Microwave-assisted synthesis of new spiro-isoxazolino-indol-3-ones and 5-aroylisoxazoles on KF-Al_2O_3 under solvent-free conditions

M. Elyazidi, K. Bougrin, B. Daou, H. Doua, M. Soufiaoui *

Laboratoire de Chimie des Plantes et de Synthèse Organique et Bio-organique, Université Mohammed V-Agdal, Faculté des Sciences, B. P. 1014 R. P. Rabat, Maroc

(Reçu le 14 Décembre 2002, accepté le 10 Avril 2003)

RESUME : De nouveaux spiro-isoxazolino-indol-3-ones et 3-aroylisoxazoles sont synthétisés avec de bons rendements sur KF-Al_2O_3 en «milieu sec» et sous irradiation micro-ondes. Tous les produits finaux et intermédiaires sont rapportés et leurs structures sont établies par les méthodes spectroscopiques.

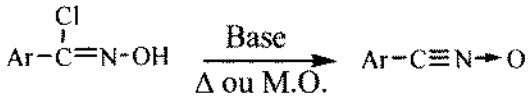
ABSTRACT : New spiro-isoxazolino-indol-3-ones and 3-aroylisoxazoles have been synthesized in good yields on KF-Al_2O_3 in «dry media» and under microwaves irradiation. All synthons and final products have been described and their structures established by spectroscopic methods.

Key words : : spiro-isoxazolino-indol-3-ones, 3-aroylisoxazoles, arylnitriloxydes, 1,3-dipolar cycloaddition, KF-Al_2O_3, dry media, microwaves.

INTRODUCTION

Considerable attention has been focused on the synthesis of isoxazolines and isoxazoles [1], both for their high pharmacological and biological activities [2-5]. The 1,3-dipolar cycloaddition of arylnitriloxide with olefinic and acetylenic derivaties is a general and one of the best procedure to get these heterocycles [1].

However the synthesis of spiroisoxazolines have been less reported [1b-d]. These compounds can be converted to β- aminoalcohols and β- hydroxy-ketones [6,7]. Arylnitriloxydes are generated *in situ* by heating hydroxamoïc chlorides with a base [8] (Scheme 1), these latter are goten by aldoximes halogenation with N- chloro or N- bromo-succinimide in dimethylformamide [9].



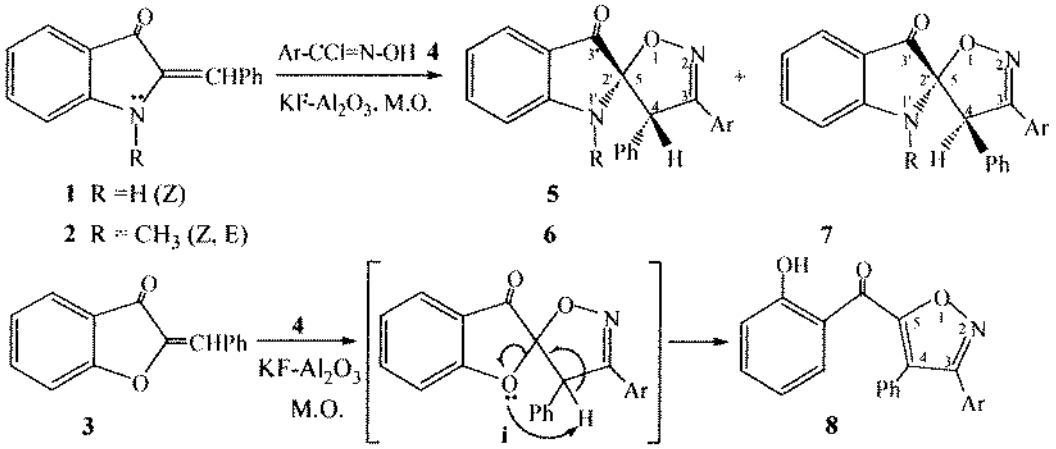
Scheme 1

In continuation of our work on the synthesis of heterocycles via 1,3-dipolar cycloaddition, and on the application of microwave irradiation for this purposes, we have recently set up a simple and an efficient route to get isoxazolines by mixing hydroxamoïc chlorides and various dipolarophiles, the whole supported on mineral solid support and irradiated with microwaves [10,11].

