Condensed Oxaziridine-Mediated [3+2] Cycloaddition: Synthesis of Polyhetero-bicyclo Compounds

Valeria Videtta, Serena Perrone, Francesca Rosato, Pietro Alifano, Salvatore M. Tredici, Luigino Troisi*

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@unisalento.it

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Abstract: Polyhetero-bicyclo compounds were synthesized by a regioselective [3+2]-cycloaddition reaction between stable condensed oxaziridines and alkenes, alkynes, and nitriles. These molecules showed considerable antimicrobial activity against several gram-positive bacteria.

Key words: condensed oxaziridines, polyhetero-bicyclo, regioselectivity, [3+2] cycloaddition, bactericidal properties

Oxaziridines are very peculiar three-membered heterocyclic compounds containing three kinds of atoms having different electronegativity in adjacent positions. They are biologically active molecules, which have been shown to possess bactericidal, viricidal, and cytoxic activities[1a–1d] The well-known reactions of oxaziridines with amines and sulfides may well explain their characteristic biological properties as compared to those of analogous compounds such as aziridines or oxiranes. The nucleophilic reaction of amines and/or sulfides occurs exclusively at the nitrogen atom of the oxaziridine ring and gives a carbonyl compound and an ylide.[2] Due to their considerable biological properties, the synthesis of more complex oxaziridines, the study of reactivity with unsaturated systems, and their action mechanism in biological systems are of great interest. [3+2]-Cycloaddition reactions between oxaziridines condensed with heterocycles and unsaturated systems have not previously been described in the literature, probably because the synthesis and isolation of oxaziridines as pure compounds is difficult. In fact, condensed oxaziridines readily isomerize into the corresponding more stable *N*-oxides, that have been used in cycloaddition reactions with various dipolarophiles. Oxazoline *N*-oxides may be synthesized following two methods. Keana has shown that oxazolines, prepared by the classical condensation between amino alcohols and iminoether hydrochlorides, can be oxidized with the magnesium salt of monoperphthalic acid followed by silica gel induced isomerization giving the oxazoline *N*-oxides.[3] Alternatively, condensation of hydroxylamino alcohols as their hydrochloride salts with triethyl orthoesters[4a] or *N*,*N*-dimethylacetamide diethyl acetal[4b] affords oxazoline *N*-oxides directly. In asymmetric cycloadditions with various electron-poor alkenes as dipolarophiles, Langlois et al. used the chiral oxazoline *N*-oxides condensed with camphor ring without further purification due to their instability.[5–12] In these cases the preparation of polycyclic tetrahydro-oxazolo[3,2-*b*]isoxazoles **1** was described. Analogously, Coates et al. obtained cycloadducts **2** by reacting oxazoline *N*-oxides with electron-poor alkenes as dipolarophiles.[4a] Likewise, they isolated the 2,3-dihydro-oxazolo[3,2-*b*]isoxazoles **3** in the reactions with alkynes activated by electron-withdrawing groups and the tetrahydro-oxazolo[3,2-*b*][1,2,4]oxadiazol-2-ones **4** by the reaction with phenyl isocyanate[4a,b] respectively (Figure 1).

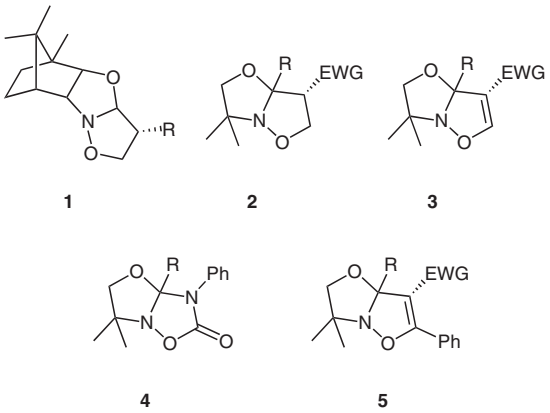

Figure 1 Cycloadducts by oxazoline *N*-oxide

Moreover, 5,6-dihydro-3a*H*-oxazolo[3,2-*b*][1,2,4]oxa diazoles **5** have been obtained by 1,3-dipolar reactions between oxazoline *N*-oxides and nitriles coordinated with Pt(II).[13] Many of these reactions were not regioselective, and various diastereomers were isolated. Furthermore, the dipolarophiles generally required activatation by electron-withdrawing groups or coordination to a transition metal.

