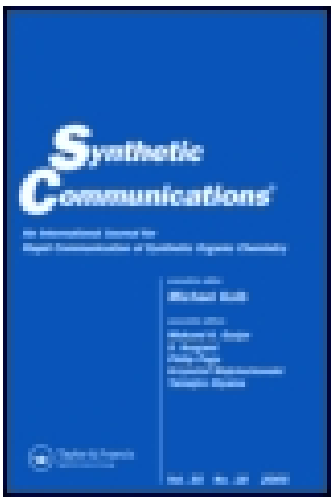

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Improved Synthesis of Oxadiazoles Under Microwave Irradiation

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IMPROVED SYNTHESIS OF OXADIAZOLES UNDER MICROWAVE IRRADIATION

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Abstract : Amidoximes **(1)** reacted with isopropenyl acetate in presence of KSF under microwave irradiation and gave 1,2,4-oxadiazoles **(2)**. 1,2,4-Oxadiazoles **(4)** can also be obtained by microwave irradiation from O-acylamidoximes **(3)** adsorbed on Alumina.
1,3,4-Oxadiazoles **(6)** were obtained by irradiation of bis (acyl) hydrazines **(5)** in thionyl chloride.

Oxadiazoles are interessing heterocycles [1] present in a variety of biological compounds [2] such as corony vasodilators, local anesthesics, anxiolytics and diuretics.

The most widely used method of synthesizing 1,2,4-oxadiazoles is the isolation and thermal cyclisation of O-acylamidoximes [3,4]. These 1,2,4-oxadiazoles can be also prepared by 1,3 dipolar cycloaddition of a nitrile oxide with a nitrile [5,6] and

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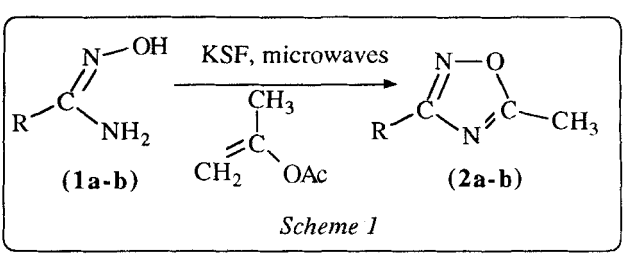
by 1,3 dipolar cycloaddition of substituted benzonitrile oxides to the C=N group of chlorocarbonyl isocyanate [7].

Refluxing bis(acyl)-hydrazines in phosphorus oxychloride [8,9] or thionyl chloride [4] afforted 1,3,4-oxadiazole in high yield.as cyclisation product. Very reactive heterocumulenic systems [10] undergo spontaneous cyclisation to 1,3,4-oxadiazoles.

Reactions of N-phenylsulfonylarenehydrazonoyl chlorides with aroylhydrazines [11] give 1,3,4-oxadiazole. 1,3,4-Oxadiazole can be obtained by the oxidation [1] of aroylhydrazone of aromatic aldehydes by lead dioxide.

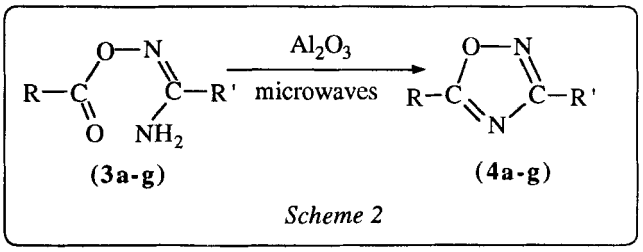
We report for the first time the synthesis of 1, 2, 4 and 1, 3, 4-oxadiazoles by microwave irradiation. 1, 2, 4-oxadiazoles were prepared throught two ways:

- In the first way, oxime **(1)** reacted with isopropenyl acetate in presence of KSF clay under microwave irradiation (monomode) (Scheme 1). The 1, 2, 4 oxadiazoles [(**2a)** and **(2b),** table 1 and 2] were obtained for irradiation time included between two and nine minutes.
- In the second way, we irradiated an O-acylated amidoxime **(3a-g)** adsorbed on Alumina in a commercial oven (Scheme 2). The 1, 2, 4 oxadiazoles **(4a-g)** were obtained in a 58-95% yield.