* corresponding author, e-mail: soufiaoui@fsr.ac.ma

RESULTS AND DISCUSSION

We report herein the synthesis of novel spiro-isoxazolino-indol-3-ones **5**, **6** and **7** and the synthesis of 5- aroylisoxazole **8** (Scheme 2).



a: Ar=C_6H_5 ; **b**: Ar = $pCH_3C_6H_4$; **c**: Ar= $pClC_6H_4$; **d**: Ar = $pCH_3OC_6H_4$

Scheme 2

Dipoles and dipolarophiles were supported on KF-Al_2O_3 and irradiated by microwaves in a domestic oven for 10 to 14 minutes. The results were compared to those obtained in conventional thermal heating according to the classical procedure [12]. We summarize our results in table I. Hydroxamoïc chlorides **4** and dipolarophile **1** were impregnated on KF-Al_2O_3. The reaction mixture was submitted to microwave irradiation in a domestic oven at 650 W during 10 min.

Adducts **5** were obtained in rather good yields (68 – 90%). Dipolarophile **2** (diastereoisomeric mixture 40/60) reacted with dipoles **4** under the same conditions used above and led to adducts **6**/**7** in 40/60 ratio with slightly better yields (77 – 92%). Diastereoisomers **6** and **7** were separated by column chromatography over silica gel.

Table I: : Results of the cycloaddition under microwaves and by conventional heating

Adducts	t [min] [a]	T_f [°C] [b] M.O.	[%] Rdt. [c] M.O.	[%] Rdt. [Δ]
5a	10	135	68	50 [d]
5b	10	132	90	80 [d]
5c	10	136	87	80 [d]
5d	10	142	85	78 [d]
6a+7a	10	132	77	65 [d]
6b+7b	10	134	88	85 [d]
6c+7c	10	136	90	85 [d]
6d+7d	10	138	92	82 [d]
8a	14	137	90	75 [e]
8b	14	135	95	85 [e]
8c	14	136	95	85 [e]
8d	14	138	95	80 [e]

[a] Microwave irradiation time. [b] final temperature of the reaction mixture, measured with a thermometric probe after the completion of the reaction. [c] Final yields of isolated adducts under microwaves. [d] Final yields of isolated products after conventional thermal heating: THF – Et_3N, oil bath, reflux, 24 h. [e] Yields of isolated products after conventional thermal heating : THF - Et_3N, oil bath, reflux, 10 h.

Dipolarophiles **3** reacted with dipoles **4** but did not lead to the expected spiro-compounds. These latter were rearranged [13] *in situ* into aroylisoxazoles **8** in very good yields (table I). The structures of all the compounds **5–8** were settled from the spectral data (^{1}H and ^{13}C NMR and IR) [14]. We also tested the microwave specific effects (athermic). In this goal, we compared results gotten in the same conditions (time and temperature of reaction) by conventional heating and microwaves.

The yields under microwaves varied from 68 to 95% against traces obtained by classical heating. The products were obtained in 10 and 14 min. in relation with the temperature measured after the completion of the reaction. The final temperatures varied between 132 and 142°C (table I). These microwave specific effects could be of multiple origins [10,11,15].

CONCLUSION

We have set up a simple and an efficient procedure to synthesize a new spiro-isoxazolines and aroylisoxazoles. The reactions occurred in short times under microwaves irradiation. The use of solid support avoided the use of polluent solvents, and products were easily recovered.

