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IMPROVED SYNTHESIS OF OXAZOLINE UNDER MICROWAVE IRRADIATION

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Abstract : Oxazolines have been prepared under microwave irradiation by two different ways. In a first one, imino ether hydrochlorides have been reacted with amino alcohols in the presence of alumina supported potassium fluoride, in an open vessel. In a second one, amino alcohols are directly reacted with imino ethers in a closed vessel.

Although the first synthesis of oxazoline was reported as soon as in 1884 [1], their high significance only emerged recently in organic chemistry [1-13]. The simplest and most inexpensive method is condensation of amino alcohols and carboxylic acids. The reaction proceeds with elimination of water at temperature between 160 and 220°C [2-4]. But this reaction is somewhat slugglish and chemical yields are generally low. If nitriles are used instead of carboxylic acids, the reaction proceeds with elimination of ammonia at hight temperature in the presence of a Lewis acid catalyst [5,6]. Other synthetic approaches involve various types of starting materials such as imidic acid ester [7-9], amide [10], haloamide [10], aziridines [4], epoxides [11], cyanoallene [12] and popargylphosphonium salt [13]. Most generally these reaction proceed slowly. In the course of our current interest in microwave promoted reactions [14] it seemed to us of interest to investigate the synthesis of oxazolines under microwave irradiation. In a first step we

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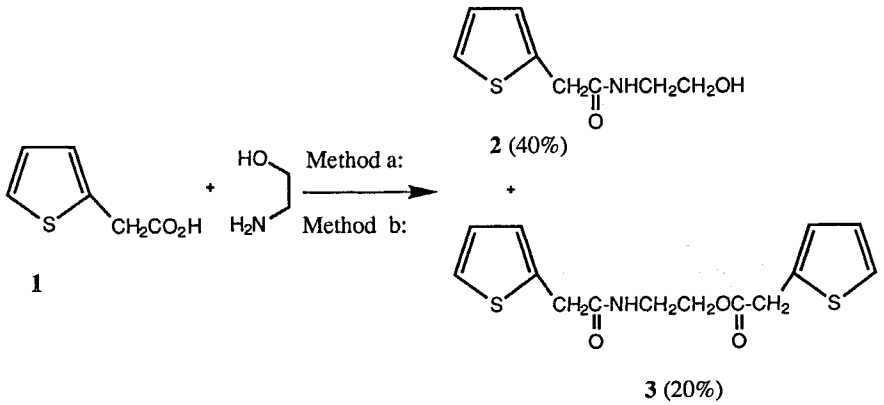
reacted 2-thienyl acetic acid **1** with ethanolamine **2** in an open vessel (OV) in a domestic microwave oven (scheme 1, method a). This gave a mixture of the amides **2** and **3** in respectively 40 and 20 % yields. An identical result was obtained with the alumina supported reagents (scheme 1, method b).

The expected oxazoline was not detected in the crude reaction mixture but is probably formed as the amide **3** probably results from its addition reaction with the starting carboxylic acid **1**. As a matter of fact, heating 2-(p nitrophenyl)- 2-oxazoline with benzoic acid for 15 min at 130 °C yields 2-(p nitrobenzamido) ethyl benzoate [15,16]. Microwave activation of reactions on solid supports is now well documented [17] and often results in much shorter reaction time and improved yield and selectivity.



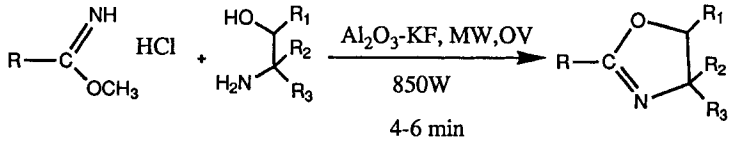
Method a: Without support, P= 850W, irradiation 4 min, open vessel

