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BIOMIMETIC SYNTHESIS OF 4,4′-DIMETHOXYCARBONYL-2,2′-BIOXAZOLE

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Abstract – Serine and oxalic acid were used as building blocks of natural origin to prepare 2,2′-bioxazole bearing methoxycarbonyl groups at 4,4′ positions.

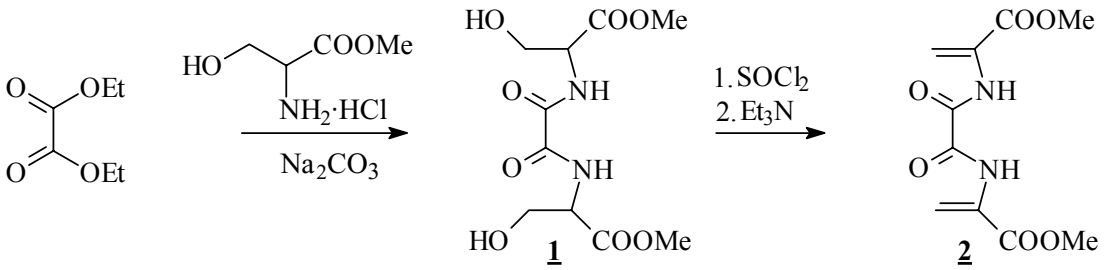
A 1,3-oxazole ring appeared to be widely distributed as a structure element of complex molecules occurring in nature, and many of the 1,3-oxazole derivatives are found to be biologically active.[1] In a number of cases, the oxazole rings create, in a single biomolecule, a polyring system, of which usually two or three oxazoles are directly joined to each other by a bond between C-2 and C-4′ of the neighboring ring.[2,3] In the natural polyoxazoles, the preferential points of attachment (C-2 and C-4), being close to nitrogen (N-3), is probably the result of a biosynthetic pathway, in which one α-amino acid molecule (e.g. serine) participates in the formation of both oxazole rings by the inclusion of its carboxylic carbon in the structure of one ring [as C(2)] and the remaining carbons and nitrogen of the serine molecule in the skeleton of the other one [C(4′), N(3′), C(5′)-O].

Of interest was if the natural occurrence of 2,4′-bioxazole derivatives is only the result of the biogenetic restriction to a limited number of substrates, or, when using other simple naturally occurring chemical compounds, an isomeric product, unsubstituted 2,2′-bioxazole or its 4,4′-dimethoxycarbonyl derivative, can also be obtained, at least, on a biomimetic pathway. The known few examples of a chemical synthesis of C-2 and C-2′ joined two oxazole rings concern the system in which they are fused with benzene or are bearing either aryl or alkyl groups, like 4,4′,5,5′-tetramethyl-2,2′-bioxazole,[4] 2,2′-dibenzoxazole obtained either by a fotodehydrodimerization,[5] or a couprous acetate oxidation,[6] and 5,5′-diphenyl-2,2′-bioxazole[7] obtained by a dimerization of 5-phenyloxazole using butyllithium, hexachloroethane and a borane complexation procedure. The last method of the 2,2′ bond formation is an original one, and its adaptation to an unsubstituted oxazole[8] could be interesting, but, similarly to the previously mentioned methods, it

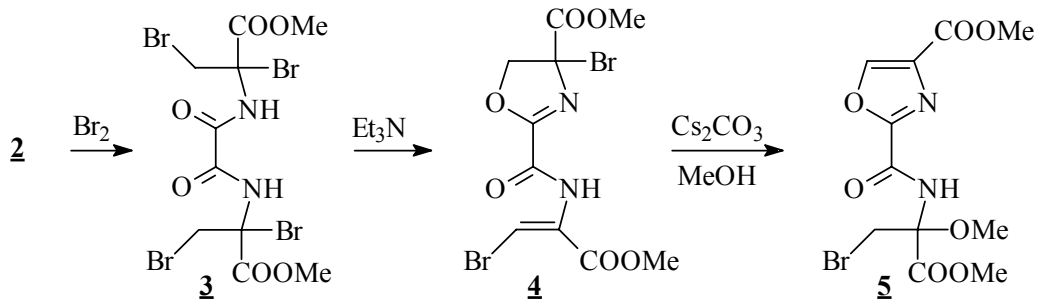
will not fulfil the requirements of the biomimetic character of a synthesis.