EXPERIMENTAL

General. Melting points (MP) were determined with a Büchi 510 apparatus. Analytical TLC was performed on 0,25 mm silica gel plates (Merck). Visualization was accomplished by UV light and iodine. Solvents for extraction and chromatograpby were technical grade and distilled from the indicated drying. All other reagents were recrystallized or distilled when necessary

Column chromatography was carried out on silica gel (Merck, 70-230 mesh). IR spectra were obtained on Perkin-Elmer 1600 series FTIR. ^{1}H and ^{13}C NMR experiment were recorded on a Bruker AC 250 to 62.89 MHz spectrometer using tetramethylsilane (0.00 ppm) or chloroform (7.26 ppm) as an internal reference in $CDCl_3$ solutions. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet) or m (multiplet). Microwave irradiations were carried out with a multimode oven (Samsung RE-995-CG, 2450 MHz, Pmax = 900W).

General Procedure for the synthesis of spiro-isoxazolino-indol-3-ones (5, 6 and 7) and 5-aroylisoxazoles (8) on KF-Al_2O_3 ***under solvent-free conditions:*** A mixture of dipolarophiles (**1**, **2** or **3**) [4 mmoles] in dichloromethane (CH_2Cl_2) [20 ml] and hydroxamoïc acid chlorides (**4**) [4 mmoles] was added to potassium fluoride on alumina [3g] under stirring. After few minutes of contact, the solvent was removed under reduced pressure. The solid was pored in an Erlenmeyer [50ml] and put in the microwave oven and irradiated. At the end of the reaction, after cooling down and extraction with CH_2Cl_2. The crude compounds **5**, **6**, **7** and **8** were extracted with dichloromethane and recrystallized from ethanol. Diastercoisomers **6** and **7** separated by column chromatography over silica gel, using ethylacetate / hexane 2:8 as elucnt.

Compound 5a : MP=230°C (EtOH); IR (KBr) cm^{-1}: 1718 (C=O), 3340 (N-H) ; NMR ^{1}H ($CDCl_3$) δ ppm : 4.47 (NH), 4.92 (s,H_4), 6.55-7.63 (m,14H); NMR ^{13}C ($CDCl_3$) δ ppm : 55.11 (C_4), 96.52 ($C_{5\text{-}2'}$), 196.90 ($C_{3'}$).

Compound 5b : MP=224°C (EtOH); IR(KBr) cm^{-1}: 1716 (C=O), 3342 (N-H); NMR ^{1}H ($CDCl_3$) δ ppm :2.35 (s,CH_3), 4.49 (s,NH), 4.96 (s,H_4), 6.58-7.72 (m,13H); NMR ^{13}C ($CDCl_3$) δ ppm: 21.50 (CH_3), 55.72(C_4), 96.64 ($C_{5\text{-}2'}$), 196.70($C_{3'}$).

Compound 5c : MP=194°C (EtOH) ; IR (KBr) cm^{-1}: 1716 (C=O), 3342 (N-H) ; NMR ^{1}H ($CDCl_3$) δ ppm : 4.50 (NH), 4.90 (s,H_4), 6.55-7.62 (m,14H); NMR ^{13}C ($CDCl_3$) δ ppm : 55.82 (C_4), 96.23 ($C_{5\text{-}2'}$), 198.20 ($C_{3'}$).

Compound 5d : MP=232°C (EtOH); IR(KBr) cm^{-1}: 1715 (C=O), 3340 (N-H); NMR ^1H ($CDCl_3$) δ ppm :3.72 (s,OCH_3), 4.52 (s,NH), 4.88 (s,H_4), 6.55-7.74 (m,13H); NMR ^{13}C ($CDCl_3$) δ ppm: 55.20 (OCH_3), 56.10(C_4), 96.33 ($C_{5:2'}$), 198.40($C_{3'}$).

Compound 6a : MP=184°C (EtOH); IR (KBr) cm^{-1}: 1715 (C=O); NMR ^1H ($CDCl_3$) δ ppm : 2.48 (s,N-CH_3), 5.21 (s,H_4), 6.46-7.64 (m,14H); NMR ^{13}C ($CDCl_3$) δ ppm : 29.88 (N-CH_3), 57.64 (C_4), 101.46 ($C_{5:2'}$), 197.52 ($C_{3'}$).

