NOVEL SYNTHESIS OF 1,2,4-OXADIAZOLES BY CONDENSATION OF ARYLAMIDOXIMES WITH *N*-SUBSTITUTED IMINOETHERS

Anis Romdhane, Rafik Gharbi and Zine Mighri*

Laboratoire de Chimie des Substances Naturelles et de Synthèse Organique.
Faculte des Sciences de Monastir - 5000, Monastir, Tunisia.

Abstract: A new efficient route to 3,5-disubstituted-1,2,4-oxadiazoles **4a-j** has been performed *via* the one-step reaction between arylamidoximes **1a-e** and *N*-substituted iminoethers **2a-c**. The structures of compounds **4** have been elucidated by mass spectrometry, infrared and ^{1}H, ^{13}C NMR measurements.

Keywords: arylamidoximes, *N*-substituted iminoethers, 1,2,4-oxadiazoles.

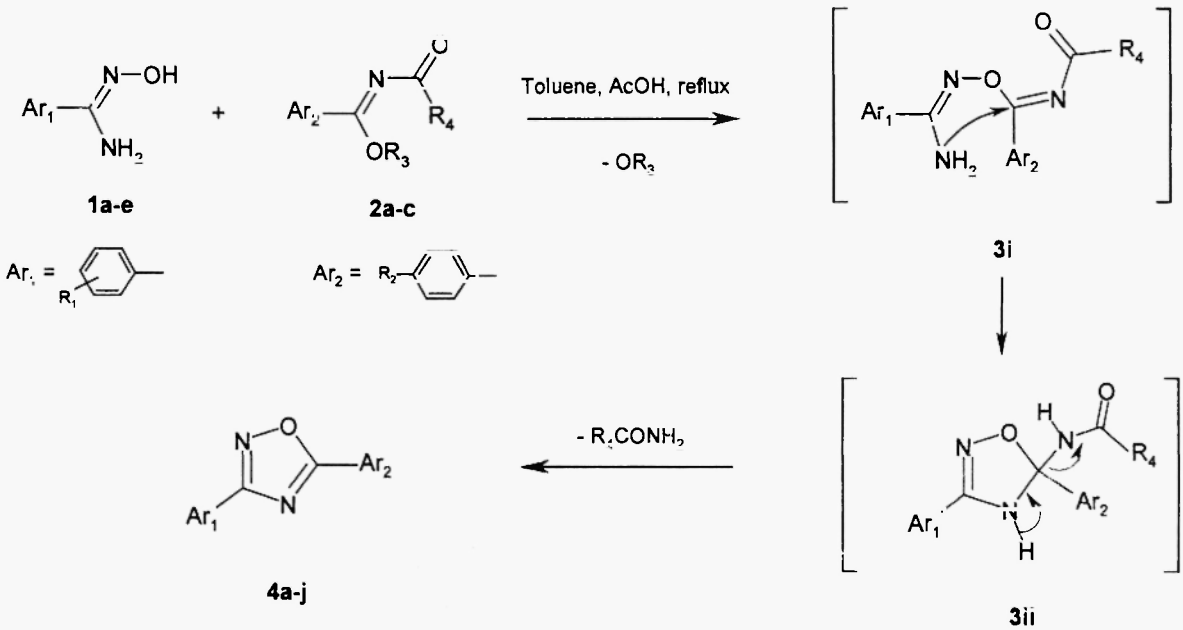
Introduction

Since the discovery of their applications as pharmaceuticals, oxadiazoles have been receiving a growing interest (1). Particularly, the synthesis of 1,2,4-oxadiazoles derivatives represents an increasing valuable goal in view of their large range of applications as analgesics (2), anti-inflammatory (3), hypertensives, bronchodilatory and vasodilatory agents (4). To this aim, several publications have been reported for the synthesis of these compounds (5-7) and among these synthetic methods; the condensation of arylamidoximes with appropriate electrophiles represents one of the most useful route to such five membered-ring heterocycles (8,9). Tiemann *et al* first reported, the preparation of a series of 1,2,4-oxadiazoles from benzotrichloride and benzamidoxime (10). Another but, lengthier, route was published by Belen'kii *et al* and involved the reaction of areneamidoximes and trichloromethylarenes (11). More recently, Russian authors realised the preparation of 1,2,4,-oxadiazoles derivatives through the trifluoroacetylation of *o*-vinylamidoximes with trifluoroacetic anhydride in pyridine (12).

