwave irradiation is not exclusively a reaction acceleration, but its intervention in the orientation of anion reactivity via **α** and **β** tautomer forms. Both microwaves effect and steric hindrance contributed to *N*-arylation reaction. These results showed the utility of microwave irradiation in organic synthesis and its advantages in comparison with classical heating, specially when we need **β** tautomer forms. In the case of microwave irradiation with solvent, we notice a high selectivity for entries **3** and a total selectivity for entries **4** due to steric effects of 2-nitrobenzene compared to 4-nitrobenzene. These results showed the utility of microwave irradiation with solvent in organic synthesis specially when we need only **α** tautomer forms.

In conclusion, we have developed an efficient and regioselective access to pyrazoles compounds which have the nitro group, using three methods: microwave irradiation with or without solvent and a classical heating. The present method is an important addition to microwave-assisted synthetic methodologies. Further developments on this subject are currently in progress. Particularly the examination of these ligands in catalytic and biologic activities.

Experimental Section

General Procedures. Melting points were determined in open glass capillaries using a Buchi 510 melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 1310 infrared spectrophotometer using the KBr disc technique. NMR spectra (^{1}H, ^{13}C) were recorded on a Bruker 300 NMR spectrometer (operating at 300 MHz for ^{1}H, 75 MHz for ^{13}C). Chemical schifts are listed in ppm and are reported relative to tetramethylsilane (TMS) as an internal standard. Splitting patterns were designed as follows: s: singlet; d: doublet; t: triplet; m: multiplet. Mass spectra were obtained an a VG7070E spectrometer. The compounds were analysed for C, H and N. The results were within 0.4% of the calculated theoretic values. The ratio of the regioisomers has been calculated through ^{1}H NMR experiments, especially from the integration of the C5-C<u>H</u>3 (**α**) and C3-C<u>H</u>3 (**β**) proton.

General methods of Synthesis of 1-(4-nitro or 2-nitrophenyl)-3,5-disubstituted pyrazoles 3, 4 (a-e)

Classical heating method. To a solution of 3,5-disubstituted pyrazoles **2 (a-e)** (2.5 mmol) in DMSO (1 mL) was added solid potassium tert-butoxide (2.75 mmol) followed by addition of 4-fluoronitrobenzene or 2-fluoronitrobenzene (2.625 mmol) in DMSO (1 mL) through a syringe. The resulting mixture was heated to 70°C and kept at this temperature for 45 min. Then the mixture was cooled to room temperature and quenched with water (25 mL). The precipitate was collected by filtration and oven-died in vacuo. The residue was passed through a short silica column (CH_2Cl_2) to give pyrazole derivatives **3, 4 (a-e)** in good yield.

Microwave irradiation without solvent method. The mixture of 3,5-disubstituted pyrazoles **2 (a-e)** (1 mmol), potassium tert-butoxide (1.1 mmol) and 4- or 2-fluoronitrobenzene (1.05 mmol) was introduced into a Pyrex tube which was then placed under microwave irradiation. The mixture was then quenched with water. The residue was passed through a short silica column (CH_2Cl_2).

Microwave irradiation with solvent method. The mixture of 3,5-disubstituted pyrazoles **2 (a-e)** (1 mmol), potassium tert-butoxide (1.1 mmol), 4- or 2-fluoronitrobenzene (1.05 mmol) and some drops of DMSO was introduced into a Pyrex tube which was then placed under microwave irradiation. The mixture was then quenched with water. The precipitate was collected by filtration and oven-died in vacuo. The residue was passed through a short silica column (CH_2Cl_2).