Method b: With support (Al_2O_3), P= 850W, irradiation 4 min, open vessel

Scheme 1

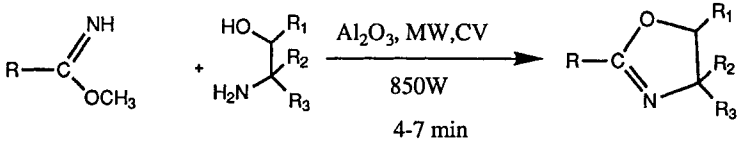
So, we then investigated the reaction of imino ethers hydrochlorides **4** with N-ephedrine in the presence of potassium fluoride supported on alumina (scheme 2, method A). The reaction was carried out in an open vessel (OV). The expected oxazolines **5a-g** (table I) are obtained in fairly good yields as reported in table II. Potassium fluoride generates the corresponding free imino ether from its hydrochloride. This prompted us to investigate the reaction of the free iminoether **4'**. This was done in a closed vessel, (CV), using alumina as solid support (scheme 2, method B). Under the same irradiation condition as before the oxazoline is obtained in almost the same yield (table II, method B).The synthesis of **5a**, according the same procedure (method B without solvent) under conventional heating at 110 °C requires 24 h to give a 65% yield. When this reaction is carried out in dichloroethane (concentration 0.07 M) under reflux (95 °C) for 19 h, we obtained **5a** in a 58 % yield.

Method A



4 **5**

Method B



4' **5**

Scheme 2

Table 1

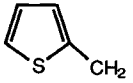
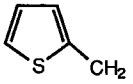
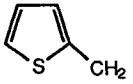
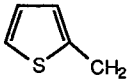
Products	R	R_1	R_2	R_3
5a	Ph	H	H	H
5b	Ph	Ph	Me	H
5c	Ph	Ph	Ph	H
5d		H	H	H
5e		H	Et	H
5f		Ph	Me	H
5g		Ph	Ph	H

Table 2

Products	Molecular Formula or Lit mp (°C)	Method of synthesis	Time (min) of microwave irradiation	Yield (%)	IR(KBr/film) ν C=N (cm^{-1})
5a	25-27 [18]	B	5	71	1647
5b	140 [19]	A	6	78	1647
5c	$C_{21}H_{17}NO$ (299,35)	B	7	93	1650
5d	C_8H_9NOS (167,22)	B	4	79	1669
5e	$C_{10}H_{13}NOS$ (195,26)	B	5	58	1645
5f	$C_{15}H_{15}NOS$ (257,34)	A	4	65	1648
5g	$C_{20}H_{17}NOS$ (319,41)	B	7	84	1669

So, it can be seen, that our experimental procedure provides a very simple and efficient way to obtain oxazolines in good yields and with very short reaction times. At this time we have no evidence to discuss about a possible "non conventional microwave effect". This needs further investigations which are currently carried out in our laboratory.

EXPERIMENTAL

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

Melting points were determined with a Büchi-Tottoli apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrometer. ^1H 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 ^1H, 62.89 MHz for ^{13}C. Chemical shifts are given in part per million positive values down field from internal TMS (^1H and ^{13}C). Coupling constants are

given in hertz. Elemental analyses were performed by the "Service de microanalyse de l'Ecole Nationale Supérieure de Chimie de Toulouse". TLC was performed on silica gel plates (Ridel 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.

Reaction of the 2-thiophenacetic acid with ethanolamine

Method b

2-thienyl acetic acid **1** (1.42g, 10^{-2} mol.) and éthanolamine (0.61 g, 10^{-2} mol.) are mixed in 20 ml of dichloromethane and 3g of alumina are added. The solvent is evacuated under vacuum and the resulting solid is irradiated for 4 min in an open vessel.

Analytic thin layer chromatography gives two spots : **2** $R_f = 0.15$ and **3** : $R_f = 0.25$ (SiO_2, ethyl acetate). Pure amides **2** and **3** are separated by column chromatography (SiO_2, ethyl acetate). Chemical yields for the isolated products are : **2** (40%) and **3** (20%).

2 : PMR ($CDCl_3$) δ : 7.26 (m, 1H, thio), 6.96 - 6.89 (m, 2H, thio), 6.54 (s, 1H, NH), 3.73 (s, 2H, CH_2 thio), 3.61 (m, 2H, CH_2 O), 3.32 (m, 2H, CH_2 N) ; CMR ($CDCl_3$) δ : 171.2 (C=O), 136.0 (C_2 thio), 127.8 (thio), 127.3 (thio), 125.5 (C_4 thio), 61.6 (CH_2O), 42.5 (CH_2N), 37.3 (C thio). IR (film) ν : 3312 (OH), 1667 (CO) ; MS m/z : 185 (10.5 %) M^+.