Herein we report the synthesis of stable condensed oxaziridines and their regioselective attack on alkenes, alkynes, and nitriles in [3+2]-cycloaddition reactions. Treatment of 2-methyl and 2-ethyl-4,5-dihydrooxazoles in diethyl ether at 0 °C with MCPBA (1.1 mmol) and evaporation of the solvent under reduced pressure at low temperature gave the desired oxaziridines **6** and **7** (yield 97%) as pure compounds which were immediately allowed to react with unsaturated substrates (Scheme 1).

It was considerd that the strained oxaziridine ring of these heterobicyclic compounds would be more reactive either than the oxazoline *N*-oxides[4–13] or than the simple uncondensed oxaziridines.[14–17] Thus, oxaziridine **6**[4a] was react-

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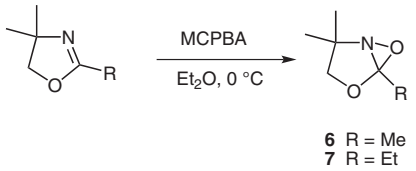
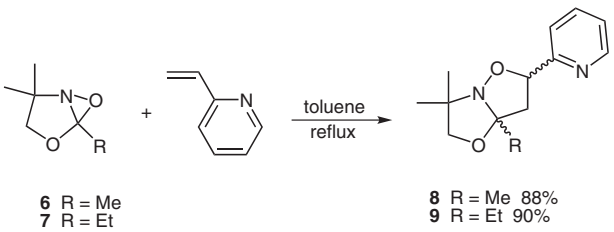


Scheme 1 Condensed oxaziridines synthesis

ed with 2-vinylpyridine (3 equiv) in refluxing toluene, and the reaction was followed by TLC and GC analysis. After five hours, when the oxaziridine was completely reacted, the reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The crude mixture was analyzed by ^{1}H NMR spectroscopy, which showed the formation of the two bicyclic products **8** with a diastereomeric ratio of 2:1. Purification by column chromatography afforded the *cis* and *trans* isomers **8** in 88% of total yield (Scheme 2). The mixture of diastereomeric adducts was partially separated by further chromatography, and the individual fractions were analyzed by ^{1}H NMR and NOESY spectroscopy showing that the *cis* isomer was major component.



Scheme 2 [3+2]-Cycloaddition reaction with 2-vinylpyridine

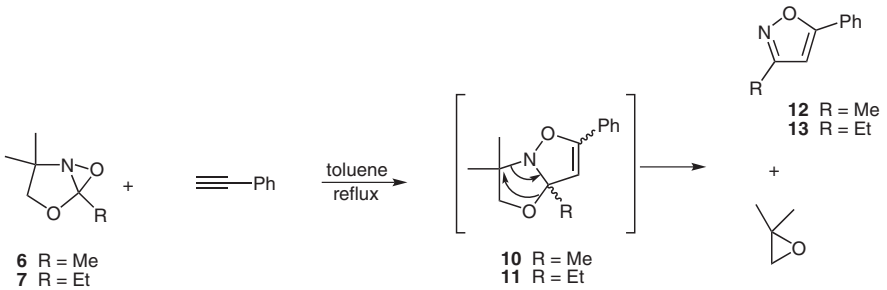
Thus, the condensed oxaziridine **6** showed excellent regioselectivity in the [3+2]-cycloaddition reaction with the 2-vinylpyridine in which the oxygen attacks the internal carbon of the dipolarophile and the oxaziridine carbon binds the external carbon. In contrast, the analogous reactions between oxazoline *N*-oxides and alkenes gives a complex mixture of regioisomers.[4a] A similar result was obtained also carrying out the reaction between the oxaziridine **7** and 2-vinylpyridine under the same experimental conditions. Only the regioisomer **9** was formed in 90% yield and with a *cis*/*trans* ratio of 2:1 (Scheme 2).

With these promising initial results, we attempted [3+2] cycloaddition between oxaziridines **6** and **7** and phenylacetylene (3 equiv) in refluxing toluene. In both cases, isoxazoles **12** and **13** (Scheme 3) were isolated as only the products in 85% yield, after a reaction time of 10 minutes. The elimination product 2,2-dimethyl-oxirane was not isolated, presumably due to its volatility.

