Cleavage of the N-O Bond in the 4-Spirocyclopropaneisoxazolidine Carboxylate and Subsequent Cycloaddition

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Abstract

1, 3 - Dipolar cycloaddition of nitrones to the double carbon – carbon bond of acceptor ring substituted methylenecyclopropanes affords thermally stable regioisomeric 4 - spirocyclopropaneisoxazolidine. Cleavage of the N - O bond in 4 - spirocyclopropaneisoxazolidine with ester groups on the three - membered ring by the action of activated zinc dust in acetic acid gives the corespoding 1, 3 - amino ancohols containing cyclopropyl ring, whose subsequent cyclization under the reaction conditions yield bi- or tri - cyclic lactams or lactones with retention of the three - membered ring - structural moieties of antibiotics and biologically active compounds.

Keywords: 4-spirocyclopropaneisoxazolidine carboxylate, 1,3-amino alcohols, lactones, cleavage of the N-O bond

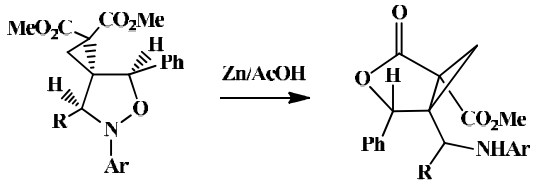
1. Introduction

5-Spirocyclopropaneisoxazolidine* regioisomers contain highly strained spiro cyclopropyl ring and a comparatively weak adjacent N-O bond that facilitates subsequent Brandi–Guarna rearrangement with the formation of piperidin-4-ones and benzoazocinones [1, 2]. In reactions between acceptor ring substituted methylenecylopropanes and aldo nitrones (C,N-disubstituted) only thermally stable regioisomeric 4-spirocyclopropane isoxazolidine is formed, which thermally stable [3]. The increased steric hindrance of N,C,C-trisubstituted nitrones causes inversion of the regioselectivity of the 1,3-dipolar cycloaddition reaction with the formation of 5-spirocyclopropane isoxazolidine. These isoxazolidines cannot be isolated and undergo reaction cascade with the formation of products containing tricyclic frameworks of benzocarbacepham and pyrrolo[1,2-*a*]quinolines – structural moieties of antibiotics and biologically active compounds [4].

Cleavage of the N-O bond is the most synthetically useful reaction for the modification of the obtained cycloadducts which can be done by a variety of methods, including hydrogenation over Raney Ni [5], Pd/C, or $Pd(OH)_2$ [6], reaction with Zn/H^+ [5a, 5b, 7], $Mo(CO)_6/H_2O$ [8]. However, isoxazolidines with cyclopropyl moiety are very reactive substances and subsequent transformations of cycloadducts are possible. A two-step transformation of 5-spirocyclopropane isoxazolidines to tetrahydropyridones and dihydropyridones by hydrogenolysis through Pd mediated processes was described [9]. SmI_2 mediated reductive cleavage of 4- and 5-spirocyclopropane isoxazolidines affords 1,3-amino alcohols [10].

2. Results and discussion

It was shown earlier in our studies, that the reactions of 4-spirocyclopropane dicarboxylates **1a**, **b** with activated Zn-dust/AcOH have resulted in smooth N-O bond cleavage with subsequent cyclization to form lactones **2a**, **b** in good isolated yields [3b].



1a,b **2a,b**

a: R= Ph, Ar = Ph

b: R=C(O)NHC$_6$H$_4$-OMe-4, Ar = 4-MeC$_6$H$_4$

We previously showed that treatment of isoxazolidines having a strong electron-donating substituent in the aromatic ring with zinc dust in acetic acid led to the formation of tricyclic lactones [11]. In this study the reaction of isoxazolidine **1c**, having strong electrono-donor substituent (OMe) in N-aromatic nucleus, with activated Zn-dust/AcOH in refluxing THF, tricyclic lactones **3c** have been received as the basic products (yields 62%). Formation of these products can be considered as a result of two consecutive processes: formations of lactame and lactone. Formation of lactame in this

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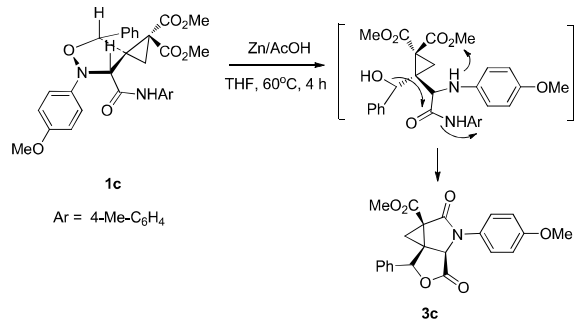
case is connected probably to the greater nucleophilicity of nitrogen atom in compounds **1c** due to substituent in aromatic ring [11].



