[3+2] Cycloaddition of Oxaziridines with Nitriles: Synthesis of 2,3-Dihydro-1,2,4-Oxadiazoles

Luigino Troisi,* Ludovico Ronzini, Francesca Rosato, Valeria Videtta

Dipartimento di Scienze e Tecnologie Biologiche ed Ambientali, University of Salento, Via Prov.le Lecce-Monteroni, 73100 Lecce, Italy
Fax +39(0832)298732; E-mail: luigino.troisi@unile.it

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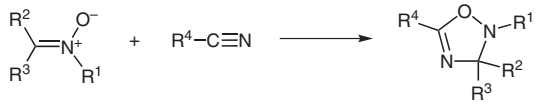
Abstract: A new and simpler preparation of 2,3-dihydro-1,2,4 oxadiazoles by synchronous [3+2] cycloaddition between oxaziridines and nitriles is presented.

Key word: cycloaddition, oxaziridines, nitriles, 2,3-dihydro-1,2,4 oxadiazoles, heterocycles

2,3-Dihydro-1,2,4-oxadiazoles (or Δ^4-1,2,4-oxadiazolines) are a lesser known class of heterocycles for which few syntheses and applications have been reported in the literature.[1] As such, the development of novel approaches toward the synthesis of these compounds is of fundamental interest. Interestingly, the isomeric 4,5-dihydro-1,2,4-oxadiazoles, which differ from the 2,3-dihydro-1,2,4-oxadiazoles only in the position of the ring double bond, have been studied in significantly more detail; numerous approaches for their synthesis[2] and subsequent application in various medical fields have been reported.[3] To date, the most common approaches for the synthesis of 2,3-dihydro-1,2,4-oxadiazoles is based on the cycloaddition reaction between nitrones and nitriles,[4–9] which proceeds with complete regiocontrol (Scheme 1).



Scheme 1 Synthesis of 2,3-dihydro-1,2,4-oxadiazoles by cycloaddition

The high degree of regioselectivity in this cycloaddition is likely to be due to the fact that, during the course of the reaction, the negatively charged oxygen atom of the nitrone dipole is oriented toward the positively polarized carbon of the nitrile. It is further correlated with the electronic nature of both components of the reaction as regioselectivity improves with nitriles bearing electron-withdrawing substituents and nitrones bearing electron-donating substituents.[10–13] It has also been reported that the formation of nitrile complexes with platinum(IV) or platinum(II)[14–16] and with palladium(II)[14] increases the overall reactivity of the cycloaddition reaction with nitrones.

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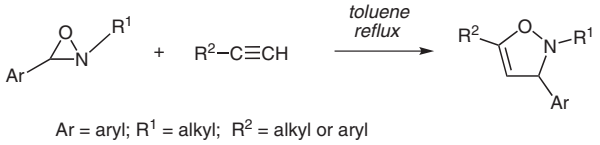
Recently, a [3+2]-cycloaddition reaction between oxaziridines and unactivated terminal alkynes was reported.[17,18] The novelty of this reaction lies in the oxaziridine C–O bond disconnection and the synchronous attack on the triple bond. In detail, the oxygen atom at the internal position and the carbon atom at the terminal position interact. As a consequence, the cycloaddition is regioselective for the formation of isoxazolines (Scheme 2).



Scheme 2 [3+2]-Cycloaddition reaction between oxaziridines and alkynes

The same reaction carried out with terminal alkenes provided direct access to isoxazolidines. Mechanistic analysis of the reaction demonstrated that the cycloaddition reaction proceeded through a synchronous attack.[19]

With these promising results as a starting point, we sought to develop a corresponding [3+2] cycloaddition between oxaziridines and nitriles to access 2,3-dihydro-1,2,4-oxadiazoles by employing the aforementioned reaction conditions. The results of our investigation are summarized in Table 1.

Only 2,3-dihydro-1,2,4-oxadiazoles **1**–**6** and the starting materials were isolated when the cycloaddition was carried out in refluxing toluene[20] for extended reaction times (Table 1, entries 1, 3, 5–8). The reaction time could be shortened and the yield increased when the nitrile was used as the solvent itself,[21] as the temperature could be raised to 140 °C (Table 1, entries 2, 4, 9). Inspection of our results indicated that there were no substantial electronic effects of either the oxaziridine or the nitrile, as was reported with previous related systems.[10–13] Electron-withdrawing groups on the oxaziridine, such as benzothiazole or pyridine, did not influence the rate or yield of the reaction, nor did changes to the identity of the substituent on the benzonitriles employed (H, 3-Cl, 3-NO_2, 4-OMe, Table 1, entries 3, 5–7).