Compound 7a : MP=170°C (EtOH); IR (KBr) cm^{-1}: 1718 (C=O); NMR ^1H ($CDCl_3$) δ ppm : 3.02 (s,N-CH_3), 5.03 (s,H_4), 6.65-7.56 (m,14H); NMR ^{13}C ($CDCl_3$) δ ppm : 27.60 (N-CH_3), 59.42 (C_4), 99.89 ($C_{5:2'}$), 193.49 ($C_{3'}$).

Compound 6b : MP=176°C (EtOH); IR (KBr) cm^{-1}: 1717 (C=O); NMR ^1H ($CDCl_3$) δ ppm : 2.33 (s,CH_3), 2.49 (s,N-CH_3), 5.22 (s,H_4), 6.45-7.62 (m,13H); NMR ^{13}C ($CDCl_3$) δ ppm : 21.52 (CH_3), 29.79 (N-CH_3), 57.67 (C_4), 101.48 ($C_{5:2'}$), 197.49 ($C_{3'}$).

Compound 7b : MP=164°C (EtOH); IR (KBr) cm^{-1}: 1720 (C=O); NMR ^1H ($CDCl_3$) δ ppm : 2.32 (s,CH_3), 3.01 (s,N-CH_3), 5.02 (s,H_4), 6.66-7.52 (m,13H); NMR ^{13}C ($CDCl_3$) δ ppm : 21.50 (CH_3), 27.43 (N-CH_3), 59.34 (C_4), 99.93 ($C_{5:2'}$), 193.53 ($C_{3'}$).

Compound 6c : MP=178°C (EtOH); IR (KBr) cm^{-1}: 1710 (C=O); NMR ^1H ($CDCl_3$) δ ppm : 2.49 (s,N-CH_3), 5.19 (s,H_4), 6.47-7.63 (m,13H); NMR ^{13}C ($CDCl_3$) δ ppm : 29.58 (N-CH_3), 57.26 (C_4), 101.73 ($C_{5:2'}$), 197.16 ($C_{3'}$).

Compound 7c : MP=160°C (EtOH); IR (KBr) cm^{-1}: 1715 (C=O); NMR ^1H ($CDCl_3$) δ ppm : 3.04 (s,N-CH_3), 4.98 (s,H_4), 6.65-7.56 (m,13H); NMR ^{13}C ($CDCl_3$) δ ppm : 27.68 (N-CH_3), 59.36 (C_4), 99.92 ($C_{5:2'}$), 193.62 ($C_{3'}$).

Compound 6d : MP=180°C (EtOH); IR (KBr) cm^{-1}: 1718 (C=O); NMR ^1H ($CDCl_3$) δ ppm : 2.48 (s,N-CH_3), 3.77 (s,OCH_3), 5.19 (s,H_4), 6.45-7.60 (m,13H); NMR ^{13}C ($CDCl_3$) δ ppm : 29.56 (N-CH_3), 57.37 (OCH_3), 57.79 (C_4), 101.40 ($C_{5:2'}$), 197.56 ($C_{3'}$).

Compound 7d : MP=168°C (EtOH); IR (KBr) cm^{-1}: 1710 (C=O); NMR ^1H ($CDCl_3$) δ ppm : 3.02 (s,N-CH_3), 3.76 (s,OCH_3), 5.01 (s,H_4), 6.65-7.56 (m,13H); NMR ^{13}C ($CDCl_3$) δ ppm : 27.43 (N-CH_3), 55.34 (OCH_3), 59.51 (C_4), 99.87 ($C_{5:2'}$), 194.10 ($C_{3'}$).