The structure of obtained compounds was established based on spectral data for compound **3c**. Thus, ^{1}H NMR spectrum of compound **3c** contains two doublet signals of protons of the cyclopropane fragment at 2.02 and 2.14 ppm (J = 5.8 Hz), and two singlet signals of CH-groups at 4.66 and 5.60 ppm. The ^{13}C NMR spectrum of compound **3c** contains characteristic signals of carbon atoms of CO-groups lactone and lactame at 166.9 and 167.1 ppm, signal of CH_2 group of cyclopropane ring at 20.7 ppm, and two signals of CH-groups, connected with N- and O-atoms at 55.2 and 79.0 ppm. The stereochemistry of the compound **3c** was unambiguously confirmed by X-ray diffraction analysis (Fig. 1).

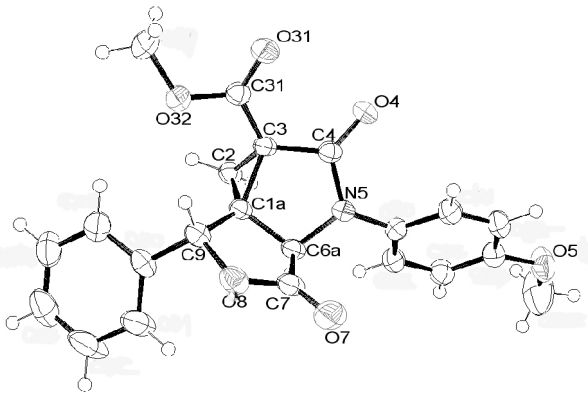
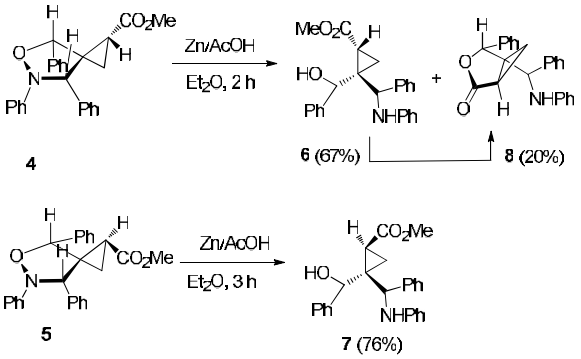


Fig. 1. ORTEP representation of compound **3c**.

Next we examined the diastereomeric isoxazolidines **4** and **5**, which have been earlier received at the reaction of N,C-diphenylnitrone with methyl 2-benzylidenecyclopropane [3d], under refluxing with activated Zn-dust/AcOH in ether. It was found that diastereomeric 4-spirocyclopropane isoxazolidines **4** and **5**, containing one methoxycarbonyl group at cyclopropane ring, react affording 1,3-aminoalcohols **6**, **7** and lactone **8**. In this case the process of the formation of the lactone proceeds more slowly than in a case of bis(methoxycarbonyl) substituted spirocyclopropane isoxazolidines and we were able to isolate as lactone **8** and aminoalcohols **6**, **7**. The amino alcohol **6** turns at the further heating in a lactone **8**, but compound **5** affords only aminoalcohol **7**, because hydroxy- and methoxycarbonyl groups are in *trans*-position relative cyclopropane ring and therefore process of the formation of lactone does not occur.



The structure of obtained compounds was established based on spectral data. Thus, ^{1}H NMR spectrum of compound **6** contains signals of protons of the cyclopropane ring at 1.39, 1.55 and 1.65 ppm and two doublet signals of CH-groups at 4.56 and 4.64 ppm. The ^{13}C NMR spectrum of the compound contains signals of carbon atoms of cyclopropane ring at 15.3 (CH_2), 24.6 (CH), 41.2 (C) ppm, and signals of carbon atoms of CH-groups at 57.0 and 72.4 ppm.

