1,3-dipolar cycloaddition of arylnitrile oxides to imidates: Synthesis of novel 1,2,4-oxadiazole derivatives

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Abstract: A series of 1,2,4-oxadiazole derivatives were prepared via a 1,3-dipolar cycloaddition reaction of various oximes with imidates. The structures of all the new synthesized compounds have been established by ^{1}H, ^{13}C-NMR and IR spectroscopy, as well as by MS spectral data.

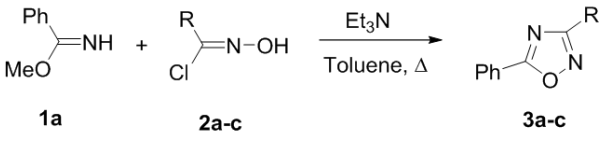
Keywords: 1,3-dipolar cycloaddition, 1,2,4-oxadiazole, imidates, arylnitrile oxides

INTRODUCTION

Heterocyclic compounds are commonly used as pharmacophores which are arranged to provide potent and selective drugs. Five membered rings heterocyclic compounds occurs to be oftenly the servers of the core compounds of many substances which possesses a wide range of interesting biological activities [1]. In fact, the interest 1,2,4-oxadiazole derivatives has increased in recent years as a consequence of their growing significance in both bioactive molecules and materials [2,3]. Indeed, studies have shown that some compounds containing 1,2,4-oxadiazole cores have a broad biological activity spectrum including analgesic [4], anti-asthmatic [5], anti-diabetic [6], anthelmintic [7], diuretic [8], anti-inflammatory [9], antiparasitic [10], anti-HIV [11], and antitumor [12], properties. Briefly, the synthesis of novel 1,2,4-oxadiazole derivatives, and investigation of their chemical properties behavior has accelerated in the last two decades [13,14]. On the other hand, the chemistry of 1,3-dipoles cycloaddition has attracted great interest and application for more than a century [15]. Especially with respect to their ability to undergo cyclization which are key processes in both academic and industrial chemistry [16,17]. Such reactions lead to five-membered rings widely encountered in bioorganic chemistry and benefited from well documented mechanistic and stereo-chemical predictability [18]. In particular, nitrile oxides which undergo efficient [3+2] cycloaddition with imines, can be a convenient access to variously substituted 1,2,4-oxadiazoles [19]. In this context we have investigated the 1.3-dipolar cycloaddition reaction of several oximes with imidates, which afforded 1,2,4-oxadiazoles. We herein report the full details of this study.

RESULTS AND DISCUSSION

The synthetic strategy adopted for the preparation of target compounds is depicted in Schemes 1-3. Dipolarophile **1a** and oximes **2** were subjected to cycloaddition reaction in toluene under reflux in presence of triethylamine. The [3+2] cycloaddition reaction leads to the formation of a series of 1,2,4-oxadiazoles **3.** In order to demonstrate the efficiency and generality of this protocol, we examined the reactions of iminoester and various



1a **2a-c** **3a-c**

Scheme 1. Synthesis of 1, 2, 4-oxadiazoles **3** *via* 1.3-dipolar cycloaddition

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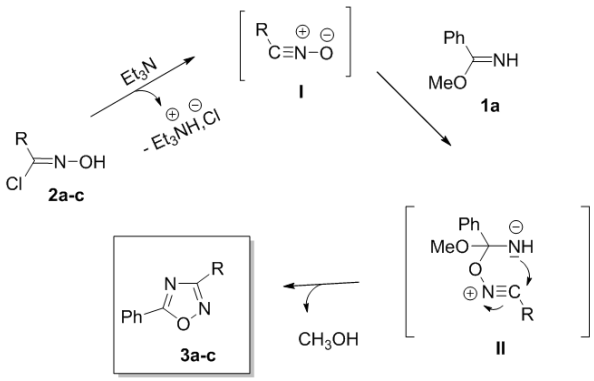
Table I. Substrate scope studies

Entry	R	Yield (%)[a]
a	*p*-CH_3Ph	78
b	*p*-ClPh	74
c	*p*-CH_3OPh	67

[a]Isolated yield.



