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№ 12111-6251/344

3 февраля 2020 г.

ЭКСПЕРТНОЕ ЗАКЛЮЧЕНИЕ О ВОЗМОЖНОСТИ ОПУБЛИКОВАНИЯ

Руководитель-эксперт Федерального государственного бюджетного учреждения науки Института элементоорганических соединений им. А.Н.Несмеянова Российской академии наук, рассмотрев ***статью Teslenko Fedor E., Churakov Artem I., Larin Alexander A., Ananyev Ivan V., Fershtat Leonid L., Makhova Nina N. « Route to 1,2,4-and 1,2,5-oxadiazole ring assemblies via a one-pot condensation/oxidation protocol», направляемую в журнал Tetrahedron Letters,*** подтверждает, что в материале ***не содержатся*** сведения, предусмотренные Постановлением Правительства РФ №1233 от 30.11.1994г. и на публикацию материала ***не следует*** получать разрешение ***Минобрнауки России и/или Президиума РАН***

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Tetrahedron Letters 61 (2020) 151678

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Route to 1,2,4- and 1,2,5-oxadiazole ring assemblies *via* a one-pot condensation/oxidation protocol

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ARTICLE INFO

Article history:
Received 14 November 2019
Revised 16 January 2020
Accepted 24 January 2020
Available online 28 January 2020

Keywords:
Oxadiazoles
Nitrogen heterocycles
Condensation
Synthetic
Methods

ABSTRACT

A novel one-pot approach for the synthesis of 1,2,4- and 1,2,5-oxadiazole ring assemblies has been developed. The synthetic strategy involves the condensation of furoxanyl amidoximes with aldehydes and subsequent iodine-mediated oxidation of the intermediate 1,2,4-oxadiazolines. The analogous reaction of 4-aminofuroxanyl-3-carboxamidoxime results not only in formation of the 1,2,4-oxadiazole subunit, but also rearrangement of the furoxan ring to the furazan one, which is the first example of a Lewis acid-promoted rearrangement in a furoxan series.

The 1,2,4-oxadiazole ring is a valuable heterocyclic scaffold incorporated in a number of pharmaceutical compounds (Fig. 1): azilsartan (treatment of hypertension) [1], prenoxdiazine (cough suppressant) [2] and ataluren (treatment of Duchenne muscular dystrophy) [3]. In addition, various 1,2,4-oxadiazole derivatives exhibit a wide range of pharmacological activities: anti-inflammatory [4], antimicrobial [5], neuroprotective [6] and anticancer [7]. The 1,2,4-oxadiazole motif is also considered as a bioisostere for amide or ester functionalities thus enabling its wide applicability in medicinal chemistry and drug design [8].

Another type of oxadiazoles – 1,2,5-oxadiazoles (furazans) and their *N*-oxides (furoxans) have been widely studied in recent years [9]. Furazans and furoxans demonstrate diverse biological activities, including antibacterial [10], antiparasitic [11] and cytotoxic [12]. Furthermore, furoxans correspond to a widely studied subclass of exogenous nitric oxide donors and possess vasodilating and anticoagulant properties [13]. Recent trends in the medicinal chemistry of these systems has shifted toward the construction of 1,2,5-oxadiazole-based hybrids comprising of a heterocyclic motif linked to a known pharmaceutical scaffold through an appropriate linker [14]. In addition, furazans and furoxans with high nitrogen and oxygen contents are of interest in the design of next-generation high-energy density materials: primary and secondary explosives, pyrotechnics and propellants [15]. Therefore, we intended to develop a simple synthetic methodology to access 1,2,4- and 1,2,5-oxadiazole ring assemblies.

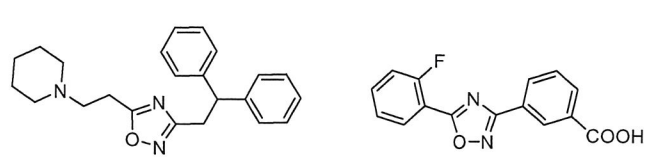

Fig. 1. Representative drugs featuring a 1,2,4-oxadiazole motif.

Several methods for the synthesis of (1,2,4-oxadiazolyl)-1,2,5-oxadiazoles were previously reported. In particular, a general route for the synthesis of (1,2,4-oxadiazolyl)furazans involved the condensation of furazanyl amidoximes with various carboxylic acid derivatives (chlorides [16], anhydrides [17], nitriles [18], amides [19]). However, such methods suffer from harsh reaction conditions and have a limited substrate scope. Another approach for the synthesis of 1,2,4-oxadiazoles is based on the condensation of amidoximes with carbonyl compounds [20]. The synthesis of several representatives of (1,2,4-oxadiazolyl)furoxans under mild

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https://doi.org/10.1016/j.tetlet.2020.151678
0040-4039/

(carbamoyl)furazan **6**. Thermal cleavage of the annulated 2,5-dihydro-1,2,4-oxadiazole ring also has literature precedent [29].