^{1}H NMR spectrum of compound **8** contains signals of protons of the cyclopropane ring at 1.16–1.24 (2H) and 1.59 ppm, singlet signal of proton of the CH-O group at 5.72 ppm and two doublet signals of protons of CH-N and NH groups at 4.36 and 6.00 ppm. The ^{13}C NMR spectrum of the compound contains signals of carbon atoms of cyclopropane ring at 13.0 (CH_2), 22.0 (CH), 38.7 (C) ppm, signals of carbon atoms of CH-groups at 55.2 and 84.2 ppm and characteristic signal of carbon atom of C=O lactone group at 174.9 ppm. The stereochemistry of the lactone **8** was established based on data of the analogy described in the literature [11].

3. Conclusions

In summary it has been found, that hydrogenation of 4-spirocyclopropane isoxazolidines with zinc and acetic acid affords 1,3-amino alcohols bearing (methoxycarbonyl)cyclopropyl group, which can undergo intramolecular cyclization in lactone or lactame derivatives with bi- or tricyclic framework with conservation of cyclopropyl ring.

4. Experimental

4.1 General

Reaction progress was monitoring using thin layer chromatography (TLC) on precoated Silufol UV–254 plates. The IR spectra were measured on a Bruker Tensor 27 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or acetone-d_6 using a Bruker Avance 400 or a Bruker DPX–300 spectrometers. CHN elemental analyses were carried out using 185-B Analyzer Hewlett Packard. The compounds **4**, **5** and **1c** were synthesized following a procedure described in the literature [3d, 3b].

4.2 General procedure

Reductive cleavage of isoxazolidines with Zn: To a solution of isoxazolidine (0.5 mmol) in Et_2O or THF (20 mL/mmol) kept in an ice bath were added glacial acetic acid (2.93 mL/mmol) and activated Zn dust (20 equiv). The suspension was allowed to reach reflux in Et_2O (or at 60°C in THF) and was stirred vigorously for 2-4 h. The solids were filtered off and the filtrate was neutralized with NaOH 2M under cooling. The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (30 mL). The combined organic phases were concentrated in a vacuum and the residue was purified by column chromatography on silicagel eluting with a petroleum ether/ethyl acetate mixture.

Methyl (1a,6a)-5-(4-methoxyphenyl)-4,7-dioxo-9-phenyl-5-aza-8-oxatricyclo[4.3.0.0^{1,3}]nonane-3-carboxylate (3c) obtained from 265 mg isoxazolidine 1c. Yield of 3c 122 mg (62%). White solid, m.p. 185–186°C. IR, ν ($CHCl_3$): 3052, 2960, 1798 s, 1724 s, 1612, 1514, 1442, 1378, 1348, 1300, 1254, 1182, 1138 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73 (d, *J* = 5.9 Hz, 1H), 2.34 (d, *J* = 5.9 Hz, 1H), 3.83 (s, 3H), 3.96 (s, 3H), 4.66 (s, 1H), 5.60 (s, 1H), 6.90–6.98 (m, 2H), 7.35–7.40 (m, 2H), 7.45–7.57 (m, 5H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7 (CH_2), 37.5 (C), 39.1 (C), 52.7 (CH_3), 55.2 (CH), 59.5 (CH_3), 79.0 (CH), 114.1 (2CH), 125.8 (2CH), 126.8 (2CH), 129.4 (2CH), 129.6 (CH), 131.3 (C), 137.9 (C), 158.2 (C), 166.9 (CO), 167.1 (CO), 171.4 (CO). $C_{22}H_{19}NO_6$; calcd. C 67.17, H 4.87, N 3.56; found C 67.24, H 5.00, N 3.54.