Scheme 2. Proposed mechanism for the formation of 1,2,4-oxadiazoles **3a-c**

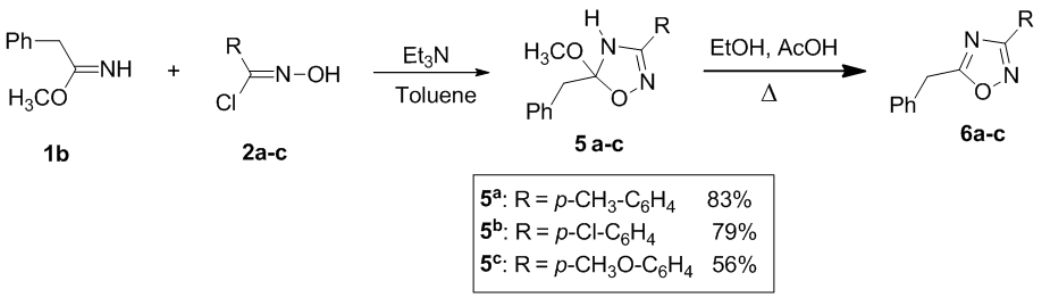
substituted oximes (Table 1). All substrates react to give the corresponding products **3a-c** in moderate to good yields.

A plausible mechanism for the formation of compounds **3a-c** is depicted in (Scheme 2). The reaction was assumed to proceed by the action of triethylamine on the oximes **2a-c** giving rise to arylnitrile oxides **(I)** as intermediates**.** A subsequent nucleophilic attack of the oxygen atom of arylnitrile oxides on the imidic carbon of dipolarophile **1a** led to the formation of intermediate **(II)** which then immediately yielded via an heterocyclization the corresponding 1,2,4-oxadiazoles.

The chemical structure of all the newly synthesized oxadiazoles is in agreement with its spectral data. In the ^{1}H-NMR spectra, we observed essentially the total disappearance of the signal around 3.8 ppm relative to the methoxy group. Moreover, the ^{13}C-NMR analysis confirmed the formation of products **3a-c** and showed the presence of all signals corresponding to the new heterocyclic rings, notably the signal of C=N carbon at 160-170 ppm (see experimental). While, the signals assigned to C=N carbon of imidate **1a** and C=N of oximes **2a-c** appear respectively at 150 and 154 ppm.

The promising results obtained with imidate **1a** as a synthetic entry to fused oxadiazoles prompted us to further investigate the behaviour of methyl-2-phenylacetimidate towards the heterocyclic rings formation in order to obtain new functionalized types of these interesting compounds. Using imidate **1b** as template substrate in the 1,3-dipolar cycloaddition to oximes **2a-c**, employing the same reaction conditions, we found that reaction afforded the desired cycloadducts **5a-c** in agreement with previously reported studies [20]. Treatment of the compounds **5a-c** in refluxing ethanol in the presence of a catalytic amount of acetic acid produced in each case 1,2,4-oxadiazoles **6a-c**, resulting from the elimination of methanol (Scheme 3). This step was monitored by TLC which showed full conversion of **5a-c** to **6a-c**. The IR spectrum of cycloadducts **6a-c** revealed the absence of NH absorption band and the presence of a new absorption band at 1570 cm^{-1} assignable to the imine moiety. Furthermore, in ^{1}H and ^{13}C-NMR spectra, we observed essentially the total disappearance of the signal related to the methoxy group.

In summary, the results of the study described above have led to the development of a simple and virtually general approach to synthesize new 1,2,4-



Scheme 3. Synthesis of the title compounds **6a-c**

Table II. Substrate scope studies of compounds **6a-c**

Entry	R	Yield (%)[a]
a	*p*-CH_3-C_6H_4	72
b	*p*-Cl- C_6H_4	69
c	*p*-CH_3O- C_6H_4	74

[a]Isolated yield.

oxadiazole scaffolds via a 1,3-dipolar cycloaddition reaction of various oximes with imidates. Study of the biological activity of the synthesized compounds is ongoing in our laboratory and will be reported in due course.

EXPERIMENTAL

Melting points were measured with a Kofler hot-staged apparatus and are uncorrected. ^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$, on a Bruker-300 spectrometer. The chemical shifts are reported in ppm relative to TMS (internal reference) for ^{1}H and ^{13}C-NMR. The coupling constants are reported in Hz. For the ^{1}H-NMR, the multiplicities of signals are indicated by the following abbreviations: s: singlet, m: multiplet. Mass spectra were determined on a VOYAGER DE STR spectrometer under MALDI ionization conditions. IR spectra were recorded on a Nicolet IR 200 spectrometer. The progress of the reactions was monitored by thin layer chromatography (TLC). TLC plates (Merck, silica gel 60 F254 0.2 mm 200×200 nm); substances were detected using UV light at 254 nm. All commercially available reagents were used directly without purification unless otherwise stated. All the solvents used in reactions were distilled before hands. The starting materials (iminoesters **1a-b** and oximes **2a-c**) were prepared according to reported procedures [21,22].

