Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2010, **20**, 50–51

Mendeleev Communications

An efficient one-pot synthesis of 3-aryl-1,2,4-oxadiazol-5-amines under solvent-free conditions

Mehdi Adib,*[a] Sharareh Bagherzadeh,[a] Mohammad Mahdavi[a] and Hamid R. Bijanzadeh*[b]

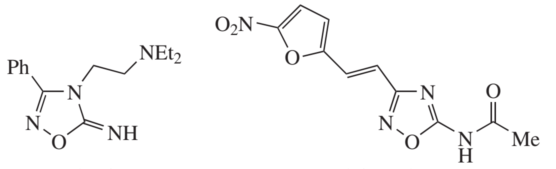
[a] *School of Chemistry, University College of Science, University of Tehran, PO Box 14155-6455, Tehran, Iran. Fax: +98 21 6649 5291; e-mail: madib@khayam.ut.ac.ir*
[b] *Department of Chemistry, Tarbiat Modarres University, PO Box 14115-175, Tehran, Iran*

DOI: 10.1016/j.mencom.2010.01.019

The *in situ* prepared amidoximes from the reaction between nitriles and hydroxylamine are condensed with carbodiimides in the presence of molecular sieves under solvent-free conditions to produce the title compounds in excellent yields.

Progress in solvent-free reactions is gaining significance due to their high efficiency, operational simplicity and environmentally benign processes.[1,2]

1,2,4-Oxadiazoles are of interest because of the occurrence of their saturated and partially saturated derivatives in biologically active compounds.[3,4] 1,2,4-Oxadiazoles have recently received considerable attention as heterocyclic amide and ester bioisosteres.[5,6] 1,2,4-Oxadiazol-5-amines have been employed as pharmaceutical agents. The drug imolamine (Figure 1) has a papaverine-like effect on animals and has found application in the treatment of *angina pectoris*.[7] The drug fulvinazole (Figure 1) is an antischistosomal agent; however, it is carcinogenic in mice.[8]



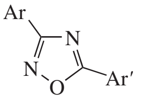
Imolamine Fulvinazole

Figure 1 Examples of pharmaceutically important 1,2,4-oxadiazol-5-amines.

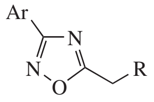
The following general synthetic methods have been reported for the preparation of 1,2,4-oxadiazole ring systems: (i) condensation of amidoximes with derivatives of carboxylic acids to give *O*-acylamidoximes which are cyclized to 1,2,4-oxadiazoles; (ii) cyclization of *N*-acylamidoximes; (iii) 1,3-dipolar cycloaddition of nitrile oxides to nitriles; (iv) electrocyclic ring closure of nitrenoids; and (v) oxidation of 4,5-dihydro-1,2,4-oxadiazoles.[3,4]

Tabei *et. al.*[9] reported that refluxing a mixture of benzamidoxime and dicyclohexyl carbodiimide in chloroform for 4 h led to 5-cyclohexylamino-3-phenyl-1,2,4-oxadiazole, *N,N′,N″*-tricyclohexylguanidine and *N,N′*-dicyclohexylurea in 52, 40 and 5.4% yields, respectively. However, this procedure has some drawbacks such as low yield of the obtained 1,2,4-oxadiazole, formation of by-products and use of environmentally toxic media. Fylaktakidou *et. al.*[10] modified this reaction by heating a mixture of an amidoxime and a carbodiimide in DMF or in boiling toluene, which increased the yields of the reactions. However, this procedure suffers from several drawbacks such as long reaction times (4–24 h), in some cases fairly low yields of the products (14–97%) and use of environmentally toxic solvents. Furthermore, in both procedures, amidoximes have to be synthesized first, so the methods are relatively time-consuming and expensive.