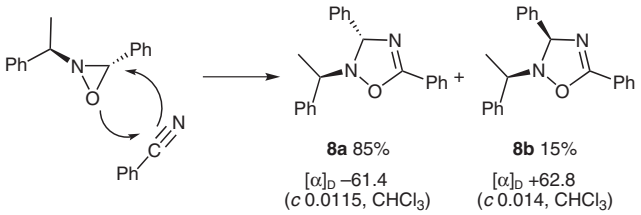
Next, the [3+2] cycloaddition was carried out under catalysis conditions, by adding 10 mol% $Pd(OAc)_2$ to a mixture of oxaziridine (Ar^1 = Ph) and benzonitrile. This process afforded oxadiazoline **1** in the same yield and

reaction time as shown in Table 1, entry 1, contrary to that reported.[14,16]

Interestingly, no product was observed when aliphatic nitriles were employed, even under the very forcing conditions described above. This may be due to more pronounced steric hindrance of the alkyl group as compared to the phenyl group.

This and the preceding results are best rationalized by a synchronous [3+2] cycloaddition as recently reported for reaction with alkenes and alkynes[17–19] rather than by a 1,3-dipolar mechanism, such as for the reactions with nitrones.[10–16]

In summary, we have applied a [3+2] cycloaddition between oxaziridines and nitriles for the synthesis of the 2,3-dihydro-1,2,4-oxadiazoles. The more ready access to oxaziridines[19] over nitrones[22] could favor the use of the described methodology for the synthesis of rare heterocycles that have not been previously accessed due to synthetic limitations. Furthermore, the formation of a new stereogenic center at C-3 suggests that the reaction may be rendered asymmetric by the incorporation of chiral oxaziridines. In a preliminary attempt (1′*R*,2*S*,3*S*)-3-phenyl-2-(1-phenylethyl)-oxaziridine[24] reacted with benzonitrile giving oxadiazolines **8a** and **8b** in 38% of yield and high diastereomeric ratio[25] (Scheme 3). These efforts are ongoing, and more results will be reported in the future.

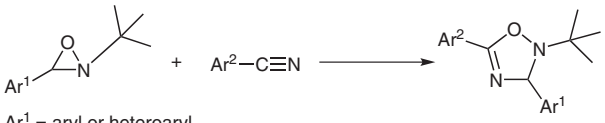


Scheme 3 Asymmetric synthesis of 2,3-dihydro-1,2,4-oxadiazoles by cycloaddition

General Procedure

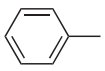
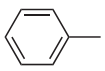
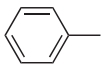
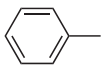
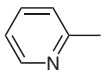
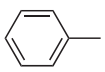
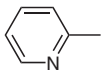
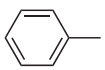
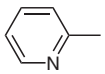
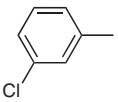
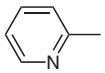
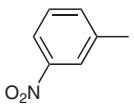
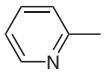
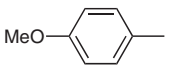
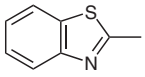
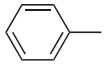
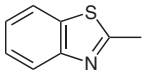
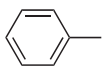
A solution of oxaziridine (1 equiv) and nitrile (3 equiv) in toluene (15 mL) was heated to reflux for 120 h. The solvent was removed under reduced pressure, and the resulting residue was purified directly by flash chromatography on silica gel deactivated with Et_3N.

Table 1 [3+2]-Cycloaddition Reaction between Oxaziridines and Nitriles



Ar^1 = aryl or heteroaryl
Ar^2 = aryl

1–6

Entry	Ar^1	Ar^2	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1			toluene	110	120	**1**[23] (76)
2			benzonitrile	140	15	**1** (86)
3			toluene	110	120	**2** (77)
4			benzonitrile	140	15	**2** (88)
5			toluene	110	120	**3** (80)
6			toluene	110	120	**4** (75)
7			toluene	110	120	**5** (70)
8			toluene	110	120	**6** (70)
9			benzonitrile	140	15	**6** (72)

[a] Yield determined by GC analysis on the base of oxaziridines transformed.

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References and Notes

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(20) Reaction conducted according to general procedure.
(21) Reaction conducted using benzonitrile as solvent (10 mL) for 15 h according to the general procedure. Yields, after chromatographic purification, were about 80%.
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(23) Compound **1**: Crude product was purified by flash chromatography on silica gel deactivated with Et_3N (PE–Et_2O, 8:2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.23 (s, 9 H), 6.11 (s, 1 H), 7.25–7.54 (m, 8 H), 7.98 (d, *J* = 8.1 Hz, 2 H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 25.0, 60.4, 85.8, 125.3, 126.6, 126.9, 128.0, 128.5, 131.9, 141.6, 161.4. GC-MS (70 eV): *m/z* = 280 (<1) [M^+], 177 (50), 121 (35), 105 (20), 77 (25), 57 (100). FTIR ($CHCl_3$): 3067, 2987, 2927, 2852, 1656, 1494, 1452, 1326 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; O, 5.71. Found: C, 77.09; H, 7.18; O, 5.69.
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(25) Diastereomeric ratio determined by ^1H NMR on the crude product.