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First Example of Direct RuO_4-Catalyzed Oxidation of Isoxazolidines to 3-Isoxazolidones

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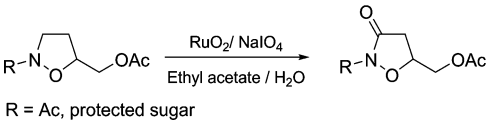

RuO_2/$NaIO_4$ oxidation of 3-unsubstituted isoxazolidines, under ethyl acetate/water biphasic conditions, affords 3-isoxazolidones in good yields. The methodology can be used on both racemic and optically active isoxazolidines.

The 3-isoxazolidone nucleus constitutes the basic skeleton of natural compounds such as the antibiotic D-cycloserine **1**,[1] the L-canavanine catabolite **2**,[2] and a series of compounds that have been designed in medicinal chemistry as ligands for different receptors of the central nervous system (Figure 1).[3] Azamuscarone **3**,[4] structurally related to the natural muscarine **4**, is a highly effective agonist of the muscarinic receptor, having a potency comparable to that of compound **4**. The muscarinic receptor population represents a class of cholinergic receptors abundant in the parasympathetic and in the central nervous system, where they mediate both excitatory and inhibitory effects. In this context, compounds **5**−**7**, which incorporate the isoxazolidin-3-one moiety, have been designed as analogues of the potent yet nonselective muscarinic agonists oxotremorine **8** and oxotremorine-M **9**. Compounds **5**−**7** displayed different binding affinities at brain and heart muscarinic subtype receptors.[5a,b]

The *N*-unsubstituted 3-isoxazolidinone system in the enolic form, such as dihydromuscimol (DHM) **10**, can be regarded as a conformationally restricted analogue of the physiological

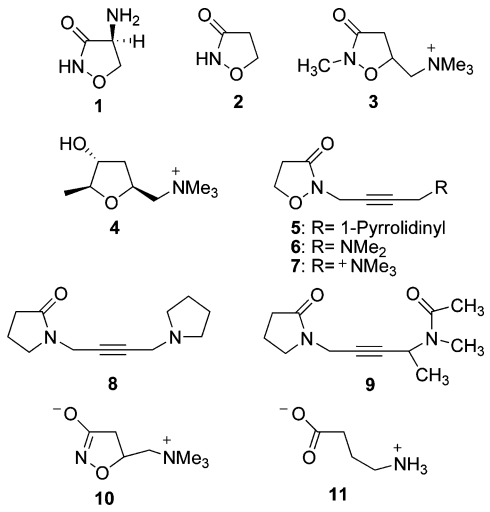

FIGURE 1. Some of the most important 3-isoxazolidinones.

neurotransmitter 4-aminobutyric acid **11** (GABA). Extensive pharmacological investigations performed on DHM have shown the existence of a powerful agonist activity at the postsynaptic GABA receptor complex.[6a,b]

In the literature, only two synthetic approaches toward the 3-isoxazolidinone system have been reported. The first approach is based on the cyclization of suitably functionalized hydroxamic acids, which may be prepared in most cases by reaction of a suitable acid derivative with a substituted hydroxylamine, with yields lower than 50%.[7] This procedure is severely limited by the availability of the hydroxamic acid precursor and the low yields of the cyclization process.

The second reaction pathway involves a 1,3-dipolar cycloaddition of bromonitrile oxide with allylic alcohol, with subsequent transformation of the cycloadducts to produce the target compounds. The major drawback of this method is linked to the synthesis of optically pure isoxazolidones. The use of a chiral alkene, such as *S*-(+)-2,2-dimethyl-4-vinyl-1,3-dioxolane, requires rather laborious manipulations to transform the obtained cycloadducts **12** into the key intermediates **13** (Scheme 1). Furthermore, the relative distribution of these intermediates is strictly dependent upon the stereoselectivity induced from the chiral alkene.[8]

The enzymatic resolution of the racemic intermediate **13** by Lipase PS, after conversion into suitable esters, has been also utilized to obtain optically pure (*R*)-(−)-**3** and (*S*)-(+)-**3**. However, this methodology can be applied only to Δ^2-isoxazoline or isoxazolin-3-one derivatives carrying a primary alcoholic group, and the enantioselectivity of enzymatic resolution is strictly dependent upon both the size of the acyl moiety and the shape of the group carrying the alcoholic part of the ester.[9]