Recently,[11] we described an efficient synthesis of 3,5-diaryl-1,2,4-oxadiazoles **1** *via* a one-pot reaction between nitriles, hydroxylamine and aldehydes under microwave irradiation and solvent-free conditions. We have also developed an efficient synthesis of 3-aryl-5-alkyl-1,2,4-oxadiazoles **2** *via* a one-pot reaction between nitriles, hydroxylamine and Meldrum's acids under microwave irradiation and solvent-free conditions.[12]



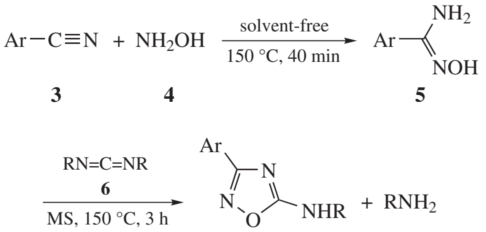
1



2

Knowing the pharmacological importance of 1,2,4-oxadiazole ring systems, herein we report a facile synthesis of 3-aryl-1,2,4-oxadiazol-5-amines. Thus, arylnitriles **3** and hydroxylamine **4** are converted *in situ* to amidoximes **5**. Next, the amidoximes are condensed with carbodiimides **6** in the presence of molecular sieves under solvent-free conditions to produce 3-aryl-1,2,4-oxadiazol-5-amines **7** in 85–93% yields (Scheme 1).

When the reaction was performed using equivalent ratios of the nitrile, hydroxylamine and carbodiimide, ^{1}H NMR analysis



7a–l

	Ar	R	Isolated yield (%)
7a	Ph	Cyclohexyl	92
7b	Ph	Isopropyl	89
7c	4-MeC_6H_4	Cyclohexyl	91
7d	4-MeC_6H_4	Isopropyl	90
7e	4-FC_6H_4	Cyclohexyl	90
7f	4-FC_6H_4	Isopropyl	91
7g	4-MeOC_6H_4	Cyclohexyl	89
7h	4-MeOC_6H_4	Isopropyl	87
7i	4-ClC_6H_4	Cyclohexyl	93
7j	4-ClC_6H_4	Isopropyl	92
7k	3-ClC_6H_4	Cyclohexyl	86
7l	3-ClC_6H_4	Isopropyl	85

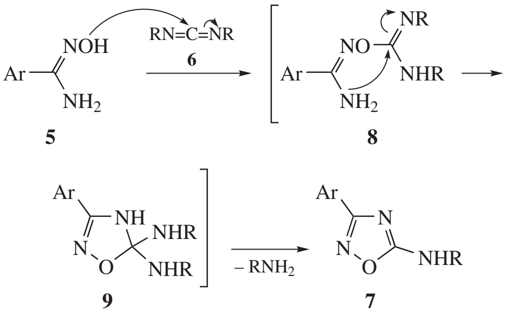
Scheme 1

of the reaction mixture indicated the formation of the corresponding 3-aryl-1,2,4-oxadiazol-5-amine in nearly 45–50% yield. Almost half of *in situ* prepared amidoxime **5** was recovered unreacted at the end of the reaction and half of the added carbodiimide reacted with the water present in the used hydroxylamine hydrate and converted to the corresponding *N*,*N*′-dialkylurea. The best results were obtained when the reactions were carried out in the presence of molecular sieves (Scheme 1).

The reactions were carried out by heating a mixture of the nitrile and hydroxylamine under solvent-free conditions. After nearly complete conversion to amidoxime **5**, as indicated by TLC monitoring, molecular sieves were added to the reaction mixture and stirred for 20 min at room temperature. Then, the carbodiimide was added to the reaction mixture, which was heated for a further 3 h. ^{1}H NMR analysis of the reaction mixtures clearly indicated the formation of 1,2,4-oxadiazoles **7** in excellent yields. Any product other than **7** could not be detected by NMR spectroscopy.[†]

The isolated 3-aryl-1,2,4-oxadiazol-5-amines **7a–l** were characterized on the basis of IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The mass spectrum of **7f** displayed the molecular ion (M$^+$) peak at *m*/*z* 221, which was consistent with the product structure. The IR spectrum of **7f** showed an absorption band at 3230 cm^{-1} indicating the presence of amine functionality. The ^{1}H NMR spectrum of **7f** exhibited characteristic signals with appropriate chemical shifts and coupling constants for seven H atoms of the isopropyl group (δ 1.26 and 3.98 ppm, J 6.5 Hz) and four H atoms of the aryl substituent (δ 7.11 and 7.98 ppm, $^3J_{\mathrm{FH}}$ 8.7 Hz, $^4J_{\mathrm{FH}}$ 5.4 Hz and $^3J_{\mathrm{HH}}$ 8.7 Hz). A fairly sharp doublet (δ 5.84 ppm, J 6.9 Hz) was observed for the NH group due to coupling with the adjacent C–H of the isopropyl group. In the ^{1}H decoupled ^{13}C NMR spectrum of **7f**, the isopropyl carbon atoms resonated at δ 22.87 and 46.25 ppm, and the signals of four carbon atoms of the aryl substituent were seen at appropriate chemical shifts and coupling constants along with two characteristic signals at δ 167.56 and 170.70 ppm arising from two carbon atoms of the 1,2,4-oxadiazole ring.[†]