1. General procedure for the preparation of cycloadducts 3 and 5.

A magnetically stirred solution of iminoesters **1** (0.5 mmol) and the appropriate oximes **2** (0.5 mmol) in dry toluene was refluxed for 15 min. Et_3N (0.5 mmol) was then added and the stirring of the reaction was continued under reflux for 72 h. After cooling and filtration of triethylamine hydrochloride, the solvent was removed by evaporation at reduced pressure. The residue was chromatographed on a silica gel column, eluting with DCM-EtOAc (7:3). Products were recrystallized from methanol to give the cycloadducts **3a-c** and **5a-c** as yellow solids.

5-Phenyl -3-(p-tolyl)-1, 2, 4-oxadiazole ***(3a)***: Yield: 78%, mp 102 °C. IR (KBr, cm^{-1}): 1618 and 1578 (C=N). ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.35 (s, 3H), 7.10-8.65 (m, 9H_{Ar}). ^{13}C-NMR ($CDCl_3$, 75 MHz): 14.2 (CH_3), 125.1, 127.23, 128.06, 129.76, 132.34, 134.12, 137.3 (C_{Ar}), 168.5, 170.6 (C=N). HRMS (EI): *m/z* calculated for $C_{15}H_{13}N_2O$ $(M+H)^+$: 237.1101, found 237.1310.

3-(4-Chlorophenyl)-5-phenyl-1, 2, 4-oxadiazole ***(3b)*****:** Yield: 74%, mp 104 °C. IR (KBr, cm^{-1}): 1658 and 1568 (C=N). ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.30-8.85 (m, 9H_{Ar}). ^{13}C-NMR ($CDCl_3$, 75 MHz): 128, 127,5, 129.8, 130.3, 133.5, 139.6 (C_{Ar}), 169.7, 171.7 (C=N). HRMS (EI): *m/z* calculated for $C_{14}H_{10}ClN_2O$ $(M+H)^+$: 257.0435, found 257.0519.

3-(4-Methoxyphenyl)-5-phenyl-1, 2, 4-oxadiazole ***(3c)*****:** Yield: 67%, mp 110 °C. IR (KBr, cm^{-1}): 1628 and 1528 (C=N). ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.65 (s, 3H), 7.10-8.65 (m, 9H_{Ar}). ^{13}C-NMR ($CDCl_3$, 75 MHz): 54.2 (OCH_3), 124.6, 125.13, 127.3, 129.8, 136.4, 144.14 (C_{Ar}), 168.5, 170.6 (C=N). HRMS (EI): *m/z* calculated for $C_{15}H_{13}N_2O_2$ $(M+H)^+$: 253.0910; found 253.1020.

5-Benzyl-5-methoxy-3-(p-tolyl)-4,5-dihydro-1,2,4-oxadiazole ***(5a)*****:** Yield: 83%, mp 121 °C. IR (KBr, cm^{-1}) : 3352 (NH) 1638 (C=N. ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.44 (s, 3H), 3.75 (s, 3H), 4.1(s, 2H), 7.13-8.14 (m, 9H_{Ar}). ^{13}C-NMR ($CDCl_3$, 75 MHz): 14.2 (CH_3), 43.9 (CH_2); 57 (OCH_3) 125.2, 127.47, 129.06, 131, 133.11, 138.01 (C_{Ar}), 140.2 (C-NH), 161.54 (C=N).

5-Benzyl-3-(4-chlorophenyl)-5-methoxy-4,5-dihydro-1,2,4-oxadiazole ***(5b)*****:** Yield: 79%, mp 129 °C. IR (KBr, cm^{-1}): 3342 (NH), 1634 (C=N). ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.80 (s, 3H), 4.20 (s, 2H), 7.11-8.15 (m, 9H_{Ar}). ^{13}C-NMR ($CDCl_3$, 75 MHz): 15.1 (CH_3), 45.2 (CH_2), 55.23 (OCH_3), 125.4, 126.9, 128, 130.11, 131.54, 133.72, 134.23 (C_{Ar}), 139.2 (C-NH), 164.3 (C=N).