Methyl (Z)-2-[hydroxy(phenyl)methyl]-2-[phenyl(phenylamino)methyl]cyclopropane carboxylate 6 obtained from 385 mg isoxazolidine 4. Yield of 6 260 mg (67%). White solid, m.p. 138–139°C. R_f 0.40 (EtOAc/hexane = 1:3). IR, ν ($CHCl_3$): 3606 br, 3420 br, 3064, 2955, 1727 s, 1620, 1509, 1453, 1320, 1175, 1123 cm^{-1}. ^{1}H NMR (300 MHz, acetone-d_6): δ = 1.39 (dd, *J* = 8.7, 5.1, 1H), 1.55 (dd, *J* = 8.7, 5.8 Hz, 1H), 1.65 (dd, *J* = 5.8, 5.1 Hz, 1H), 3.67 (s, 3H), 4.42–4.47 (m, 1H), 4.56 (d, *J* = 4.4 Hz, 1H), 4.64 (d, *J* = 5.1 Hz, 1H), 5.10 (d, *J* = 4.4 Hz, 1H), 6.03–6.10 (m, 2H), 6.43–6.50 (m, 1H), 6.83–6.92 (m, 2H), 7.12–7.23 (m, 3H), 7.25–7.36 (m, 5H), 7.42–7.50 (m, 2H) ppm. ^{13}C NMR (75 MHz, acetone-d_6): δ = 15.3 (CH_2), 24.6 (CH), 41.2 (C), 51.7 (CH_3), 57.0 (CH), 72.4 (CH), 113.1 (2CH), 117.0 (CH), 126.0 (2CH), 127.2 (2CH), 128.3 (2CH), 128.5 (2CH), 128.7 (2CH), 129.8 (2CH), 132.5 (C), 141.1 (C), 147.9 (C), 172.3 (CO) ppm. $C_{25}H_{25}NO_3$: calcd. C 77.49, H 6.50, N 3.61; found C 77.45, H 6.55, N 3.56.

Methyl (E)-2-[hydroxy(phenyl)methyl]-2-[phenyl(phenylamino)methyl]cyclopropane carboxylate 7 obtained from 385 mg isoxazolidine 5. Yield of 7 296 mg (76%). White solid, m.p. 139–140°C. R_f 0.20 (EtOAc/hexane = 1:5). IR, ν ($CHCl_3$): 3610 br, 3434 br, 3074, 2959, 1726 s, 1602, 1509, 1490, 1445, 1318, 1178 cm^{-1}. ^{1}H NMR (300 MHz, acetone-d_6): δ = 1.75–1.78 (m, 2H), 2.49 (dd, *J* = 8.0, 6.5 Hz, 1H), 3.32 (s, 3H), 4.09 (d, *J* = 6.5 Hz, 1H), 4.50 (d, *J* = 4.4 Hz, 1H), 4.65 (d, *J* = 6.5 Hz, 1H), 4.68 (d, *J* = 4.4 Hz, 1H), 6.43–6.50 (m, 1H), 6.87–6.95 (m, 2H), 7.29–7.32 (m, 4H), 7.38–7.40 (m, 5H) ppm. ^{13}C NMR (75 MHz, acetone-d_6): δ = 17.9 (CH_2), 22.1 (CH), 39.5 (C), 51.7 (CH_3), 58.2 (CH), 71.8 (CH), 112.4 (2CH), 116.9 (CH), 128.1 (2CH), 128.4 (2CH), 128.5 (CH), 128.8 (2CH), 129.0 (2CH), 129.3 (2CH), 132.4 (C), 140.3 (C), 143.6 (C), 147.4 (C), 172.3 (CO). $C_{25}H_{25}NO_3$: calcd. C 77.49, H 6.50, N 3.61; found C 77.38, H 6.58, N 3.52.

4-phenyl-5-[phenyl(phenylamino)methyl]-3-oxabicyclo[3.1.0]hexan-2-one 8 obtained from 385 mg isoxazolidine 4. Yield of 8 71 mg (20%). White solid, m.p. 82–83°C. R_f 0.32 (EtOAc/hexane = 1:3). IR, ν ($CHCl_3$): 3422 br, 3054, 2936, 1768 s, 1604, 1504, 1498, 1432, 1310, 1170, 1116 cm^{-1}. ^{1}H NMR (300 MHz, acetone-d_6): δ = 1.16–1.24 (m, 2H), 1.59 (dd, *J* = 8.7, 3.6 Hz, 1H), 4.36 (d, *J* = 8.0 Hz, 1H), 5.72 (s, 1H), 6.00 (d, *J* = 8.0 Hz, 1H), 6.24 (d, *J* = 7.3 Hz, 2H), 6.42–6.52 (m, 1H), 6.87–6.96 (m, 2H), 7.24–7.38 (m, 8H), 7.42–7.48 (m, 2H) ppm. ^{13}C NMR (75 MHz, acetone-d_6): δ = 13.0 (CH_2), 22.0 (CH), 38.7 (C), 55.2 (CH), 84.2 (CH), 113.4 (CH), 117.3 (CH), 127.4 (2CH), 128.4 (2CH), 128.7 (2CH), 129.2 (2CH), 129.3 (CH), 129.4 (2CH), 129.6 (2CH), 133.2 (C), 137.9 (C), 147.1 (C), 174.9 (CO) ppm. $C_{25}H_{25}NO_3$: calcd. C 77.49, H 6.50, N 3.61; found C 77.38, H 6.55, N 3.59.