Mechanistically, it is reasonable to assume that *in situ* prepared amidoxime **5** initially attacks carbodiimide **6** to give isourea intermediate **8**. This intermediate is probably cyclized to 4,5-dihydro-1,2,4-oxadiazole intermediate **9**. Isolated 1,2,4-oxadiazole **7** is finally formed by removal of an amine molecule from **9** under the reaction conditions (Scheme 2).



Scheme 2

In conclusion, we have developed an efficient one-pot reaction for the preparation of 3-aryl-1,2,4-oxadiazol-5-amines of potential synthetic and pharmacological interest.

This study was supported by the Research Council of the University of Tehran (research project no. 6102036/1/03).

References

1 *Solvent-free Organic Synthesis*, 1st edn., ed. K. Tanaka, Wiley-VCH, Weinheim, 2004.

2 K. Tanaka and F. Toda, *Chem. Rev.*, 2000, **100**, 1025.

3 J. C. Jochims, in *Comprehensive Heterocyclic Chemistry II*, eds. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, London, 1996, vol. 4, ch. 4, pp. 179–228 and references therein.

4 K. Hemming, in *Comprehensive Heterocyclic Chemistry III*, eds. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier Science, Oxford, 2008, vol. 5, ch. 4, pp. 243–309 and references therein.

5 C. B. Vu, E. G. Corpuz, T. J. Merry, S. G. Pradeepan, C. Bartlett, R. S. Bohacek, M. C. Botfield, B. A. Lynch, I. A. MacNeil, M. K. Ram, M. R. van Schravendijk, S. Violette and T. K. Sawyer, *J. Med. Chem.*, 1999, **42**, 4088.

6 J. W. Clithirow, P. Beswick, W. J. Irving, D. I. C. Scopes, J. C. Barnes, J. Clapham, J. D. Brown, D. J. Evans and A. G. Hayes, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 833.

7 I. M. Coupar, A. Hedges, H. L. Metcalfe and P. Turner, *J. Pharm. Pharmacol.*, 1969, **21**, 474.

8 H. A. Dunsford, C. H. Keysser, P. M. Dolan, J. L. Seed and E. Bueding, *J. Natl. Cancer Inst.*, 1984, **73**, 151 (*Chem. Abstr.*, 1984, **101**, 143603p).