1-(4-nitrophenyl)-3-phenyl-5-methylpyrazole (3b). Mp : 124-125°C (CH_2Cl_2 / EtOH : 60/40); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.33 (d, 2H, H3', J = 9.0 Hz); 8.83 (d, 2H, o-H, J = 8.1 Hz); 7.76 (d, 2H, H2', J = 9.3 Hz); 7.40 (m, 3H, m-H, p-H); 6.58 (s, 1H; C4-H); 2.49 (s, 3H, C5-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.29 (C3); 146.21 (C4'); 145.39 (C1'); 140.97 (C5); 132.88 (C1''); 129.10 (C3''); 129.01 (C4''); 126.19 (C2''); 125.15 (C3'); 124.20 (C2'); 106.99 (C4); 13.77 (C5-CH_3). Anal. Calcd for $C_{16}H_{13}N_3O_2$: C 68.81, H 4.65, N 15.05. Found: C 68.86, H 4.68, N 15.01; m/z: 279 (M^+); IR (cm^{-1}, KBr Disk): 3080 ($\nu_{C-H,\ arom.}$); 2905 ($\nu_{C-H,\ CH3}$); 1602 ($\nu_{C=N}$); 1570 ($\nu_{C=C}$); 1550, 1500 ($\nu_{a\ NO2}$); 1468, 1452, 1400, 1361, 1328 ($\nu_{s\ NO2}$).

Methyl-1-(4-nitrophenyl)-5-methylpyrazol-3-carboxylate (3d). Mp : 120-121°C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.37 (d, 2H, H3', J = 11.2 Hz); 7.73 (d, 2H, H2', J = 11.2 Hz); 6.78 (s, 1H; C4-H); 3.93 (s, 3H, O-CH_3); 2.43 (s, 3H, C5-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.79 (C5); 125.99 (C3'); 125.35 (C2'); 111.04 (C4); 52.49 (O-CH_3); 13.22 (C5-CH_3). Anal. Calcd for $C_{12}H_{11}N_3O_4$: C 55.17, H 4.21, N 16.09. Found: C 55.16, H 4.25, N 15.99; m/z: 261 (M^+); IR (cm^{-1}, KBr Disk): 3090 ($\nu_{C-H,\ arom.}$); 2930 ($\nu_{C-H,\ CH3}$); 1712 ($\nu_{C=O}$); 1609 ($\nu_{C=N}$); 1583, 1523 ($\nu_{a\ NO2}$); 1493, 1440, 1420, 1378, 1361 ($\nu_{s\ NO2}$); 1242 (ν_{C-O}).

Ethyl-1-(4-nitrophenyl)-5-methylpyrazol-3-carboxylate (3e). Mp : 102-103°C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.35 (d, 2H, H3', J = 9 Hz); 7.70 (d, 2H, H2', J = 9 Hz); 6.77 (s, 1H, C4-H); 4.40 (q, 2H, CH_2-CH_3, J = 7.2 Hz); 2.43 (s, 3H, C5-CH_3); 1.36 (t, 3H, CH_2-CH_3, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.67 (C3); 145.99 (C1'); 144.49 (C4'); 141.27 (C5); 125.71 (C3'); 124.94 (C2'); 111.08 (C4); 61.29 (CH_2-CH_3); 14.48 (CH_2-CH_3); 13.25 (C5-CH_3).

Anal. Calcd for $C_{13}H_{13}N_3O_4$: C 56.72, H 4.72, N 15.27. Found: C 56.83, H 4.78, N 15.21; m/z: 275 (M^+); IR (cm^{-1}, KBr Disk): 3103, 3082, 3050 ($\nu_{C\text{-}H,\ arom.}$); 2958, 2905, 2878 ($\nu_{C\text{-}H,\ CH3}$); 1725 ($\nu_{C=O}$); 1620, 1609 ($\nu_{C=N}$); 1575, 1528 ($\nu_{a\ NO2}$); 1513, 1453, 1432, 1377 ($\nu_{s\ NO2}$); 1238 ($\nu_{C\text{-}O}$).