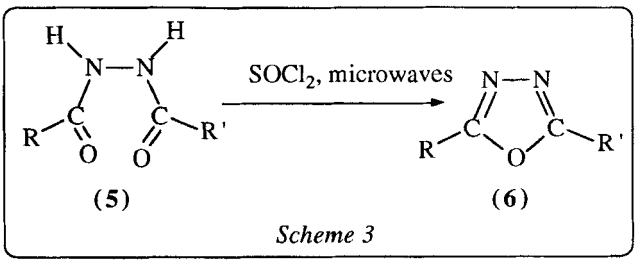


(1a-b) **(2a-b)**

Scheme 1



Scheme 2



Scheme 3

1,3,4-Oxadiazoles **(6a-c)** were prepared by microwave irradiation of bis(acyl)-hydrazines **(5a-c)** in thionyl chloride (Scheme 3). After 5 to 7 minutes of microwave irradiation in a Maxidigest®, we obtained compounds **(6a-c)** (78-92%) (table 2).

We compared the speeds of reactions performed under classical heating with those performed under microwave irradiation. In the case of compound **(2b)** in acetic anhydride the starting oxime **(1b)** (C=0.2 mol.l^{-1}) diseappeared at the same speed (9 mn) under classical heating (T=95°C) or with microwave irradiation (ending temperature T=95°C).

Under classical heating, for the synthesis of **(4e)**, it was necessary to heat 40 hours at 110°C in the toluene, leading to a total reaction (C=0,016 mol.l^{-1}). With a microwave irradiation of **(4e)** adsorbed on alumina the reaction finished after 5 minutes.

Table 1: molecular formula of oxadiazoles

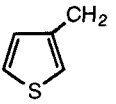
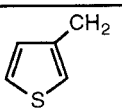
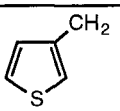
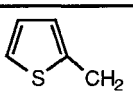
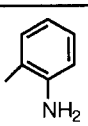
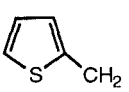
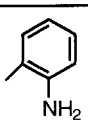
Products	R	R'
2a		
2b		
4a		
4b		tBu
4c		
4d		tBu
4e		tBu
4f		
4g		
6a		Me
6b		
6c		Ph

Table 2: yield and physical properties of oxadiazoles

Products	Molecular Formula or Lit mp (°C)	Time (min) of microwave irradiation	Yields (%)	IR (KBr/film) νC=N (cm^{-1})
2a	$C_7H_6N_2OS$ (166.20)	2	50	1584
2b	oil [2]	9	67	1586
4a	$C_{10}H_6N_2OS_2$ (234.28)	5	58	1597
4b	$C_{10}H_{12}N_2OS$ (208.28)	5	93	1596
4c	$C_{11}H_8N_2OS_2$ (248.31)	10	73	1592
4d	$C_{11}H_{14}N_2OS$ (222.30)	10	61	1590
4e	$C_{11}H_{14}N_2OS$ (222.30)	5	95	1581
4f	$C_{12}H_9N_3OS$ (243.27)	10	80	1606
4g	$C_{13}H_{11}N_3OS$ (257.30)	10	88	1612
6a	$C_7H_6N_2OS$ (166.20)	10	83	1620
6b	oil [10]	7	92	1579
6c	116-117 [10]	5	78	1618

In the synthesis of **(6b)**, working in thionyl chloride (C=0.16 $mol.l^{-1}$,, the reaction takes place with the same speed (7 mn) under conventional heating (T=95°C) or under microwave irradiation (ending temperature T=95°C).

Specific effect of microwave irradiation was not observed for reaction in solvent (compounds **(2b)** and **(6b)**), as it is already

noticed in litterature[12]. These results highlight the great acceleration of the speed reaction when using microwave irradiation with a solid support (compound **(4e)**). The acceleration was due to acido-basic catalysis of the support and specific microwave activation.

The biological properties of the oxadiazoles will be tested in the near future.

EXPERIMENTAL

All commercially available reagents were used as received from the suppliers.