In summary, we have developed a direct one-pot method for the synthesis of 1,2,4- and 1,2,5-oxadiazole ring assemblies based on the condensation of furoxanyl amidoximes with aldehydes followed by iodine-mediated oxidation of the formed 1,2,4-oxadiazolines [30]. In the case of an amidoxime bearing an aminofuroxan motif the reaction proceeds further enabling rearrangement of the furoxan ring to the furazan one. To the best of our knowledge, it is the first example of a Lewis acid-promoted rearrangement in a furoxan series. Overall, a facile synthesis of (1,2,4-oxadiazolyl)furazans and furoxans potentially enables the wider application of these derivatives in medicine and related fields.

This work was supported by the Russian Foundation for Basic Research (grant # 18–33-20030). I.V. Ananyev is thankful to the Russian President's Council for Grants (project MK-3372.2019.3) for the support of X-ray diffraction studies and theoretical calculations. Generous allotment of computational time from Computational Center of Novosibirsk State University (www.nusc.ru) is gratefully acknowledged.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151678.

References

[1] C.M. Perry, Clin. Drug Invest. 32 (2012) 621.
[2] L. Csuros, Ther. Hung. (English edition) 37 (1989) 50.
[3] E.M. Welch, E.R. Barton, J. Zhuo, Y. Tomizawa, W.J. Friesen, P. Trifillis, S. Paushkin, M. Patel, C.R. Trotta, S. Hwang, R.G. Wilde, G. Karp, J. Takasugi, G. Chen, S. Jones, H. Ren, Y.-C. Moon, D. Corson, A.A. Turpoff, J.A. Campbell, M.M. Conn, A. Khan, N.G. Almstead, J. Hedrick, A. Mollin, N. Risher, M. Weetall, S. Yeh, A.A. Branstrom, J.M. Colacino, J. Babiak, W.D. Ju, S. Hirawat, V.J. Northcutt, L.L. Miller, P. Spatrick, F. He, M. Kawana, H. Feng, A. Jacobson, S.W. Peltz, H.L. Sweeney, Nature 447 (2007) 87.
[4] (a) M.A. Weidner-Wells, T.C. Henninger, S.A. Fraga-Spano, C.M. Boggs, M. Matheis, D.M. Ritchie, D.C. Argentieri, M.P. Wachter, D. Hlasta, Bioorg. Med. Chem. Lett. 14 (2004) 4307;
(b) N.M.M. Bezerra, S.P. De Oliveira, R.M. Srivastava, J.R. Da Silva, Il Farmaco 60 (2005) 955.
[5] (a) A.G. Tyrkov, L.T. Sukhenko, Pharm. Chem. J. 38 (2004) 376;
(b) Y.W. Jo, W.B. Im, J.K. Rhee, M.J. Shim, W.B. Kim, E.C. Choi, Bioorg. Med. Chem. 12 (2004) 5909;
(c) D. Rakesh, R.B. Sun, R.P. Lee, P. Tangallapally, R.E. Lee, Eur. J. Med. Chem. 44 (2009) 460;
(d) C.G. Fortuna, C. Bonaccorso, A. Bulbarelli, G. Caltabiano, L. Rizzi, L. Goracci, G. Musumarra, A. Pace, A.P. Piccionello, A. Guarcello, P. Pierro, C.E.A. Cocuzza, R. Musumeci, Eur. J. Med. Chem. 65 (2013) 533.
[6] (a) T. Huhtiniemi, T. Suuronen, V.M. Rinne, C. Wittekindt, M. Lahtela-Kakkonen, E. Jarho, E.A.A. Wallren, A. Salminen, A. Poso, J. Leppanen, J. Med. Chem. 51 (2008) 4377;
(b) M. Koufaki, C. Kiziridi, F. Nikoloudaki, M.N. Alexis, Bioorg. Med. Chem. Lett. 17 (2007) 4223;
(c) S.B. Tiwari, D.V. Kohli, Med. Chem. Res. 17 (2008) 386;
(d) M. Ono, M. Haratake, H. Saji, M. Nakayama, Bioorg. Med. Chem. 16 (2008) 6867.