To achieve our goal, we assumed the use of oxalic acid to afford the central bond in the final product, which should be formed by a symmetrical functionalization of both termini of the acid molecule. First, we tried to oxidize 2,2′-bioxazoline prepared by a cyclization of an intermediate, *N*,*N*′-bis(2-hydroxyethyl)oxamide, according to the Wenker procedure,[9] but the known methods which were proved to be perfect or, at least, satisfactory for a single oxazoline ring oxidation, failed in our case, leading to a decomposition of the starting material when NiO_2, MnO_2, DDQ or $CuBr_2$ was used. Surprisingly, the bicyclic compound was inert to bromine oxidation, and, therefore, we tried to carry out such a synthesis, using 2,2′-bioxazoline, bearing methoxycarbonyl groups at C-4 and C-4′ in the molecule, of which the formation of the intermediate containing bromine and the α,β-unsaturated ester from it should be easier, because of the presence of the electrophilic substituent.

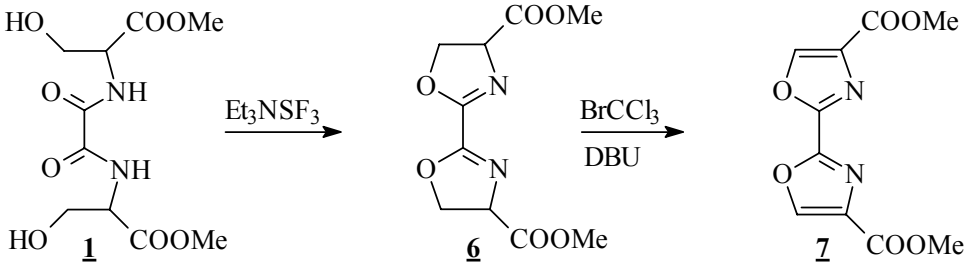
In attempts to carry out a synthesis of such a bioxazoline derivative, diethyl oxalate was allowed to react with serine methyl ester and the resulting *N*,*N*′-bis(2-hydroxy-1-methoxycarbonylethyl)oxamide (**1**) was subjected to cyclodehydration by treating the product successively with thionyl chloride [to *N*,*N*′-bis-(2-chloro-1-methoxycarbonylethyl)oxamide], and, then, with triethylamine, from the result of which the occurrence of an elimination reaction, yielding *N*,*N*′-bis(1-methoxycarbonylvinyl)oxamide (**2**), was the only process observed. Similar results were obtained when **1** was allowed to react with mesyl chloride in the presence of triethylamine.



The ready formation of the undesirable, unsaturated product prompted us to verify the possibility of making use of this material. A bromine addition to both vinyl fragments of the molecule of **2** and, next, an elimination of one pair of hydrogen bromides should lead to a corresponding dibromobioxazoline formation, while the successive elimination of the second pair should change the oxazoline system into the final bioxazole derivative. Such a procedure was found to be successful only for a half of a molecule yielding indeed first *N*,*N*′-bis(1,2-dibromo-1-methoxycarbonylethyl)oxamide (**3**), which, however, when treated successively with triethylamine and cesium carbonate in MeOH was transformed into *N*-(2-bromo-1-methoxycarbonylvinyl)-4-bromo-4-methoxycarbonyl-2-oxazolinecarboxamide (**4**) and *N*-(2-bromo-1-methoxy-1-methoxycarbonylethyl)-4-methoxycarbonyl-2-oxazolecarboxamide (**5**),[10] respectively.



Finally, the synthesis of the desired bioxazole system was achieved by a dehydrative cyclization of **1** under the influence of (diethylamino)sulfur trifluoride (DAST)[11] to 4,4′-dimethoxycarbonyl-2,2′-bioxazoline (**6**),[12] which, when treated with $BrCCl_3$ in the presence of DBU, underwent oxidation to 4,4′-dimethoxycarbonyl-2,2′-bioxazole (**7**).[13,14]



In summary, we have demonstrated that, based on oxalic acid and serine as a natural starting material, a synthesis of 2,2′-bioxazole, bearing substituents at 4 and 4′ positions, is possible. However, we also found that during such a symmetrically, simultaneously carried out construction of both the termini of the molecule being built, though remaining under identical external reactions conditions, the termini do not always behave in exactly the same manner, due to intramolecular interactions. Probably for the same reason, the two rings composing a 2,2′-bioxazoline molecule, often reveal different chemical properties from those of the separated, single ring.