As a contribution to the search of efficient methodologies for the synthesis of 1,2,4-oxadiazole and in a continuation of our studies on the preparation of heterocyclic compounds using iminoethers as starting reagents (13), we report here a novel one-step synthesis of 3,5-disubstituted-1,2,4-oxadiazoles **4a-j** by condensation of arylamidoximes **1a-e** with *N*-substituted iminoethers **2a-c**.

Results and discussion

Arylamidoximes **1** constitute a class of compounds which are highly reactive towards electrophiles species such as nitriles (8) or aldehydes (9) and have been at several times used as efficacious synthon precursor to many five-membered heterocycles (10-12). For this purpose we planned and succeeded in the preparation of a series of 3,5-disubstituted-1,2,4-oxadiazoles **4a-j** from arylamidoximes **1a-e** and *N*-substituted iminoethers **2a-c**. Our trials to optimise the experimental conditions showed that the best yields were reached on heating equimolar amounts of reactants **1** and **2** in dry toluene in the presence of few drops of acetic acid as catalyst. Under these experimental conditions, the reaction progress monitored by thin layer chromatography (petroleum ether-ethyl acetate, 8:2) revealed in all cases the formation of a single products which was, on the basis of its spectral data, assigned as the expected 3,5-diaryl-1,2,4-oxadiazoles **4** (scheme 1).



1	R_1
a	H
b	4-Me
c	4-NO_2
d	2-Cl
b	4-Cl

2	R_2	R_3	R_4
a	H	Me	Me
b	Me	Et	Me
c	H	Et	NHPh

4	a	b	c	d	e	f	g	h	i	j
R_1	H	H	4-Me	4-Me	4-Cl	4-Cl	4-NO_2	4-NO_2	2-Cl	2-Cl
R_2	H	Me	H	Me	H	Me	H	Me	H	Me

Scheme 1: Synthetic pathway for compounds **4a-j**

Mass spectra provided correct molecular peak [$M^{+\cdot}$] for all the examined compounds and their infrared spectra showed essentially an absorption band at 1630-1660 cm^{-1} characteristic of the oxadiazole ring C=N vibration [14]. ^1H NMR spectra of derivative **4a-j** exhibited sets of signals relative to aromatic and alkyl groups protons for which chemical shifts and multiplicities were in good agreement with the proposed structure . Additional proofs for the suggested structure arised from the ^{13}C data which are listed in table 1. Particularly the high shift-values attributed to the quaternary carbons C_3 and C_5 (166.4-169.7 ppm and 175.8-176.8 ppm, respectively) agree with the strong deshielding effects caused by nitrogens and oxygens proximities; this confirms the proposed regiochemistry and is in accordance of anteriorly described 1,2,4-oxadiazoles (1).

Table 1 : ^{13}C chemical shifts for compounds **4a-j**

Comp. /δC(ppm)	$\underline{C}H_3$ (R_1)	$\underline{C}H_3$ (R_2)	C_3	C_5	$C_{arom.}$
4a	-	-	166.4	176.1	124.7 - 133.2
4b	-	21.7	168.8	175.8	121.5 - 143.5
4c	21.9	-	169.4	175.9	124.5 - 141.9
4d	21.9	22.1	169.7	176.3	122.3 - 142.3
4e	-	-	168.5	176.2	124.5 - 137.7
4f	-	22.1	168.4	176.4	121.7 - 144.0
4g	-	-	167.8	176.8	124.1 - 149.8
4h	-	21.8	167.3	176.6	121.1 - 149.4
4i	-	-	168.0	176.2	112.3 - 157.5
4j	-	22.1	168.3	176.4	115.1 - 158.6