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References

[1]. A. Hassner, I. Namboothiri, Organic Syntheses based on Name Reactions; Pergamon, Elsevier (2012) p. 60. (b) A. Brandi, A. Guarna, A. Goti, F. De Sarlo, Tetrahedron Lett. (1986) 27, 1727.

[2]. A. Brandi, S. Garro, A. Guarna, A. Goti, F. Cordero, F. De Sarlo, J. Org. Chem. (1988), 53, 2430. (b) F. M. Cordero, A. Goti, F. De Sarlo, A. Guarna, A. Brandi, Tetrahedron. (1989), 45, 5917. (c) A. Brandi, Y. Dürüst, F. M. Cordero, F. De Sarlo, J. Org. Chem. (1992), 57, 5666. (d) F. M. Cordero, A. Brandi, C. Querci, A. Goti, F. De Sarlo, A. Guarna, J. Org. Chem. (1990), 55, 1762. (e) A. Brandi, F. M. Cordero, F. De Sarlo, A. Goti, A. Guarna, Synlett. (1993), 1. (f) F. M. Cordero, F. De Sarlo, A. Brandi, Monatsh. Chem. (2004), 135, 649.

[3]. Diev V.V., Tran Q.T., Molchanov A. P. Eur. J. Org. Chem. (2009), 525; b) T. Q. Tran, V. V. Diev, A. P. Molchanov, Tetrahedron (2011), 67, 2391. c) A. P. Molchanov, T. Q. Tran, R. R. Kostikov, Russ. J. Org. Chem. (2011), 47, 269; d) A. P. Molchanov, T. Q. Tran, Russ. J. Org. Chem. (2012), 48, 1283; e) A. P. Molchanov, T. Q. Tran, Chem.Heterocycl. Comp. (2013), 49, 479; f) A.P. Molchanov, T.Q. Tran, A.V. Stepakov, G.L.Starova, R.R. Kostikov, Russ. J. Org. Chem. (2014), 50, 78.

[4]. Tran T.Q., Diev V.V., Starova G. L., Gurzhiy V.V., Molchanov A.P. Eur. J. Org. Chem. (2012), 2054

[5]. Huisgen R., Hauck H., Grashey R., Seidl H. Chem. Ber. (1968), 101, 2568; b) Huisgen R., Hauck H., Grashey R., Seidl H. Chem. Ber. (1969), 102, 736; c) LeBel N. A., Post M. E., Whang J. J. J. Am. Chem.. Soc. (1964), 86, 3759.

[6]. Budzińska A., Sas W. Tetrahedron, (2001), 57, 2021–2030; b) Tice C. M., Ganem B. J. Org. Chem, (1983), 48, 5048–5050; c) Chiacchio U., Piperno A., Rescifina A., Romeo G., Uccella N. Tetrahedron, (1998), 54, 5695–5708; d) LeBel N. A., Post M. E., Whang J. J. J. Am. Chem.. Soc. (1964), 86, 3759; e) Tice C. M., Ganem B. J. Org. Chem. (1983), 48, 5048.

[7]. Merino P., Mates J.A., Revuelta J., Tejero T., Chiacchio U., Romeo G., Iannazzo D., Romeo R. Tetrahedron: Asymmetry, (2002), 13, 173; b) Cordero F.M., Pisaneschi F., Batista K.M., Valenza S., Machetti F., Brandi A. J. Org. Chem., (2005), 70, 3, 856.

[8]. Cicchi S., Goti A., Brandi A., Guarna A., De Sarlo F. Tetrahedron Lett. (1990), 31, 3351; b) F. Pisaneschi, C. Della Monica, F. M. Cordero, A. Brandi, Tetrahedron Lett. (2002), 43, 5711.

[9]. S. Cicchi, J. Revuelta, A. Zanobini, M. Betti, A. Brandi Synlett, (2003), 2305.

[10]. Revuelta, J.; Cicchi, S.; Brandi, A. Tetrahedron Lett. (2004), 45, 8375.

[11]. Molchanov A.P., Tran T.Q., Stepakov A.V., Kostikov R.R. Russ. J. Org. Chem. (2016), 52, 404.