9 E. Kawashima and K. Tabei, *J. Heterocycl. Chem.*, 1986, **23**, 1657.

10 M. Ispikoudi, K. E. Litinas and K. C. Fylaktakidou, *Heterocycles*, 2008, 75, 1321.

11 M. Adib, A. Haghighat Jahromi, N. Tavoosi, M. Mahdavi and H. R. Bijanzadeh, *Tetrahedron Lett.*, 2006, **47**, 2965.

12 M. Adib, M. Mahdavi, N. Mahmoodi, H. Pirelahi and H. R. Bijanzadeh, *Synlett*, 2006, 1765.

[†] The procedure for the preparation of *N*-cyclohexyl-3-(4-methylphenyl)-1,2,4-oxadiazol-5-amine **7c** is described as an example. A mixture of 4-methylbenzonitrile (0.23 g, 2 mmol) and hydroxylamine 50% (0.13 g, 2 mmol) was stirred at 150 °C for 40 min. After nearly complete conversion to the corresponding amidoxime as was indicated by TLC monitoring, 3 Å molecular sieves (1.1 g) were added to the reaction mixture and stirred for 20 min at room temperature. Then dicyclohexyl carbodiimide (0.41 g, 2 mmol) was added to the reaction mixture, which was additionally stirred for 3 h at 150 °C. After cooling to room temperature, the residue was purified by column chromatography using *n*-hexane–EtOAc (4:1) as an eluent. The solvent was removed and the product was obtained as colourless crystals, mp 112 °C, yield 0.47 g, 91%. IR (KBr, ν_{max}/cm^{-1}): 3250 (NH), 1649, 1612, 1578, 1499, 1463, 1450, 1416, 1389, 1300, 1182, 1005, 1010, 827, 766. ^{1}H NMR (500.1 MHz, $\mathrm{CDCl_3}$) δ: 1.15–2.09 [m, 10H, $\mathrm{CH(C}H_2)_5$], 2.39 (s, 3H, Me), 3.64–3.68 [m, 1H, $\mathrm{C}H\mathrm{(CH_2)_5}$], 5.59 (d, 1H, NH, J 7.5 Hz), 7.24 (d, 2H, 2CH, J 8.0 Hz), 7.88 (d, 2H, 2CH, J 8.0 Hz). ^{13}C NMR (125.8 MHz, $\mathrm{CDCl_3}$) δ: 21.49 (Me), 24.62, 25.48 and 33.21 ($\mathrm{3CH_2}$), 52.84 (NHCH), 124.95 (C), 127.18 and 129.27 (2CH), 140.88 (C), 132.04 (C), 168.44 (NCN), 170.58 (NCO). EI-MS, *m*/*z* (%): 257 (M$^+$, 14), 241 (7), 228 (11), 202 (21), 176 (37), 161 (23), 149 (31), 142 (26), 132 (21), 117 (23), 76 (54), 70 (38), 64 (92), 59 (100). Found (%): C, 69.9; H, 7.5; N, 16.2. Calc. for $\mathrm{C_{15}H_{19}N_3O}$ (257.34) (%): C, 70.01; H, 7.44; N, 16.33.

3-(4-Fluorophenyl)-N-*isopropl-1,2,4-oxadiazol-5-amine* **7f**: colourless crystals, mp 136 °C, yield 0.40 g, 91%. IR (KBr, ν_{max}/cm^{-1}): 3230 (NH), 1630, 1600, 1545, 1481, 1421, 1381, 1344, 1254, 1229, 1151, 847, 768. ^{1}H NMR (500.1 MHz, $\mathrm{CDCl_3}$) δ: 1.26 (d, 6H, $\mathrm{CH}Me_2$, J 6.5 Hz), 3.98 (octet, 1H, $\mathrm{C}H\mathrm{Me_2}$, J 6.5 Hz), 5.84 (d, 1H, NH, J 6.9 Hz), 7.11 (dd, 2H, 2CH, $^3J_{\mathrm{FH}}$ 8.7 Hz, $^3J_{\mathrm{HH}}$ 8.7 Hz), 7.98 (dd, 2H, 2CH, $^4J_{\mathrm{FH}}$ 5.4 Hz, $^3J_{\mathrm{HH}}$ 8.7 Hz). ^{13}C NMR (125.8 MHz, $\mathrm{CDCl_3}$) δ: 22.87 ($\mathrm{CH}Me_2$), 46.25 ($C\mathrm{HMe_2}$), 115.69 (d, CH, $^2J_{\mathrm{FC}}$ 22.0 Hz), 123.93 (d, C, $^4J_{\mathrm{FC}}$ 3.1 Hz), 129.35 (d, CH, $^3J_{\mathrm{FC}}$ 8.6 Hz), 164.33 (d, C–F, $^1J_{\mathrm{FC}}$ 250.7 Hz), 167.56 (NCN), 170.70 (NCO). EI-MS, *m*/*z* (%): 221 (M$^+$, 83), 206 (14), 179 (48), 163 (100), 149 (12), 136 (63), 121 (40), 109 (25), 95 (29), 75 (21), 57 (19), 43 (59). Found (%): C, 59.5; H, 5.6; N, 18.7. Calc for $\mathrm{C_{11}H_{12}FN_3O}$ (221.23) (%): C, 59.72; H, 5.47; N, 18.99.

Received: 24th August 2009; Com. 09/3383