5-Benzyl-5-methoxy-3-(4-methoxyphenyl)-4,5-dihydro-1,2,4-oxadiazole ***(5c)*****:** Yield: 56%, mp 123 °C. IR (KBr, cm^{-1}): 3333 (NH), 1618 (C=N). ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.73 (s, 3H), 3.75 (s,

3H), 4.22(s, 2H), 7.12-8.15 (m, $9H_{Ar}$), 9.40 (s, NH). ^{13}C-NMR ($CDCl_3$, 75 MHz): 44.9 (CH_2), 52.1 (OCH_3), 125.73, 127.7, 128.6, 129.9, 136.4, 142 (C_{Ar}), 145.2 (C-NH), 165.46 (C=N).

2. Synthesis of compounds 6.

To a well-stirred solution of compounds **5** (0.01 mol) in ethanol (10mL) was added catalytic amount of acetic acid. The reaction mixture was refluxed for 48 h, then allowed to cool to room temperature and the solvent was removed under reduced pressure. Purification of the residue was carried out by flash silica gel chromatography using DCM-EtOAc (3:1) as eluent. Products were recrystallized from methanol to give compounds **6a-c** as yellow solids.

5-Benzyl-3-(p-tolyl)-1,2,4-oxadiazole ***(6a)*****:** Yield: 72%, mp 112 °C. IR (KBr, cm^{-1}): 1688 and 1638 (C=N). ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.44 (s, 3H), 4.51(s, 2H), 7.18-8.12 (m, $9H_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): 14.2 (CH3), 43.9 (CH_2), 124.13, 126.76, 128.56, 130.42, 131.94, 13217, 136.3 (C_{Ar}), 166.2, 170.03 (C=N). HRMS (EI): *m/z* calculated for $C_{16}H_{15}N_2O$ $(M+H)^+$: 251.1119, found 251.1301.

5-Benzyl-3-(4-chlorophenyl)-1,2,4-oxadiazole ***6b)*****:** Yield: 69%, mp 117 °C. IR (KBr, cm^{-1}): 1657 and 1588 (C=N). ^{1}H-NMR ($CDCl_3$, 300 MHz): 4.25 (s, 2H), 7.13-8.15 (m, $9H_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): 43.9 (CH_2), 126.15, 127, 129.32, 131, 133.18, 134.72, 138.23 (C_{Ar}), 160.98, 165.23 (C=N). HRMS (EI): *m/z* calculated for $C_{15}H_{12}ClN_2O$ $(M+H)^+$: 271.0652, found 271.0910.

5-Benzyl-3-(4-methoxyphenyl)-1,2,4-oxadiazole ***(6c)*****:** Yield: 74%, mp 115 °C. IR (KBr, cm^{-1}): 1698 and 1618 (C=N). ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.73 (s, 3H), 4.22 (s, 2H), 7.18-8.25 (m, $9H_{Ar}$), 9.40 (s, NH). ^{13}C-NMR ($CDCl_3$, 75 MHz): 44.9 (CH_2), 52.1 (OCH_3), 127.8, 128.9, 129.2, 130.43, 132.67, 142.98 (C_{Ar}), 163.67, 168.46 (C=N). HRMS (EI): *m/z* calculated for $C_{16}H_{15}N_2O_2$ $(M+H)^+$: 267.1471, found 267.1490.

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REFERENCES

[1] (a) A. Matin, N. Gavande, M. S. Kim, N. X. Yang, N. K. Salam, J. R. Hanrahan, R. H. Roubin, and D. E. Hibbs, *J. Med. Chem.,* **2009**, *52*, 6835. (b) E. M. Priego, J. V. F. D. Kuenzel, A. P. Ijzerman, M. J. Camarasa, M. J. Perez-Perez, *J. Med. Chem.,* **2002**, *45*, 3337.

[2] (a) J. C. Jochims, In Comprehensive Heterocyclic Chemistry II; A. R. Katritzky, C. W. Rees, E. F. V. Scriven, R. C. Storr, Eds.; Pergamon: Oxford, **1996**, Vol. 4, Chapter 4.04, 179. (b) L. A. Kayukova, *J. Pharm. Chem.*, 2005, 39, 539.

[3] P. Paolo Grunanger, P. VitaFinzi, P. In The Chemistry of Heterocyclic Compounds; E. C. Taylor, A. Weissberger, Eds.; John Wiley & Sons: New York, **1991**, Vol. 49, Part 1.