3 : PMR ($CDCl_3$) δ : 7.26 - 7.20 (m, 2H, thio), 6.99 - 6.90 (m, 4H, thio), 5.90 (s, 1H, NH), 4.16 (t, 2H, $^3J = 6.0$, CH_2O), 3.80 (s, 2H, CH_2 thio), 3.74 (s, 2H, CH_2 thio), 3.51 (m, 2H, CH_2N) ; CMR ($CDCl_3$) δ : 170.2 (C=O), 170.0 (C=O), 135.8 (C_2 thio), 134.7 (C_2 thio), 127.5 (thio), 127.4 (thio), 127.0 (thio), 126.9 (thio), 125.7 (thio), 125.2 (thio), 63.5 (CH_2O), 38.7 (CH_2) , 37.4 (CH_2) , 35.3 (CH_2) ; IR (film) ν : 3294 (NH), 1731 (CO), 1650 (C=O) ; MS m/z : 309 (3,1 %) M^+.

Synthesis of oxazolines, general procedure

Method A :

Imino ether hydrochloride **4** (10^{-2} mol.), N-ephedrine (10^{-2} mol.) and KF supported on alumina [18] (3g) are mixed in a mortar and finely powdered. The resulting mixture is irradiated with microwaves for 4-7 min. The reactions are monitored by TLC (Silica gel-cyclohexane/ethyl acetate 1/1). The organic products are extracted by treating the solid with 100 ml of dichloromethane in an ultrasonic bath for 5 min. This extraction is repeated three times ; the CH_2Cl_2 solutions are combined and the solvent is evacuated under vacuum. The oxazoline is isolated by column, chromatography (SiO_2-cyclohexane/ethyl acetate).

Method B :

Imino ether (**4'**) (10^{-2} mol.) and amino alcohol are dissolved in 20 ml of dichloromethane. Alumina (3g) is added and the solvent evacuated under vacuum. The resulting solid is irradiated for 4-7 min in a closed teflon reactor. The resulting oxazoline is isolated in the same way as in method A.

5a : PMR ($CDCl_3$) δ : 7.95 - 7.91 (m, 2H, arom), 7.46 - 7.35 (m, 3H, arom), 4.40 (t, 2H, ^3J = 9.7, CH_2O), 4.03 (t, 2H, ^3J = 9.7 , CH_2N) ; CMR ($CDCl_3$) δ : 164.6 (C=N), 131.2 (arom), 128.3 (arom), 128.1 (arom), 127,7 (C_1arom), 67.5 (CH_2O), 54.9 (CH_2N).

5b : PMR ($CDCl_3$) δ = 8.05 (m, 2H, arom), 7.51 - 7.33 (m, 8H, arom), 5,10 (d, 1H, ^3J = 7.8, CHO), 4.25 - 4.19 (m, 1H, CHN), 1.50 (d, 3H, ^3J = 6.6 , CH_3) ; CMR ($CDCl_3$) δ : 162.7 (C=N), 140.5 (C_1 arom), 131.4 (arom), 128.8 (arom), 128.4 (arom), 128.3 (arom), 128.2 (arom), 127.7 (C_1 arom), 125.6 (arom), 82.2 (CHO), 71.0 (CHN), 21.4 (CH_3).

5c : PMR ($CDCl_3$) δ : 8.21 - 8.17 (m, 2H, arom), 7.55 - 7.50 (m, 3H, arom), 7.08 - 6.92 (m, 10H, arom), 6.03 (d, 1H, ^3J = 10.0, CHO) 5.76 (d, ^3J = 10.0, CHN) ; CMR ($CDCl_3$) δ : 164.9 (C = N), 137.7 (arom), 136.8 (arom), 131.8 (arom), 128.6 (arom), 128.5 (arom), 127.9 (arom), 127.8 (arom), 127.7 (arom), 127.6 (arom), 127.4 (arom), 127.0 (arom), 126.3 (arom), 85.3 (CHO), 74.5 (CHN) ; Mp = 68-69 °C.

5d : PMR ($CDCl_3$) δ : 7.18 (m, 1H, thio), 6,92 (m, 2H, thio), 4.25 (t, 2H, ^3J = 10.0, CH_2O), 3.87 - 3.80 (m, 4H, CH_2 thio and CH_2N) ; CMR ($CDCl_3$) δ : 166.0 (C=N), 136.5 (C_2 thio), 127.2 (thio), 126.8 (thio), 124.8 (thio), 67.8 (CHO), 54.4 (CHN), 28.9 (CH_2).