From a mechanistic point of view, the reaction process is assumed to follow a two-steps pathway, thus according to previous studies relative to the condensation of amidoximes with electrophiles (11,15) the reaction first proceeded by the addition of arylaldoximes oxygen atom on the iminoethers C=N double bond and led to intermediate **3i**, which was readily cyclised into **3ii** through a nucleophilic attack of the free NH_2 group at imidic carbon. Hetero-aromatisation of **3ii** took then place *via* a *1,3*-proton shift with loss of amide molecule to afford the final isolable 1,2,4-oxadiazoles **4**.

Conclusion

Since the condensation of arylamidoximes **1** with a variety of electrophilic species have found wide-spread uses for the synthesis of various five-membered heterocycles incorporating the N-C=N-O unit (8-9), the one-step synthesis we have described above illustrates a simple and efficient new method for the preparation of 3,5-diaryl-1,2,4-oxadiazoles **4** in good yield *via* condensation of **1** with *N*-substituted iminoethers **2**.

Experimental

Melting points were taken on a Buchi-510 capillary melting point apparatus. Infrared spectra (potassium bromide) were run on a Perkin-elmer IR-197 infrared spectrometer. ^{1}H and ^{13}C nmr spectra were recorded on a Brüker spectrometer AC-300 using $CDCl_3$ as solvent. Mass spectra were obtained with an Automass Multi Thermo Finnigan (electron impact mode, 70 eV) spectrometer. All the reactions were followed by TLC using aluminium sheets of Merck silica gel 60 F_{254}, 0.2 mm. Starting materials **1** and **2** were prepared according to the litterature (16,17).

General Procedure for the preparation of 3,5-disubstituted-1,2,4-oxadiazoles 4:

To a stirred solution of arylamidoximes **1** (1mmol) and *N*-substituted iminoether **2** (1.2 mmol), in dry toluene (15 mL), we added a catalytic amount of acetic acid and the mixture was heated under reflux. A TLC control showed that the reaction was completed after an hour, the solvent was then removed *in vacuo* and the obtained crude purified by chromatography on a silica gel column using petroleum ether-ethyl acetate (8:2) to give oxadiazoles **4a-j** in good yield. All compounds **4** were obtained as colourless crystals, only the nitro derivative which is yellow.

3,5-diphenyl-[1,2,4]oxadiazole 4a : (yield = 75%); mp: 99 °C; IR: $\nu_{C=N}$ = 1638 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm): 7.35 (d, $2H_{arom.}$, J = 7.8 Hz), 7.52 (m, 3 H_{arom}), 8.12 (d, $2H_{arom.}$, J = 8.4 Hz), 8.19 (m, 3H); IE m/z (rel. Int.%) 222 (M^+) (66), 119 (100), 103 (11), 91 (26), 77 (29), 64 (20), 51 (29).

3-(4-methyl)phenyl-5-phenyl-[1,2,4]oxadiazole 4b : (yield = 76%); mp: 123 °C; IR: $\nu_{C=N}$ = 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm): 2.35 (s, 3H), 7.31 (d, 2 $H_{arom.}$, J = 7.8 Hz), 7.45 (m, 3 H_{arom}), 8.1 (m, 2 H_{arom}), 8.15 (d, 2 $H_{arom.}$, J – 7.8 Hz); IE m/z (rel. Int.%) 236 ($M^{+\cdot}$) (80), 119 (100), 103 (9), 91 (29), 77 (12), 63 (14), 51 (10).