[7] (a) H.-Z. Zhang, S. Kasibhatla, J. Kuemmerle, W. Kemnitzer, K. Ollis-Mason, L. Qiu, C. Crogan-Grundy, B. Tseng, J. Drewe, S.X. Cai, J. Med. Chem. 48 (2005) 5215;
(b) K.A. Jessen, N.M. English, J.Y. Wang, S. Maliartchouk, S.P. Archer, L. Qiu, R. Brand, J. Kuemmerle, H.-Z. Zhang, K. Gehlsen, J. Drewe, B. Tseng, S. Xiong Cai, S. Kasibhatla, Mol. Cancer Ther. 4 (2005) 761;
(c) S. Fujii, K. Ohta, T. Goto, H. Kagechika, Y. Endo, Bioorg. Med. Chem. 17 (2009) 344.
[8] (a) K. Luthman, S. Borg, U. Hacksell, Methods Mol. Med. 23 (1999) 1;
(b) J. C. Jochims, in Comprehensive Heterocyclic Chemistry, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, Oxford, 2nd edn., 1996, vol. 4, ch. 4.04, pp. 179–228.;
(c) K. Hemming, in Comprehensive Heterocyclic Chemistry, ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, Amsterdam, 3rd edn., 2008, vol. 5, ch. 5.04, pp. 243–314.
[9] (a) L.L. Fershtat, N.N. Makhova, Russ. Chem. Rev. 85 (2016) 1097;
(b) N.N. Makhova, L.L. Fershtat, Tetrahedron Lett. 59 (2018) 2317.
[10] N.D. Segretti, R.A.M. Serafim, M.C.F. Segretti, M. Miyata, F.R. Coelho, O. Augusto, E.I. Ferreira, Bioorg. Med. Chem. Lett. 26 (2016) 3988.
[11] (a) L. Boiani, G. Aguirre, M. González, H. Cerecetto, A. Chidichimo, J.J. Cazzulo, M. Bertinaria, S. Guglielmo, Bioorg. Med. Chem. 16 (2008) 7900;
(b) R.A.M. Serafim, J.E. Gonçalves, F.P. de Souza, A.P. de Melo Loureiro, S. Storpirtis, R. Krogh, A.D. Andricopulo, L.C. Dias, E.I. Ferreira, Eur. J. Med. Chem. 82 (2014) 418;
(c) P. Hernández, R. Rojas, R.H. Gilman, M. Sauvain, L.M. Lima, E.J. Barreiro, M. González, H. Cerecetto, Eur. J. Med. Chem. 59 (2013) 64;
(d) S. Guglielmo, D. Cortese, F. Vottero, B. Rolando, V.P. Kommer, D.L. Williams, R. Fruttero, A. Gasco, Eur. J. Med. Chem. 84 (2014) 135;
(e) G.F. dos Santos Fernandes, P.C. de Souza, L.B. Marino, K. Chegaev, S. Guglielmo, L. Lazzarato, R. Fruttero, M.C. Chung, F.R. Pavan, J.L. dos Santos, Eur. J. Med. Chem. 123 (2016) 523.
[12] (a) A. S. Kulikov, A. A. Larin, L. L. Fershtat, L. V. Anikina, S. A. Pukhov, S. G. Klochkov, M. I. Struchkova, A. A. Romanova, I. V. Ananyev, N. N. Makhova, Arkivoc, 2017, iii, 250.;
(b) A.S. Kulikov, M.A. Epishina, A.I. Churakov, L.V. Anikina, L.L. Fershtat, N.N. Makhova, Mendeleev Commun. 28 (2018) 623;
(c) S.A. Pukhov, L.V. Anikina, A.A. Larin, L.L. Fershtat, A.S. Kulikov, N.N. Makhova, Russ. Chem. Bull., Int. Ed. 68 (2019).
[13] (a) N.E. Ustyuzhanina, L.L. Fershtat, M.L. Gening, N.E. Nifantiev, N.N. Makhova, Mendeleev Commun. 26 (2016) 513;
(b) N.E. Ustyuzhanina, L.L. Fershtat, M.L. Gening, N.E. Nifantiev, N.N. Makhova, Mendeleev Commun. 28 (2018) 49;
(c) B.V. Lyalin, V.L. Sigacheva, L.L. Fershtat, N.N. Makhova, V.A. Petrosyan, Mendeleev Commun. 28 (2018) 518.
[14] L.L. Fershtat, N.N. Makhova, ChemMedChem 12 (2017) 622.
[15] L.L. Fershtat, N.N. Makhova, ChemPlusChem (2020), https://doi.org/10.1002/cplu.201900542.
[16] V.G. Andrianov, E.N. Rozhkov, A.V. Eremeev, Chem. Heterocycl. Compd. 30 (1994) 470.
[17] (a) M.D. Coburn, J. Heterocycl. Chem. 5 (1968) 83;