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10. Found for **5**: Y: 78%, mp 198-200ºC; EIMS m/z: 366, 364 (0.8%, M^+), 307, 305 (100%); MS FAB (NBA): 367, 365 (100%, M + 1); HRMS: for $C_{11}H_{14}N_2O_7{}^{79}Br$ calcd 364.99844, found 364.99498, for $C_{11}H_{14}N_2O_7{}^{81}Br$ calcd 366.99640, found 366.99580; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.53 (d, *J* 10.2, 1H, CH_2Br), 3.73 (s, 3H), 3.80 (s, 3H), 3.96 (s, 3H), 4.03 (d, *J* 10.2, 1H, CH_2Br), 7.71 (s, 1H, H-5), 7.99 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 34.4 (CH_2Br), 52.1 (OCH_3), 53.8 (OCH_3), 63.2 (OCH_3), 74.9 (C-1′), 103.1, 156.7 and 158.1 (C-2, C-4 and C-5), 162.3, 163.8 and 165.2 (C=O); IR (KBr) cm^{-1}: 3197, 3113, 1772, 1740, 1647, 1280, 1254, 1194, 1157, 1095, 1053.
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12. Found for **6**: Y: 57%, mp 194-196ºC; EIMS m/z: 256 (8%, M^+), 197 (100%, M – CO_2Me), 169 (59%); HRMS: for $C_{10}H_{12}N_2O_6$ calcd 256.06955, found 256.06799; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.81 (2 lines separated by Δν = 0.55 Hz, OCH_3), 4.60-4.67 (4 lines, 1H, H-5), 4.72-4.78 (6 lines, 1H, H-5), 4.95-5.01 (8 lines, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ: 52.92 (CH_3), 68.62 (C-4), 70.53 (C-5), 156.64 (C-2), 169.99, 170.02 (2 lines separated by Δν = 2.46 Hz, C=O); IR (KBr) cm^{-1}: 1739, 1613, 1211, 1149, 1039. The absorption splitting of both the carbonyl carbons and methyl protons, as well as the complicated pattern of the ring protons, even at 600 MHz, showed a presence of a diastereomeric mixture (*meso* and racemic modification). The *meso* form was separated by recrystallization from PhH-CH_2Cl_2 (mp 196ºC) and its structure was proved by NMR spectrum and X-Ray diffraction method. When L-serine was used as a starting material, the obtained enantiomeric product (**6**) of mp 104°C and $[\alpha]_D$ = +249,7° ($CHCl_3$) showed a simple proton spectrum, δ: 3.81 (CH_3), 4.64 (dd, J_{gem} 9.1, J_{vic} 11.0, H-5), 4.75 (dd, J_{gem} 9.1, J_{vic} 8.6, H-5), 4.98 (dd, J_{vic} 11.0 and 8.6, H-4).
13. Found for **7**: Y: 33%, mp 259-260ºC; EIMS m/z: 252 (100%, M^+); HRMS: for $C_{10}H_8N_2O_6$ calcd 252.03824, found 252.03961; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.97 (s, 3H, OCH_3), 8.41 (s, 1H, H-5), ^{13}C NMR ($CDCl_3$) δ: 52.54 (OCH_3), 135.18 (C-4), 145.43 (C-5), 150.59 (C-2), 160.53 (C=O); IR (KBr) cm^{-1}: 3147, 3107, 2967, 1730, 1567, 1488, 1437, 1316, 1288,1203, 1160, 1120, 1095, 1001, 936, 915, 810, 774 and 687. [Except for the first three medium absorptions, all the other signals were of a strong intensity].
14. To prepare 2,2′-bioxazole and **7**, a few other approaches were checked, mainly using *N*,*N*′-bis(2,2-dimethoxyethyl)oxamide and *N*,*N*′-bis[2-(1,3-diethoxymalonyl)]oxamide as the intermediates [in the last case, adapting the method described by R. Shapiro, *J. Org. Chem.*, 1993, **58**, 5759], but no positive results were obtained.