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(1) Peisach, D.; Chipman, D. M.; Van Ophem, P.W.; Manning, J. M.; Ringe, D. *J. Am. Chem. Soc.* **1998**, *120*, 2268.
(2) Rosenthal, G. A. *Plant Physiol.* **1990**, *94*, 1.
(3) Grunwald, C.; Rundfeldt, C.; Lankau, H. J.; Arnold, T; Höfgen, N.; Dost, R.; Egerland, U.; Hofmann, H. J.; Unverferth, K. *J. Med. Chem.* **2006**, *49*, 1855.
(4) De Amici, M.; De Micheli, C.; Grana, E.; Rodi, R.; Zonta, F.; Santagostino-Barbone, M. G. *Eur. J. Med. Chem.* **1989**, *24*, 171.
(5) (a) Conti, P.; Dallanoce, C.; De Amici, M.; De Micheli, C.; Ebert, B. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1033. (b) Dallanoce, C.; Conti, P.; De Amici, M.; De Micheli, Barocelli, E.; Chiavarini, M.; Ballabeni, V.; Bertoni, S.; Impicciatore, M. *Bioorg. Med. Chem.* **1999**, *7*, 1539.
(6) (a) Krogsgaard-Larsen, P.; Nielsen, L.; Falch, E.; Curtis, D. R.; Lodge, D.; Johnston, G. A. *J. Neurochem.* **1979**, *32*, 1717. (b) Krogsgaard-Larsen, P.; Nielsen, L.; Falch, E.; Curtis, D. R. *J. Med. Chem.* **1985**, *28*, 1612.
(7) Caldirola, P.; De Amici, M.; De Micheli, C. *Tetrahedron Lett.* **1986**, *27*, 4651.
(8) De Amici, M.; Magri, P.; De Micheli, C.; Cateni, F.; Bovara, R.; Carrea, G.; Riva, S.; Casalone, G. *J. Org. Chem.* **1992**, *57*, 2825.
(9) Carrea, G.; De Amici, M.; De Micheli, C.; Liverani, P.; Carnielli, M.; Riva, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1063.

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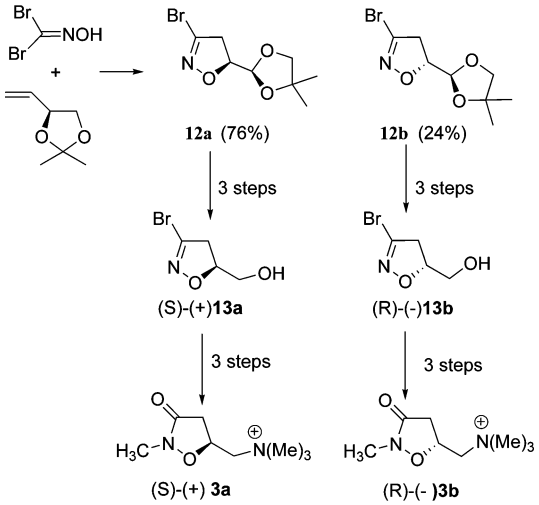
SCHEME 1. Synthetic Procedure toward Compounds 3 by 1,3-Dipolar Cycloaddition of a Chiral Alkene and Bromonitrile Oxide



Because of these considerations, we have devised a new synthetic route for the 3-isoxazolidone system, which can be successfully exploited for the preparation of enantiomerically pure derivatives. In this paper we report the first example of a direct oxidation of the isoxazolidine nucleus to the 3-isoxazolidone system by the use of $RuO_2/NaIO_4$, under ethyl acetate/water biphasic conditions. This two-phase oxidation was reported some years ago for the conversion of cyclic α-aminoacids into α-aminodicarboxylic acids,[10a−c] and more recently, this procedure has been applied to the conversion of protected proline derivatives into pyroglutamic acid derivatives.[11a,b] The oxidation reaction of the isoxazolidine nucleus is uncommon because of the sensitivity of the N−O bond toward the usual oxidizing agents; only a few papers report the oxidative treatment of isoxazolidines to give corresponding isoxazolines.[12a,b,13]

The starting 3-unsubstituted isoxazolidine **18** has been prepared in racemic form by the 1,3-dipolar cycloaddition reaction of the *N*-pyranosyl nitrone **14** with allylic alcohol (Scheme 2). This cycloaddition produced the expected mixture of inseparable diastereomers **16**. Deprotection by treatment with *p*-toluensulphonic acid and subsequent acetylation gave the protected isoxazolidine **18**, which was purified by flash chromatography. The oxidation of **18** was carried out in aqueous ethyl acetate by using RuO_4 (generated in situ from catalytic $RuO_2.nH_2O$ and $NaIO_4$ in excess), leading to compound **19** with a yield of 60%.