1-(2-nitrophenyl)-3,5-diphenylpyrazole (4c). Mp : 112-113°C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.85 (d, 1H, H3', J = 8.4 Hz); 7.85 (d, 2H, H2'', J = 6.9 Hz); 7.55 (t, 1H, H5', J = 8.4 Hz); 7.48 (t, 1H, H4', J = 8.4 Hz); 7.39 (d, 2H, H2''', J = 6.3 Hz); 7.37 (d, 1H, H6', J = 6.3 Hz); 7.27–7.31 (m, 6H, H3'', H4'', H3''', H4''); 6.84 (s, 1H; C4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.68 (C3); 146.33 (C2'); 145.99 (C5'); 134.00 (C5); 133.49 (C1'); 132.88 (C1''); 129.89 (C1'''); 129.68 (C4''); 129.40 (C4'); 129.16 (C3'); 129.09 (C3'''); 129.04 (C3''); 128.96 (C2'''); 128.70 (C4'''); 126.31 (C2''); 125.51 (C6'); 105.42 (C4). Anal. Calcd for $C_{21}H_{15}N_3O_2$: C 73.90, H 4.39, N 12.31. Found: C 73.86, H 4.42, N 12.35; m/z: 341 (M^+); IR (cm^{-1}, KBr Disk): 3062 ($\nu_{C\text{-}H,\ arom.}$); 1780, 1618 ($\nu_{C=N}$); 1598, 1546 ($\nu_{C=C}$); 1522 ($\nu_{a\ NO2}$); 1494, 1445, 1378 ($\nu_{s\ NO2}$).

Methyl-1-(2-nitrophenyl)-5-methylpyrazol-3-carboxylate (4d). Mp : 128-129°C (CH_2Cl_2) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.09 (d, 2H, H3', J = 6.6 Hz); 7.73 (t, 1H, H5', J = 6.3 Hz); 7.67 (t, 1H, H4', J = 6.3 Hz); 7.50 (d, 1H, H6', J = 6.3 Hz); 6.74 (s; 1H; C4-H); 3.78 (s, 3H, O-CH_3); 2.19 (s, 3H, C5-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.92 (C=O); 146.47 (C3); 145.14 (C2'); 142.83 (C5'); 134.18 (C1'); 132.87 (C5); 131.09 (C4'); 130.53 (C3'); 125.93 (C6'); 109.18 (C4); 52.50 (O-CH_3); 11.83 (C5-CH_3). Anal. Calcd for $C_{12}H_{11}N_3O_4$: C 55.17, H 4.21, N 16.09. Found: C 55.13, H 4.28, N 16.01; m/z: 261 (M^+); IR (cm^{-1}, KBr Disk): 3085 ($\nu_{C\text{-}H,\ arom.}$); 2980 ($\nu_{C\text{-}H,\ CH3}$); 1745 ($\nu_{C=O}$); 1613 ($\nu_{C=N}$); 1533 ($\nu_{a\ NO2}$); 1474, 1442, 1397, 1376 ($\nu_{s\ NO2}$); 1273 ($\nu_{C\text{-}O}$).

Ethyl-1-(2-nitrophenyl)-5-methylpyrazol-3-carboxylate (4e).[19] Mp : 88-89°C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.06 (d, 1H, H3', J = 8.1 Hz); 7.73 (t, 1H, H5', J = 7.8 Hz); 7.64 (t, 1H, H4', J = 7.8 Hz); 7.48 (d, 1H, H6', J = 7.8 Hz); 6.72 (s, 1H; C4-H); 4.33 (q, 2H, CH_2-CH_3, J = 7.2 Hz); 2.17 (s, 3H, C5-CH_3); 1.33 (t, 3H, CH_2-CH_3, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.53 (C=O); 146.40 (C3); 145.46 (C2'); 142.75 (C5'); 134.20 (C1'); 132.88 (C5); 131.07 (C4'); 130.57 (C3'); 125.89 (C6'); 109.14 (C4); 61.45 (CH_2-CH_3); 14.74 (CH_2-CH_3); 11.81 (C5-CH_3). Anal. Calcd for $C_{13}H_{13}N_3O_4$: C 56.72, H 4.72, N 15.27. Found: C 56.79, H 4.77, N 15.20; m/z: 275 (M^+); IR (cm^{-1}, KBr Disk): 3020 ($\nu_{C\text{-}H,\ arom.}$); 2963 ($\nu_{C\text{-}H,\ CH3}$); 1742 ($\nu_{C=O}$); 1630 ($\nu_{C=N}$); 1610, 1534 ($\nu_{a\ NO2}$); 1520, 1456, 1385 ($\nu_{s\ NO2}$); 1352, 1315, 1232 ($\nu_{C\text{-}O}$).