Compound 8a : MP=154°C (EtOH); IR (KBr) cm^{-1}: 1635 (C=O), 3115 (OH); NMR ^1H ($CDCl_3$) δ ppm : 6.88-7.96 (m,14H), 11.64 (s,OH); NMR ^{13}C ($CDCl_3$) δ ppm : 137.77 (C_3), 162.12 (C_5), 187.27 (C=O).

Compound 8b : MP=130°C (EtOH); IR (KBr) cm^{-1}: 1635 (C=O), 3118 (OH); NMR ^1H ($CDCl_3$) δ ppm : 2.37 (s,CH_3), 6.88-8.02 (m,13H), 11.66 (s,OH); NMR ^{13}C ($CDCl_3$) δ ppm : 21.40 (CH_3), 140.27 (C_3), 162.13 (C_5), 187.31 (C=O).

Compound 8c : MP=140°C (EtOH); IR (KBr) cm^{-1}: 1635 (C=O), 3120 (OH); NMR ^1H ($CDCl_3$) δ ppm : 6.92-8.16 (m,13H), 11.61 (s,OH); NMR ^{13}C ($CDCl_3$) δ ppm : 137.77 (C_3), 162.15 (C_5), 187.29 (C=O).

Compound 8d : MP=142°C (EtOH); IR (KBr) cm^{-1}: 1630 (C=O), 3120 (OH); NMR ^1H ($CDCl_3$) δ ppm : 3.61 (s,OCH_3), 6.84-8.01 (m,13H), 11.86 (s,OH); NMR ^{13}C ($CDCl_3$) δ ppm : 55.35 (OCH_3), 137.74(C_3), 161.76 (C_5), 187.30 (C=O).

REFERENCES

[1] a/ Skiles, J.W.; Menil, D., *Tetrahedron Lett.*, **1990**, *31*, 7277. b/ Yamagishi, M.; Yamada, Y.; Ozaki, K.; Asao, M.; Shimizu, K.; Suzuki, M.; Matsumoto, M.; Mat-Suoka, Y.; Matsumoto, K., *J. Med. Chem.*,**1992**, *35*, 208500. c/ Dannhardt, G.; Kiefer, W.; Lambrecht, G.; Laufer, S.; Mutschler, E.; Schweiger, J.; Striegel, H.G., *Eur. J. Med. Chem.*, **1995**, *30*, 839.