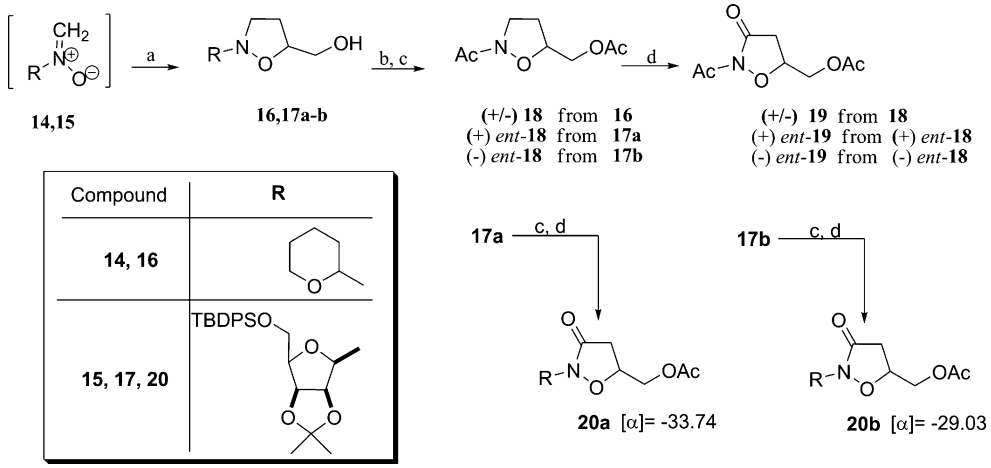
The oxidation process was also performed directly on **16**, after protection of the hydroxyl group with acetic anhydride, but in this case, the yield decreased and the ^1H spectrum of the crude reaction mixture showed the presence of a complex mixture of oxidized compounds. In this case, the ethereal methylene group of the pyranosyl moiety is probably a competitive site for the oxidation processes.

We have, then, exploited our methodology for the synthesis of enantiomerically pure 3-isoxazolidones, starting from the chiral isoxazolidines **17a** and **17b** prepared from the Vasella-like nitrone **15**.[14] Thus, nitrone **15** was reacted with allylic alcohol in toluene for 12 h to give a mixture of the two chiral isoxazolidines **17a** and **17b** (50% and 40% yield, respectively), epimeric at C-5, which were separated by MPLC chromatography. The first eluted compound, **17a**, was hydrolyzed by treatment with 37% aqueous HCl in ethanol at reflux and acetylated to give (+)-*ent*-**18** [α] = +31, whereas the reaction on the second eluted compound **17b** afforded the enantiomer (−)-*ent*-**18** [α] = −31. These data confirm that **17a** and **17b** are epimers at C_5 of the isoxazolidine ring. Two purified enantiomers **18** were independently oxidized, under the same conditions used for racemic **18**, to afford the dextrorotatory isoxazolidinone **19**, [α] = +13, from (+)-*ent*- **18** and the levorotatory isoxazolidinone **19**, [α] = −13 from (−)-*ent*-**18**.

However, the RuO_4-mediated oxidation can be directly carried out on acetylated **17a** and **17b** without preventive removal of the sugar moiety at the nitrogen atom. Thus, from **17a** and **17b** we obtained the corresponding 3-isoxazolidinone **20a**, [α] = −33.74, and **20b**, [α] = −29.03, with a yield of 65% for both the substrates.

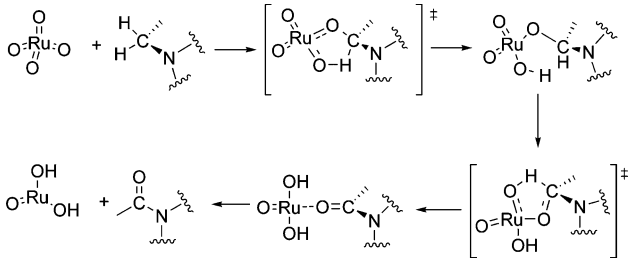
As reported in the literature,[14] the oxidation process can be explained according to two separate steps. The activation of the α-CH bond, in a concerted five-membered transition state, leads to an alcohol product, coordinated to the Ru(VI), which undergoes a second hydrogen transfer giving the corresponding oxygenated compound and Ru(IV) (Scheme 3).