5-(4-mehtyl)phenyl-3-phenyl-[1,2,4]oxadiazole 4c : (yield = 80%); mp : 143 °C; IR: $\nu_{C=N}$ = 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 2.46 (s, 3H), 7.36 (d, 2 $H_{arom.}$, *J* = 7.8 Hz), 7.55 (m, 3 $H_{arom.}$), 8.0 (m, 2 $H_{arom.}$), 8.12 (d, 2 $H_{arom.}$, *J* = 8.1 Hz), IE m/z (rel. Int.%) 236 (M^+) (80), 119 (100), 103 (9), 91 (29), 77 (12), 63 (14 %), 51 (10).

3,5-bis(4-mehtyl)phenyl-[1,2,4]oxadiazole 4d : (yield = 78%); mp: 122 °C ; IR: $\nu_{C=N}$ = 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm) 2.43 (s, 3H), 2.45 (s, 3H), 7.32 (d, 2 $H_{arom.}$, *J* = 8.1 Hz), 7.36 (d, 2 $H_{arom.}$, *J* = 8.4 Hz), 8.7 (d, 2 $H_{arom.}$, *J* = 8.1 Hz), 8.12 (d, 2 $H_{arom.}$, *J* = 8.4 Hz); IE m/z (rel. Int.%) 250 ($M^{+\cdot}$) (60), 133 (100), 119 (31), 103 (29), 91 (24), 77 (19), 65 (20), 51 (7).

3-(4-chloro)phenyl-3-phenyl-[1,2,4]oxadiazole 4e : (yield = 82%); mp:135 °C; IR: $\nu_{C=N}$ = 1648 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 7.4 (m, 5 $H_{arom.}$), 7.9 (d, 2 $H_{arom.}$, *J* = 8.1 Hz), 8.1 (d, 2 $H_{arom.}$, *J* = 8.1 Hz), IE m/z (rel. Int.%) 256 ($M^{+\cdot}$) (62), 153 (100), 137 (7), 125 (19), 103 (11), 90 (29), 77 (34), 63(19), 51 (30).

3-(4-chloro)phenyl-5-(4-methyl)phenyl-[1,2,4]oxadiazole 4f : (yield = 83%); mp: 184 °C; IR: $\nu_{C=N}$ = 1651 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 2.3 (s, 3H), δ 7.36 (d, 2 $H_{arom.}$, *J* = 7.8 Hz), 7.5 (d, 2 $H_{arom.}$, *J* = 8.1 Hz), 8.1 (m, 4 $H_{arom.}$); IE m/z (rel. Int.%) 270 ($M^{+\cdot}$) (83), 153 (100), 125 (15), 116 (10), 102 (9), 90 (30), 75 (12), 65 (16), 51 (10).

3-(4-nitro)phenyl-5-phenyl-[1,2,4]oxadiazole 4g : (yield = 87%); mp: 127 °C; IR: $\nu_{C=N}$ = 1650 cm^{-1} ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 7.35 (d, 2 $H_{arom.}$, *J* = 8.4 Hz), 8.10 (d, 2 $H_{arom.}$, *J* = 8.4 Hz), 8.4 (m, 5 $H_{arom.}$); IE m/z (rel. Int.%) 267 ($M^{+\cdot}$) (100), 164 (60), 134 (28), 105 (23), 88 (24), 77 (40), 62 (12), 51 (22).

5-(4-methyl)phenyl-3-(4-nitro)phenyl-[1,2,4]oxadiazole 4h : (yield = 73%); mp: 146 °C; IR: $\nu_{C=N}$ = 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 2.39 (s, 3H), 7.25 (d, 2 $H_{arom.}$, *J* = 8.4 Hz), 8.0 (d, 2 $H_{arom.}$, *J* = 8.4 Hz), 8.28 (m, 4 $H_{arom.}$); IE m/z (rel. Int.%) 281 (M^+) (60), 164 (11), 117 (100), 91 (37), 77 (12), 65 (23), 51 (12).