Melting points (Mp) were determined with a Büchi-Tottoli apparatus and are uncorrected (°C). IR spectra were recorded on a Perkin-Elmer 257 spectrometer. ^{1}H and ^{13}C spectra were recorded on a Brucker AC 80 or Bruker AC 250 spectrometers operating at 80.13 and 250.13 MHz for ^{1}H, 62.89 MHz for ^{13}C. Chemical shifts are given in part per million positive values down field from internal TMS (^{1}H and ^{13}C). Coupling constants are given in Hz. Elemental analysis were performed by the "Service de microanalyse de l'Ecole Nationale Supérieure de Chimie de Toulouse". TLC was performed on silica gel plates (Riedel de Haën réf.37333) and preparative chromatography on columns of silica gel (70-230 mesh).

Microwave irradiations were carried out with a commercial microwave oven Brandt ME 210B at 850 W and 2450 MHz, in a focussed microwave oven Maxidigest®(Prolabo) or in a Cavité Resonante E013 of MES.

1,2,4-oxadiazoles synthesis: ***2a or 2b***

2a : oxime (5×10^{-3} mole (0.71 g)) was stirred in acetonitrile (40 ml) with 1.5 g montmorillonite KSF. Solvent was evaporated in vacuum. Ethyl acetate (0.5 ml) and isopropenyl acetate (2ml) were added. The product was irradiated under microwave (monomode, 40 W, 2 min) in a pyrex tube. The solid was extracted in acetonitrile (3X100 ml). After filtration and evaporation, the solid was purified by chromatography column (ethyl acetate/cyclohexane: 80/20).

^{1}H NMR ($CDCl_3$) δ : 7.76 (dd, 1H, $^4J_{35}$ = 1.2, $^3J_{34}$ = 3.6, H3), 7.48 (dd, 1H, $^4J_{35}$ = 1.2 , $^3J_{45}$ = 5.0, H5), 7.14 (dd, 1H, $^3J_{45}$ = 5.0, $^3J_{34}$ = 3.6, H4), 2.61 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ : 176.5 (C-O), 171.4 (C=N), 134.0 (thio), 129.3 (thio), 129.2 (thio), 128.0 (thio), 12.3 (CH_3); Mp =40° C

2b : oxime (10^{-3} mole (0.156 g) and isopropenyl acetate (5ml) with 1.5 g montmorillonite KSF were irradiated for 9 mn in a resonance cavity (150W). After extraction with acetonitrile (3X100ml) under sonification (5mn) and filtration, the solvant was evaporated and the crude product was chromatographied on silica (ethyl acetate/cyclohexane: 8/2). The spectra was similar to those described in literature[2].

Synthesis of 1,2,4-oxadiazoles ***4a-g***

General procedure:

O-acylamidoxime (10^{-3} mole) prepared according to the literature [1,2,11] and neutral alumina (5g) were mixed. The mixture was irradiated with a microwave oven.

The solide was extracted with acetonitrile (3X100ml) under sonification (5mn). After filtration, the solvant was evaporated and the residue was chromatographied on silica (ethyl acetate/cyclohexane).

4a : ^{1}H NMR ($CDCl_3$) δ : 7.94 (dd, 1H, $^4J_{35}$ = 1.2, $^3J_{34}$ = 3.7, H3), 7.84 (dd, 1H, $^4J_{35}$ = 1.2 , $^3J_{34}$ = 3.6, H3), 7.64 (dd, 1H, $^4J_{35}$ = 1.2, $^3J_{45}$ = 5.0, H5), 7.56 (dd, 1H, $^4J_{35}$= 1.2, $^3J_{45}$ = 5.0, H5) 7.17 (dd, 1H, $^3J_{34}$ = 3.7, $^3J_{45}$= 5.0 , H4), 7.10 (dd, 1H, $^3J_{34}$= 3.6, $^3J_{45}$ = 5.0, H4); ^{13}C NMR ($CDCl_3$) δ : 177.1 (C-O), 164.9 (C=N), 134.7 (thio), 133.6 (thio), 132.2 (thio), 129.8 (thio), 129.4 (thio), 128.5 (thio), 127.9 (thio) , 125.5 (thio); Mp=116-117° C.