SCHEME 2. General Procedure for the Oxidation Reaction of 18 with $RuO_2/NaIO_4$[a]



[a] Reaction conditions: (a) allyl alcohol, toluene, reflux, 12 h, yield 90%; (b) PTSA, MeOH, 2 h, reflux or 37% aqueous HCl in ethanol at reflux; (c) Ac_2O, ETA, DCM, 3 h, yield 99%; (d) RuO_2, $NaIO_4$, ethyl acetate, H_2O, yield 60−65%.

SCHEME 3. Mechanism of the RuO_4-Catalyzed Oxidation of Activated CH_2 Groups



The regioselectivity of the oxidation, which occurs exclusively at position 3 of the isoxazolidine ring, can be also rationalized, in accord with literature data,[14] by considering that the presence of the activating nitrogen atom promotes the conversion rate.

In conclusion, we report the first example of a direct oxidation of the isoxazolidine nucleus to 3-isoxazolidones by the use of $RuO_2/NaIO_4$. The method can be used on both racemic and optically active isoxazolidines. The methodology is general and, as suggested by preliminary data, may be efficaciously exploited for homochiral isoxazolidines, differently C-4 and/or C-5 substituted, to allow access to the corresponding optically active 3-isoxazolidones, which are otherwise difficult to prepare.

Experimental Section

General Procedure for 1,3-Dipolar Cycloaddition Reaction of *N*-Pyranosyl (14) and *N*-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl) nitrone (15). A mixture of 5-hydroxypentanal oxime[15] (5.5 mmol) or *E*/*Z* (2.9/1) mixture of (4*S*,5*R*)-5-[(1*R*)-2-[[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy]-1-hydroxyethyl]-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde oxime[16] (5.5 mmol), paraformaldehyde (11 mmol), and allylic alcohol (11 mmol) in toluene (70 mL) was heated at reflux for 12 h. The reaction mixture was filtered and then evaporated under reduced pressure to give the cycloadducts, which were purified by MPLC chromatography with cyclohexane/ethyl acetate (5:5) as eluent.

[2-(Tetrahydro-2*H*-pyran-2-yl)isoxazolidin-5-yl]methanol (16): yield 87.5%; yellow oil.

(2-(6-((*tert*-Butyldiphenylsilyloxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl) isoxazolidin-5-yl)methanol (17a): yield 50%; oil, R_f (cyclohexane/ethyl acetate 5/5) = 0.55; $[\alpha]^{25}_D = +3.01$ (*c* 0.32, $CHCl_3$).

(2-(6-((*tert*-Butyldiphenylsilyloxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)isoxazolidin-5-yl)methanol (17b): yield 40%; oil, R_f (cyclohexane/ethyl acetate 5/5) = 0.45; $[\alpha]^{25}_D = +4.58$ (*c* 0.48 , $CHCl_3$).

General Procedure for the Hydrolysis of Cycloadducts and Subsequent Acetylation. A solution of cycloadducts **16** (10 mmol) and *p*-toluensulfonic acid (0.5 mmol) in MeOH (20 mL) or isoxazolidines **17a,b** and 37% HCl solution (w/w) in EtOH (20 mL) was heated at reflux for 12 h. The reaction mixture was neutralized with potassium carbonate and evaporated. The residue was purified by chromatography (chloroform/methanol 9:1) to furnish the corresponding isoxazolidin-5-ylmethanol, with a yield of 70%, identified by ^{1}H NMR ($CDCl_3$, 300 MHz): 2.05(m, 1H), 2.15(m, 1H), 2.68(sb, 2H), 3.08(t, 2H, J = 5.3 Hz), 3.61(dd, 1H, J = 4.55, 9.8 Hz), 3.81(dd, 1H, J = 3.6, 9.8 Hz), 4.20(m, 1H). To a solution of isoxazolidin-5-ylmethanol (7 mmol) and $N(Et)_3$ (14.5 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise acetyl chloride (14.5 mmol), and the reaction mixture was stirred at room temperature for 4 h and then concentrated in vacuo. The residue was treated with ethyl acetate and filtered; the solution was washed with aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and evaporated to dryness to afford **18** in a quantitative yield.