[4] (a) R. Antunes, H. Batista, R. M. Srivastava, G. Thomas, and C. C. Araujo, *Bioorg. Med. Chem. Lett.,* **1998**, *8*, 3071. (b) G. Daidone, D. Raffa, B. Maggio, F. Plescia, V. M. C. Cutuli, N. G. Mangano, A. Caruso, *Arch. Pharm. Pharm. Med. Chem.,* **1999**, *332*, 50.

[5] (a) J. T. Palmer, R. M. Rydzewski, R. V. Mendonca, D. Sperandio, J. R. Spencer, B. L. Hirschbein, J. Lohman, J. Beltman, M. Nguyen, and L. Liu, *Bioorg. Med. Chem. Lett.,* **2006**, *16*, 3434. (b) J. W. H. Watthey, M. Desai, R. Rutledge, and R. Dotson, *J. Med. Chem.,* **1980**, *23*, 690.

[6] (a) J. Xu, L. Wei, R. Mathvink, J. He, Y. J. Park, H. He, B. Leiting, K. A. Lyons, F. Marsilio, R. A. Patel, J. K. Wu, N. A. Thornberry, and A. E. Weber, *Bioorg. Med. Chem. Lett.,* **2005**, *15*, 2533. (b) M. Benltifa, S. Vidal, B. Fenet, M. Msaddek, P. G. Goekjian, J. P. Praly, A. Brunyanszki, T. Docsa, P. Gergely, *Eur. J. Org. Chem.,* **2006**, 4242. (c) S. E. Dahlgren, T. Dalhamn, *Acta Pharmacol. Toxicol.,* **1972**, *31*, 193

[7] (a) R. D. Haugwitz, A. J. Martinez, J. Venslavsky, R. G. Angel, B. V. Maurer, G. A. Jacobs, V. L. Narayanan, L. R. Cruthers, and J. Szanto, *J. Med. Chem.,* **1985**, *28*, 1234. (b) D. M. Cottrell, J. Capers, M. M. Salem, K. DeLuca-Fradley, S. L. Croft, and K. A. Werbovetz, *Bioorg. Med. Chem.,* **2004**, *12*, 2815.

[8] T. Sakamoto, M. D. Cullen, T. L. Hartman, K. M. Watson, R. W. Buckheit, C. Pannecouque, E. De Clercq, and M. Cushman, *J. Med. Chem.,* **2007**, *50*, 3314.

[9] C. B. Vu, E. G. Corpuz, S. G. Pradeepan, S. Violette, C. Bartlett, and T. K. Sawyer, *Bioorg. Med. Chem. Lett.,* **1999**, *9*, 3009.

[10] (a) A. H. Moustafa, *Synthesis,* **2003**, 837. (b) T. Suyama, N. Suzuki, M. Nishimura, Y. Saitoh, H. Ohkoshi, J. I. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **2005**, *78*, 873.

[11] A. Padwa, T. Stengel, *Tetrahedron Lett.,* **2004**, *45*,

5991. (b) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.,* **2005**, *127*, 210.
[12] T. Curtius, *Ber. Dtsch. Chem. Ges*., **1883**, 16, 2230.
[13] R. Huisgen, in: A. Padwa (Ed.), 1,3-Dipolar Cycloaddition Chemistry, Wiley, New York, **1984**.
[14] K.V. Gothlf, K.A. Jorgensen, *Chem. Rev*., **1998**, *98*, 863.
[15] K.N. Houk, J. Gonzalez, Y. Li, *Acc. Chem. Res.,* **1995**, *28*, 81.
[16] A. I. Almansour, R. K. Suresh, N. Arumugam, and D. Sriram, *Eur. J. Med. Chem*., **2012,** *53*, 416.
[17] H. Jiang, J. Zhao, H. Xiaobing, and S. Zhu, *Tetrahedron*, **2006**, *62*, 11008.
[18] V. I. Kelarev, R. A. Karakhanov, Gasanov SSh, Polivan YuN, A. I. Mikaya, *Zh. Org. Khim*., **1993**, 29, 763.
[19] W**.** Szczepankiewicz, T. Borowiak, M. Kubicki, J. Suwinski, and P. Wagner, *Pol. J. Chem*., **2002**, *76*, 1137, [*Chem. Abstr*. 2003;138:24522].
[20] K. B. G. Torssell, "Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis", Ed. H. Feuer, VCH Publishers, Inc., New York, **1988**.
[21] A. Pinner, *Chem. Ber.*, **1984**, *42*, 2861.
[22] K.CHANG, B.R. SHELTON and R. K. HOWE*, J. Org. Chem*, **1980**, *45*, 3916.