[2] a/ Torssel, K.B.G; '' Nitrile oxides, Nitrones and Nitronates in Organic Synthesis-Novel Strategie in Synthesis'' VCH Publishers Inc. **1988**. b/ Fariña, F.; Fraile, M.T.; Martín, M.R.; Martín, M.V.; De Guereñu, A.M., *Heterocycles*, **1995**, *40*, 285. c/ Auricchio, S.; Bini, A.; Pastormerlo, E.; Truscello, A.M., *Tetrahedron*, **1997**, *53*, 10911. d/ Diab, J.; Laurent A.; Le Dréan, L., *J. Fluorine Chem.*, **1997**, *84*, 145. e/ Adembri, G.; Paoli, M.L.; Rossi, P.; Sega, A., *Tetrahedron Asym.*, **2001**, *12*, 619. f/ Kang, K.H.; Pae, A.N.; Choi, K.I.; Cho, Y.S.; Chung, B.Y.; Lee, J.E.; Jung, S.H.; Koh, H.Y.; Lee, H.Y., *Tetrahedron Lett.*, **2001**, *42*, 1057. g/ Cokun, N.; Tirli Tat, F.; Güven, Ö,Ö., *Tetrahedron*, **2001**, *57*, 3413.
[3] a/ Janssen, F.W.; Jusko, W.J.; Chang, S.T.; Kirkman, S.K., *Chim. Pharmacol. Ther.*, **1980**, *27*, 352. h/ Pevarello, P.; Amici, R.; Colombo, M.; Varasi, M., *J. Chem. Soc. Perkin Trans I*, **1993**, 2151.
[4] a/ Meguro, K.; Toward, H.; Sugiyama, Y.; Fijta, T.; *Chem. Pharm. Bull.*, **1986**, *34*, 2840. b/ Rockwell, A.L.; Rafalski, M.; Pitts, W.J.; Batt, D.G.; Petraitis, J.J.; DeGrado, W.F.; Mousa, S.; Jadhav, P.K., *Bioorg. Med. Chem. Lett.*, **1999**, *9*, 937. c/ Kang, Y.K.; Shin, K.J.; Yoo, K.H.; Seo, K.J.; Hong, C.Y.; Lee, C.S.; Park, S.Y.; Kim, D.J.; Park, S.W., *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 95.
[5] a/ Shiraishi, S.; '' The Japanese United States Congres of Pharmaceutical Sciences'' Honolulu, Hawai, **1987**, Symposia Abst., P.130. b/ Pruitt, J.R.; Pinto, D.J.; Estrella, M.J.; Bostrom, L.L.; Knabb, R.M.; Wong, P.C.; Wright, M.R.; Wexler, R.R., *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 685. c/ Morishita, W.; Sastry, B.R., *Neuroscience*, **1995**, *68*, 1127.
[6] Kozikowski, A.P., *Ac. Chem. Res.*, **1984**,*17*,410
[7] Bennani, A.K; Soufiaoui, M.; Kerbal, A.; Fkih Tetouani, S; Bitit, N., *Tetrahedron*, **1995**, *51*,10923.
[8] Baba, N.; Soufiaoui, M., *Tetrahedron Lett.*, **1990**, *31*, 1709.
[9] Soufioui, M.; Syassi, B.; Daou, B.; Baba, N., *Tetrahedron Lett.*, **1991**, *32*, 3699.
[10] Bougrin, K.; Soufiaoui, M.; Loupy, A.; Jacquault, P., *New J. Chem.*,**1995**, *19*, 213.
[11] Syassi, B.; Bougrin, K.; Soufiaoui, M., *Tetrahedron Lett.*, **1997**, *38*, 8855.
[12] Liu, K.C; Shelton, B.R.; Howwe, R.K., *J. Org. Chem.*,**1980**, *45*, 3916.
[13] M'Sadek, M; Rammah, M.; Schmitt, G.; Vebrel, J., *Bull. Soc. Chim. Belg.*, **1992**, *101*, 323.
[14] a/ Shawali, A.S; Farag, A.M; Algharib, M.S.; Abar, H.A.; *J. Chem. Res. (S)*,**1993**, 80. b/ Argyropoulou, E.C.; Argypulos, N.G.; Thessaloui, K.E., *J. Chem. Res. (S)*, **1990**, 202. c/ Chekti, R.; Soufiaoui, M.; Toupet, L., *Bull. Soc. Chim. Belg.*, **1991**, *100*, 153. d/ Mishriky, N.; Asaad, F. M.; Ibrahim, Y. A.; Girgis, A. S., *J. Chem. Res. (M)*, **1997**, *12*, 2758.
[15] a/ Berlan, J., *Rad. Phys. Chem.*, **1995**, *45*, 581. b/ Loupy, A.; Pigeon, P.; Ramdani, M., *Tetrahedron*, **1996**, *52*, 6705. c/ Michaud, D.; Texier-Boullet, F.; Hamelin, J., Tetrahedron Lett., **1997**, *38*, 7563. d/ Loupy, A.; Régnier, S., *Tetrahedron Lett.*, **1999**, *40*, 6221. e/ Vidal, T.; Petit, A.; Loupy, A.; Gedye, R.N., *Tetrahedron*, **2000**, *56*, 5473. f/ Bougrin, K.; . Loupy, A.; Petit, A.; Daou, B.; Soufiaoui, M., *Tetrahedron*, **2001**, *57*, 163. g/ Rissafi, B.; Rachiqi, N.; El Louzi, A.;Loupy, A.; Petit A.; Fkih-Tétouani, S., *Tetrahedron*, **2001**, *57*, 2761.