(2-Acetylisoxazolidin-5yl)methyl acetate (18): yield 70%; yellow oil, R_f (chloroform/methanol 98/2) = 0.36; (+)-*ent*-**18** $[\alpha]^{25}_D = +31$ (*c* 0.44, CH_2Cl_2); (−)-*ent*-**18** $[\alpha]^{25}D = -31$ (*c* 0.44, CH_2Cl_2).

General Procedure for $RuO_2/NaIO_4$ Oxidation. To a solution of $NaIO_4$ (4.0 g, 18.71 mmol) in water (67 mL) was added $RuO_2 \cdot H_2O$ (0.2 g 1.48 mmol) under nitrogen. The resulting green-yellow solution was stirred for 30 min and was followed by addition of protected isoxazolidine (7.49 mmol) in EtOAc (32 mL) in one portion. The solution remained yellowish during the reaction; if its color changed to black more $NaIO_4$ was added (4.0 g, 18.71 mmol), and after 6 h of stirring at room temperature the mixture was diluted with EtOAc and filtered through a pad of Celite. The organic layer was washed with saturated $NaHSO_3$, which resulted in precipitation of black Ru. The precipitate was filtered off through a pad of Celite. The EtOAc layer was washed with brine and dried with anhydrous Na_2SO_4; the solvent was removed by evaporation in a rotary evaporator to obtain the crude product. All products were purified by MPLC chromatography.

(2-Acetyl-3-oxoisoxazolidin-5-yl)methyl acetate (19): yield 60%; white oil, R_f (EtOAc/cyclohexane 4/6) = 0.42; (+)-*ent*-**19** $[\alpha]^{25}_D = +13$ (*c* 0.26, CH_2Cl_2); (−)-*ent*-**19** $[\alpha]^{25}_D = -13$ (*c* 0.26, CH_2Cl_2).

(2-(6-((*tert*-Butyldiphenylsilyloxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-3-oxoisoxazolidin-5-yl)methyl acetate (20a): yield 65%; white oil, R_f (EtOAc/cyclohexane 3/7) = 0.66; $[\alpha]^{25}_D = -33.74$ (*c* 0.31, $CHCl_3$).

(2-(6-((*tert*-Butyldiphenylsilyloxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*] [1,3]dioxol-4-yl)-3-oxoisoxazolidin-5-yl)-methyl acetate (20b): yield 65%; white oil, R_f (EtOAc/cyclohexane 5/5) = 0.54; $[\alpha]^{25}_D = -29.03°$ (*c* 0.15, $CHCl_3$).

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Supporting Information Available: Experimental procedures and complete characterization of all compounds; copies of the ^{1}H NMR spectra for compounds **17a**, **17b**, **19**, **20a**, **20b**; and ^{13}C NMR spectra for compound **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) Plietker, B. S*ynthesis* **2005**, 15, 2453. (b) Kaname, M.; Yoshifuji, S. *Tetrahedron Lett.* **1992**, *33*, 8103. (c) Yoshifuji, S.; Kaname, M. *Chem. Pharm. Bull.* **1995**, *43*, 1617.

(11) (a) Zhang, X.; Schmitt, A. C.; Jiang, W. *Tetrahedron Lett.* **2001**, *42*, 5335. (b) Merino, P.; Revuelta, J.; Tejero, T.; Chiacchio, U.; Rescifina, A.; Piperno, A.; Romeo, G. *Tetrahedron: Asymmetry* **2002**, *13*, 167.

(12) (a) Li, P.; Gi, H. J.; Sun, L.; Zhao, K. *J. Org. Chem*. **1998**, *63*, 366. (b) Mzengeza S.; Whitney, R. A. *J. Org. Chem*. **1988**, *53*, 4074.

(13) Chiacchio, U.; Romeo, G.; Uccella, N. *Trends Heterocycl. Chem.* **1995**, *4*, 261.

(14) (a) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599. (b) Plietker, B. *Synthesis* **2005**, *15*, 2453.

(15) Mzenga, S.; Whitney, A. R. *J. Chem. Soc., Chem. Commun*. **1984**, 606.

(16) Chiacchio, U.; Corsaro, A.; Gumina, G.; Rescifina, A.; Iannazzo, D.; Piperno, A.; Romeo, G.; Romeo, R. *J. Org. Chem.* **1999**, *64*, 321.