5e : PMR ($CDCl_3$) δ : 7.24 (m, 1H, thio), 6.98 - 6.92 (m 2H, thio), 3.82 - 3.54 (m, 5H, CH_2O, CH_2 thio, CH), 1.54 - 0.83 (m, 5H, CH_2 CH_3) ; CMR ($CDCl_3$) δ : 170.8 (C = N), 136.1 (C_2 thio), 128.3 (thio), 126.8 (thio), 125.6 (thio), 65.1 (CH_2O), 53.6 (CH), 37.6 (CH_2 thio), 24.0 (CH_2 CH_3), 10.4 (CH_3).

5f : PMN ($CDCl_3$) δ : 7.30 - 6.85 (m, 8H, arom and thio), 4.92 (d, 1H, ^3J = 7.6, CHO), 4.02 - 3.90 (m, 3H, CH_2 and CHN), 1.40 (d, ^3J = 6.5, CH_3) ; CMR ($CDCl_3$ δ : 170.4 (C = N), 141.4 (C_1 arom), 135.9 (C_2 thio), 128.4 (thio), 128.3 (arom), 127.7 (arom), 127.4 (arom), 126.2 (thio) 125.5 (thio), 76.9 (CHO), 51.5 (CHN), 37.4 (CH_2 thio), 17.2 (CH_3).

5g : PMR ($CDCl_3$) δ : 7.29 - 6.79 (m, 13H, arom and thio), 5.86 (d, 1H, ^3J = 10.2, CHO), 5.56 (d, 1H, ^3J = 10.2 CHN) 4.11 (s, 2H, CH_2) ; CMR ($CDCl_3$) δ : 166.6 (C = N) 137.5, 136.3, 128.3, 128.1, 127.9, 127.7, 127.6, 127.3, 127.0, 126.9, 126.3, 125.0, 85.6 (CHO), 74.0 (CHN), 29.4 (CH_2 thio) ; Mp = 102°C.

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References

1 - Andreasch R., *Monatsh. Chem* . **1884,** *5, 33.*

2 - Allen P. and Ginos J., *J. Org. Chem.,* **1963**, 28, 2759.

3 - Lion C. and Dubois J.E., *Tetrahedron,* **1973**, 29, 3417.

4 - Meyers A.I., Temple D.L., Haidukewych D. and Mihelich J., *J. Org. Chem.,* **1974**, 39, 2787.

5 - Witte H. and Seeliger W., *Liebig. Ann. Chem.,* **1974**, 996.

6 - Bolmn C., Weickhardt K., Zehnder M. and Ranff T., *Chem. Ber.,* **1991**, 124, 1173.

7 - Meyers A.I., Knaus G. and Kama K., *J. Am. Chem. Soc.,* **1974**, 95, 268.

8 - Meyers A.I., Knaus G., Kamata K. and Ford M., *J. Am. Chem. Soc.,* **1976,** 98, 567.

9 - Reuman M. and Meyers A.I., *Tetrahedron*, **1985**, 41, 837.

10- Frump J.A., *Chem. Rev.*, **1971**, 71, 483.

11- Gassman P.G. and Guggenheim T.L., *J. Am. Chem. Soc.,* **1982**, 104, 5849.

12- Forum Z.T., Landor P.D., Landor S.R. and Mpango G.M., *Tetrahedron Lett.* , **1975**, 1101.

13- Scheveitzer E.E. and Deroe S.V., *J. Org. Chem.,* **1975**, 40, 144.

14- Berlan J., Giboreau P., Lefeuvre S. and Marchand C., *Tetrahedron Lett.,* **1991**, 32, 2363.

15- Lambert R.F. and Kristofferson C.E., *J. Org. Chem.,* **1965**, 30, 3938.

16- Fry E.M., *J. Org. Chem.,* **1950**, 15, 802.

17- Bram G., Loupy A. and Villemin D., in Solid Supports and Catalysis in Organic Synthesis, Smith K. and Horwood E., **1992**, 302.

18- Vorbrüggen H. and Krolikiewicz K., *Tetrahedron,* **1993**, 49, 9353.

19- Nagai W.N. and Kanao S., *Ann.,* **1929**, 470,175.

20 - Alloum A.B. and Villemin D., *Synth. Commun.*, **1989**, 2567.

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