4b : ^{1}H NMR ($CDCl_3$) δ : 7.85 (dd, 1H, $^4J_{35}$ = 1.2, $^3J_{34}$ = 3.7, H3), 7.58 (dd, 1H, $^4J_{35}$ = 1.2 , $^3J_{45}$ = 5.1, H5), 7.15 (dd, 1H, $^3J_{45}$ = 5.1, $^3J_{34}$ = 3.7, H4), 1.41 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ : 178.2 (C-O), 170.7 (C=N), 131.4 (thio), 130.8 (thio), 128.3 (thio), 126.2 (thio), 32.5 (C-CH_3), 28.7 (CH_3).

4c : ^{1}H NMR ($CDCl_3$) δ : 8-7.19 (m, 6H, thio), 4.14 (m, 2H, CH_2); MS m/z(%) : 248 (100) M^+

4d : ^{1}H NMR ($CDCl_3$) δ : 7.54 (ddt, 1H, $^{4}J_{25}$ = 2.9, $^{3}J_{45}$ = 4.9, ^{5}J = 0.3, H_5), 7.42 (ddt, 1H, $^{4}J_{25}$ = 2.9 , $^{4}J_{24}$ = 1.3, ^{4}J = 0.4 , H_2), 7.08 (ddt, 1H, $^{4}J_{24}$ = 1.3, $^{3}J_{45}$ = 4.9, ^{4}J = 0.4, H_4), 4.33 (m, 2H, CH_2), 1.29 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ : 177.3 (C-O), 177.0 (C=N), 133.6 (thio), 128.2 (thio), 127.6 (thio), 123.4 (thio), 35.7 (C-CH_3), 27.9 (CH_3), 27.0 (CH_2).

4e : ^{1}H NMR ($CDCl_3$) δ : 7.21-7.16 (m, 1H, thio), 6.99-6.91 (m, 2H, thio), 4.38 (d, 2H, ^{4}J = 0.6, CH_2), 1.35 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ : 177.8 (C-O), 176.2 (C=N), 134.7 (thio), 127.1 (thio), 127.0 (thio), 125.3 (thio), 32.3 (C-CH_3), 28.3 (CH_3), 27.3 (CH_2).

4f : ^{1}H NMR ($CDCl_3$) δ : 8.08 (m, 1H, arom) 7.94 (dd, 1H, $^{4}J_{35}$ = 1.2, $^{3}J_{34}$ = 3.7, H_3 thio), 7.62 (dd, 1H, $^{4}J_{35}$ = 1.2 , $^{3}J_{45}$ = 5.0 ,H_5), 7.28-6.78 (m, 4H, H_4 thio and arom.), 5.20 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ : 177.1, 168.6, 148.6, 132.0, 131.9, 130.1, 128.5, 127.4, 125.7, 117.2, 116.2, 109.8; Mp=135-136° C.

4g : ^{1}H NMR ($CDCl_3$) δ : 8.0 (dd, 1H, J = 8.4 and 1.3, arom), 7.26-6.68 (m, 6H, arom and thio), 4.48 (d, 2H, ^{4}J = 0.8, CH_2); ^{13}C NMR δ : 175.2, 168.5, 146.5, 134.4, 132.0, 129.9, 127.3, 125.5, 125.4, 117.2, 116.2, 109.2, 27.2 (CH_2); Mp=81° C.

Synthesis of 1,3,4-oxadiazole (6)

Bis(acyl)-hydrazine (**5**) ($0.8.10^{-3}$ mol.) and thionyl chloride (5 ml) were irradiated under microwave in a Maxidigest (150 W) for 5 to 7 mn. After distillation of the exces of thionyl chloride, the solid was chromatographied on silica (ethyl acetate/cyclohexane).

6a : ^{1}H NMR ($CDCl_3$) δ : 7.69 (dd, 1H, $^{4}J_{35}$ = 1.3, $^{3}J_{34}$ = 3.6, H_3), 7.50 (dd, 1H, $^{4}J_{35}$ = 1.3, $^{3}J_{45}$ = 5.1, H_5), 7.14 (dd, 1H, $^{3}J_{34}$ = 3.6, $^{3}J_{45}$ = 5.1, H_4), 2.57 (s, 3H, CH_3); MS m/z(%) : 166 (100) M^+.

Compounds (**6b**) and (**6c**) obtained were already described in literature [10].

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