3-(2-chloro)phenyl-5-phenyl-[1,2,4]oxadiazole 4i : (yield = 77%); mp: 195 °C; IR: $\nu_{C=N}$ = 1656 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 7.35 (m, 2 $H_{arom.}$), 7.5 (m, 4 $H_{arom.}$), 7.93 (m, 1$H_{arom.}$), 8.14 (m, 2 $H_{arom.}$); IE m/z (rel. Int.%) 256 ($M^{+\cdot}$) (57), 153 (100), 125 (10), 105 (16), 90 (40), 77 (45), 63 (23), 51 (38).

3-(2-chloro)phenyl-5-(4-methyl)phenyl-[1,2,4]oxadiazole 4j : (yield = 75%); mp: 195 °C; IR: $\nu_{C=N}$ = 1652 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 2.5 (s, 3H), 7.39 (d, 2 H_{arom}, J = 8.4 Hz), 7.46 (m, 2 H_{arom}), 7.6 (m, 1H_{arom}), 8.05 (m, 1H_{arom}), 8.15 (d, 2 H_{arom}, J = 8.4 Hz); IE m/z (rel. Int.%) 270 (M^+) (76), 153 (100), 119 (15), 102 (10), 90 (30), 77 (10), 65 (17), 51 (9).

References

1 W. D. Ma, L. H. Zhang, Y. Lu, F. Guo and Q. T. Zheng, *Tetrahedron:Asymmetry*, **11**, 1527-1536, (2000).

2 R. M. Srivastava, G. M. Seabra, *J. Braz. Chem. Soc.*, **8(4)**, 397-405, (1997).

3 R. M. Srivastava, L. P. F. De Morais, M. T. J. A. Catanho, G. M. L. De Souza, G. M. Sebra, A. M. Simas, M. A. L. Rodrigues, *Heterocycl. Commun.*, **6(1)**, 41-48, (2000).

4 C. Fauran, H. Bergeron, G. Raynaud, J. Thomas and J. Eberle, French Demande, 2,262,513 (CI. A61K, CO7D), 26 Sept., (1975), *Appl.* 74 07, 002, 01 March, 1974, *Chem. Abtr.*, **84**, P121843v, (1976).

5 P. Rajagopalan, ***Tetrahedron Lett.***, 311-312, (1969).

6 Y. Yang, F. Hiromi, O. Masatomi, E. Shoji, *Synthesis*, 498-500, (1995).

7 R. M. Srivastava, L. P. F. De Morais, M. T. J. A. Catanho, G. M. L. De Souza, G. M. Sebra, A. M. Simas, M. A. L. Rodrigues, *Heterocycl. Commun.*, **6(1)**, 41-48, (2000).

8 V. N. Yarovenko, V. K. Taralashvili, I. V. Zavarzin, M. M. Krayushkin, *Tetrahedron*, **46(11)**, 3941-3952, (1990).

9 D. Korbonits, P. Kolonits, *Acta Chim. Hung.*, **127**(6), 795-802, (1990).

10 F. Tiemann, P. Krüger, *Ber.*, **17**, 1685-1698, (1884).

11 L. I. Belen'kii, D. B. Brokhovetskii, M. M. Krayushkin, N. D. Zelinsky, *Tetrahedron*, **46(5)**, 1659-1668, (1990).

12 A. T. Boris, Y. S. Elena, M. V. Alexander, I. M. Al'bina, B. Z. Alexey, V. M. Ludmila, G. G. Alexander, H. Jochemann, A. Jan-Dirk, *Synthesis*, **16**, 2427-2430, (2000).

13 A. Harizi, A. Romdhane, Z. Mighri, *J. Tetrahedron Lett.*, **41**, 5833-5836, (2000).

14 A. Terzis and D. Mentzafos, *J. Heterocyclic Chem.*, **27**, 1425-1432, (1990).

15 J. Stieglitz, *Ber.*, **22**, 3148, (1889).

16 A. Pinner; in " Die imidoather und ihre derivative " Openheim Berlin, (1892).

17 B. D. Repke, P. H. Albrecht, G. J. Moffat, *J. Org. Chem.*, **40**, 2481-2487, (1975).

Received on November 24, 2003.