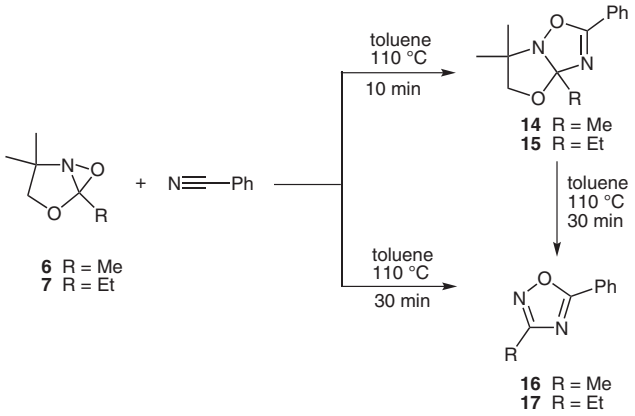
Once again, the [3+2]-cycloaddition reactions were regioselective with the oxygen attacking the internal carbon and the oxaziridine carbon attacking the external carbon of the alkyne, affording the initial cycloadducts **10** and **11** that decompose to the more stable isoxazoles **12**[18] and **13**.[19] Repeating the reaction under the same conditions, but at lower temperature (40 °C), only the rearranged compounds **12** and **13** were observed. Analogous results have been reported for the cycloaddition reactions between oxazoline *N*-oxides and methyl propargyl ester in presence of dimethylamine hydrochloride.[4b]

Oxaziridines **6** and **7** were also applied to [3+2]-cycloaddition reaction with benzonitrile (3 equiv) in refluxing toluene (Scheme 4). Reaction was complete after 30 minutes and evaporation of the solvent and purification of the crude mixture on silica gel gave the 1,2,4-oxadiazoles **16**[20] and **17**[21] in 88% of yield. In these cases, it was clear that **16** and **17** resulted from decomposition of the initial bicyclic cycloadducts, so the cycloadditions were conducted under the same experimental conditions for a shorter reaction time. After 10 minutes the 5,6-dihydro-3a*H*-oxazolo[3,2-*b*][1,2,4]oxadiazoles **14** and **15**[13] were isolated in 93% and 89% yield, respectively. Subsequent heating **14** and **15** in refluxing toluene for 30 minutes resulted in complete transformation into **16** and **17** (Scheme 4). Once again, cycloaddition had occurred with excellent regioselectivity; the oxygen attacking the carbon and the carbon adding to the nitrogen of the nitrile group.

No reaction between oxazoline *N*-oxides and nitrile moieties has been previously observed, probably because of the low reactivity of the nitrile groups and the instability of the dipoles; although it has been demonstrated that coordination of nitriles to Pt centers markedly enhances the reactivity with the *N*-oxide compounds.[13] The higher reactivity of the condensed oxaziridines **6** and **7** described herein, with respect to unstrained oxazoline *N*-oxides, was evidenced by the fact that attempted reaction between 2,4,4-trimethyloxazoline *N*-oxide[4a] and phenylacetylene, in toluene at reflux led to no new product after 24 hours.

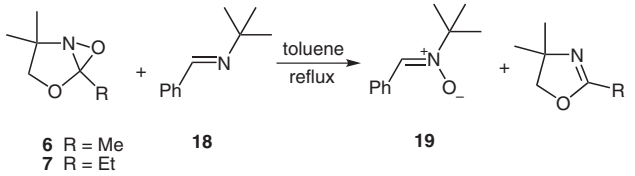


Scheme 3 [3+2]-Cycloaddition reaction with phenylacetylene



Scheme 4 [3+2]-Cycloaddition reaction with benzonitrile

Finally, we decided to react the condensed oxaziridines **6** and **7** with a C–N double bond, specifically with imine **18**[22] under the same cycloaddition conditions (Scheme 5). However, either due to the imine basicity or steric hindrance, **6** and **7** acted as oxygenating agents[23] giving the nitrone **19** and the corresponding 4,5-dihydrooxazoles in quantitative yield.



Scheme 5 Reaction between condensed oxaziridines and imine

The antimicrobial properties of these molecules were also assayed on a battery of gram-positive (*Staphylococcus aureus* SA1; *Staphylococcus epidermidis* SE1; *Micrococcus luteus* ML1) and gram-negative (*Escherichia coli* FB8; *Salmonella enterica* sv. Typhimurium LT2; *Vibrio harveyi* AK1) bacterial strains using standard microbiological procedures. They showed considerable/moderate antimicrobial activity that will be discussed in another manuscript.

In summary, in this communication the preparation of condensed oxaziridines and their reactivity with diverse dipolarophiles (alkenes, alkynes, nitriles, and imines) is described wherein condensed isoxazolidines, isoxazolines, oxadiazoles, and nitrones were synthesized, respectively. Due to the strained rings, the oxaziridines are very reactive, undergoing [3+2]-cycloaddition reactions with dipolarophiles without any activation with electron-withdrawing groups and Pt(II). Moreover, the reactions proceeded with an excellent regioselectivity, with the oxygen attacking the internal carbon of the unsaturated system.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are detailed experimental procedures and characterization data for compounds **7–9**.

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