References

1. Kost, A. N.; Grandberg, I.I. *In Advances in Heterocyclic Chemistry*; Kartrizky, A. R.; Boulton, A. J. Eds.; Academic Press: New York, 1966; Vol. *6*, p347.
2. Murray, W.; Wachter, D. B.; Barton, D.; Forero-Kelly, Y. *Synthesis* **1991**, 18.
3. Kashima, C.; Harada, H.; Kita, I.; Fukuchi, I.; Hosomi, A. *Synthesis* **1994**, 61.
4. Luo, Y.; Potvin, P. G. *J. Org. Chem.* **1994**, *59*, 1761.
5. Sugaya, T.; Mimury, Y.; Ikuta, M.; Mimury, T.; Kasai, M.; Tomioka, S. *Synthesis* **1994**, 73.
6. Cerrada, M. L.; Elguero, J. ; De La Fuente, J. ; Pardo, C. ; Ramos, M. *Synth. Commun.* **1993**, *23*, 1947.
7. Park, K. H.; Cho, S. Y.; Yum, E. K.; Yu, C. M.; Hwang, K. J. *Bull. Kor. Chem. Soc.* **1995**, *16*, 799.
8. Finar, I. L.; Hurlock, R. J. *J. Chem. Soc.* **1957**, 3024.
9. Wang, X. J.; Tan, J.; Grozinger, K.; Betageri, R.; Kirrane, T.; Proudfoot, J. R. *Tetrahedron Lett.* **2000**, *41*, 5321.
10. Wang, X. J.; Tan, T.; Zhang, L. *Org. Lett.* **2000**, *2*, 3107.
11. Malek, F.; Ramdani, A.; Zidane, I.; Yahyi, A.; Radi, S. *Tetrahedron* **2005**, *61*, 2995.
12. Bouabdallah, I.; Ramdani, A.; Zidane, I.; Touzani, R.; Eddike, D.; Radi, S.; Haidoux, A. *J. Chem. Res.* **2005**, *4*, 242.
13. Radi, S. ; Ramdani, A. ; Lekchiri, Y. ; Morcellet, M. ; Crini, G. ; Janus, L. *Tetrahedron* **2004**, *60*, 939.
14. Malek, F.; Ramdani, A. ; Radi, S. *J. Chem. Res.* **2004**, *9*, 640.
15. Radi, S. ; Ramdani, A. ; Lekchiri, Y. ; Morcellet, M. ; Crini, G. ; Janus, L. ; Bacquet, M. *New J. Chem.* **2003**, *27*, 1224.
16. Radi, S. ; Ramdani, A. ; Lekchiri, Y. ; Morcellet, M. ; Crini, G. ; Morcellet, J. ; Janus, L. *J. Chem. Res.* **2003**, *11*, 712.
17. Radi, S. ; Ramdani, A. ; Lekchiri, Y. ; Morcellet, M. ; Crini, G. ; Morcellet, J. ; Janus, L. *Eur. Polym. J.* **2000**, *36*, 1885.
18. (a) Elguero, J. ; Jacquier, R. *Bull. Soc. Chim. Fr.* **1966**, *9*, 2832. (b) Mukherjee, A.; Subramanyam, U.; Puranik, V. G.; Mohandas, T. P.; Sarkar, A. *Eur. J. Inorg. Chem*. **2005**, 1254.
19. Huppatz, J. L. *Tetrahedron Lett.* **1972**, 35, 3637.