(b) T.I. Godovikova, S.K. Vorontsova, L.D. Konyushkin, S.I. Firgang, O.A. Rakitin, Russ. Chem. Bull., Int. Ed. 57 (2008) 2440.
[18] V.N. Yarovenko, V.K. Taralashvili, I.V. Zavarzin, M.M. Krayushkin, Tetrahedron 46 (1990) 3941.
[19] S.D. Shaposhnikov, N.V. Korobov, A.V. Sergievskii, S.V. Pirogov, S.F. Mel'nikova, I.V. Tselinskii, Russ. J. Org. Chem. 38 (2002) 1351.
[20] (a) W. Wang, H. Xu, Y. Xu, T. Ding, W. Zhang, Y. Ren, H. Chang, Org. Biomol. Chem. 14 (2016) 9814;
(b) M. Adib, A.H. Jahromi, N. Tavoosi, M. Mahdavi, H.R. Bijanzadeh, Tetrahedron Lett. 47 (2006) 2965.
[21] L.L. Fershtat, I.V. Ananyev, N.N. Makhova, RSC Adv. 5 (2015) 47248.
[22] (a) H. Wei, C. He, J. Zhang, J.M. Shreeve, Angew. Chem., Int. Ed. 54 (2015) 9367;
(b) A.I. Stepanov, V.S. Sannikov, D.V. Dashko, A.G. Roslyakov, A.A. Astrat'ev, E. V. Stepanova, Chem. Heterocycl. Compd. 51 (2015) 350.
[23] A.B. Sheremetev, D.E. Dmitriev, N.K. Lagutina, M.M. Raihstat, A.S. Kiselyov, M. N. Semenova, N.N. Ikizalp, V.V. Semenov, Mendeleev Commun. 20 (2010) 132.
[24] J. C. Jochims in Comprehensive Heterocyclic Chemistry, 2nd ed., Vol. 4 (Eds. A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, 1996, pp. 179-228.
[25] E. Kobayashi, A. Kishi, H. Togo, Eur. J. Org. Chem. (2019) 7335.
[26] L.L. Fershtat, A.A. Larin, M.A. Epishina, I.V. Ovchinnikov, A.S. Kulikov, I.V. Ananyev, N.N. Makhova, RSC Adv. 6 (2016) 31526.
[27] (a) D.M. Bystrov, L.L. Fershtat, N.N. Makhova, Chem. Heterocycl. Compd. 55 (2019) 1143;
(b) M.A. Epishina, A.S. Kulikov, N.N. Makhova, Russ. Chem. Bull., Int. Ed. 57 (2008) 644;
(c) E.S. Zhilin, D.M. Bystrov, I.V. Ananyev, L.L. Fershtat, N.N. Makhova, Chem. Eur. J. 25 (2019) 14284;
(d) E.S. Zhilin, L.L. Fershtat, D.M. Bystrov, A.S. Kulikov, A.O. Dmitrienko, I.V. Ananyev, N.N. Makhova, Eur. J. Org. Chem. (2019) 4248.
[28] (a) J.E. Baldwin, J. Chem. Soc., Chem. Commun. (1976,) 734;
(b) I.V. Alabugin, K. Gilmore, Chem. Commun. 49 (2013) 11246.
[29] D.M. Bystrov, E.S. Zhilin, L.L. Fershtat, A.A. Romanova, I.V. Ananyev, N.N. Makhova, Adv. Synth. Catal. 360 (2018) 3157.
[30] General procedure. A mixture of amidoxime **1a,b** (1 mmol), aldehyde (8 mmol), I_2 (0.4 g, 1.57 mmol) and $Sc(OTf)_3$ (0.1 mmol) was stirred at 65 °C for 24 h. Then the reaction mixture was cooled to room temperature and EtOAc (20 mL) was added. The resulted solution was washed with 1M $Na_2S_2O_3$ (1x20 mL) to remove the excess iodine. The organic layer was separated and the solvent was removed under reduced pressure. The residue was dissolved in acetone (25 mL) and a solution of $KMnO_4$ (1.42 g, 8 mmol) in H_2O (20 mL) was added. The resulted mixture was heated at reflux for 2 h to oxidize the excess aldehyde. Oxalic acid was added until the complete dissolution of the formed MnO_2. Then $NaHCO_3$ (4.7 g, 56 mmol) was added. The final mixture was extracted with EtOAc (3x30 mL), the organic extracts were combined, washed with brine (2x30 mL) and dried over $MgSO_4$. Filtration of the drying agent and evaporation of the solvent afforded a crude product which was purified by flash chromatography on SiO_2.