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ЭКСПЕРТНОЕ ЗАКЛЮЧЕНИЕ О ВОЗМОЖНОСТИ ОПУБЛИКОВАНИЯ

Руководитель-эксперт Федерального государственного бюджетного учреждения науки Института элементоорганических соединений им. А.Н.Несмеянова Российской академии наук, рассмотрев ***статью Fershtat Leonid L., Chaplygin Daniil A., Ananyev Ivan V., Makhova Nina N. «Divergent Synthesis of Five-Membered Nitrogen Heterocycles via Cascade Reactions of 4-Arylfuroxans», направляемую в журнал SYNTHESIS-STUTTGART,*** 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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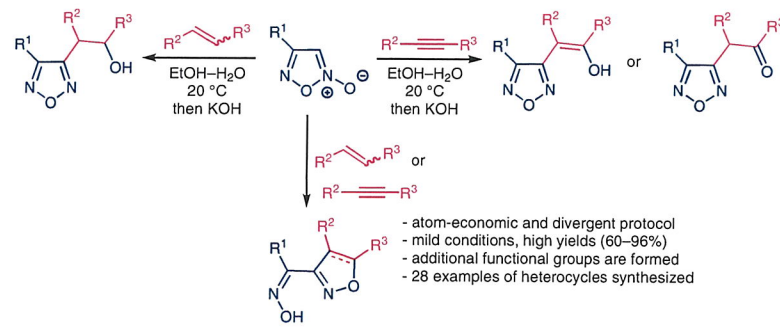
Synthesis D. A. Chaplygin et al. Paper

Divergent Synthesis of Five-Membered Nitrogen Heterocycles via Cascade Reactions of 4-Arylfuroxans

Daniil A. Chaplygin[a]
Ivan V. Ananyev[b,c]
Leonid L. Fershtat*[a]
Nina N. Makhova[a]

[a] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Leninsky prosp., 47, Moscow, Russian Federation
fershtat@bk.ru
[b] A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991, Vavilova str., 28, Moscow, Russian Federation
[c] National Research University Higher School of Economics, 101000, Moscow, Russian Federation



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Abstract A novel method for the synthesis of a diverse series of functionally substituted five-membered heterocyclic compounds via atom-economic, regio-, and diastereoselective one-pot reaction cascade was developed. This approach involves a ring opening in 4-arylfuroxans to α-oximinoarylacetonitrile oxides followed by [3+2] cycloaddition to various dipolarophiles to afford multisubstituted isoxazoles and isoxazolines. Subsequent azole–azole rearrangement of (oximino)isoxazolines/-isoxazoles, which can be conducted in a one-pot manner, results into functionally substituted furazans formation. The developed protocol is operationally simple, proceeds in mild conditions and with high yields of target heterocyclic systems. Overall, this study represents a new mode of isoxazole and 1,2,5-oxadiazole functionalization strategy, which is useful in medicinal and materials chemistry.

Key words nitrogen heterocycles, 1,2,5-oxadiazole, rearrangement, cascade reactions, [3+2] cycloaddition

Nitrogen heterocycles are the most frequently occurring structural motifs in various pharmaceuticals and promising drug candidates.[1] Recent analysis of a database of U.S. FDA approved drugs revealed that 59% of clinically used small-molecule medicines incorporate a nitrogen heterocycle subunit.[2] However, the construction of individual pharmaceutical scaffolds using known synthetic methodologies often involves multi-step and energy-consuming procedures or suffers from a lack of reproducibility and scalability. Therefore, a creation of novel step-economy protocols for the assembly of various nitrogen-containing heterocyclic scaffolds remains highly urgent.[3]

Among nitrogen heterocycles isoxazoles and their partially hydrogenated analogues isoxazolines are of special interest due to numerous pharmacological activities displayed by these heterocyclic systems.[4,5] In addition, isoxazole core is a common structural subunit in various pharmaceuticals, such as flucloxacillin, valdecoxib, and leflunomide. Another structural derivatives of isoxazole family – 1,2,5-oxadiazoles (furazans) – constitute an important class of heterocycles that have found a myriad of applications in organic chemistry.[6] Furazans possess a number of useful properties to be part of organic solar cells[7] and exhibit various pharmacological activities.[8] Recently, azofurazan derivative was recommended as a broad-spectrum antibiotic with a desired pharmacological profile.[9] On the other hand, furazan subunit is an essential structural motif in a number of modern energetic materials with excellent performance and a high level of environmental compatibility.[10]

Despite the structural similarity, synthetic routes to the isoxazole (isoxazoline) and furazan scaffolds are different. A construction of the isoxazole core is usually achieved through a [3+2] cycloaddition of various dipolarophiles to nitrile oxides, which are generated in situ from the corresponding chloroximes,[11] nitrolic acids,[12] or aliphatic nitro compounds[13] (Scheme 1a). However, these methods for nitrile oxides generation have some limitations on functional group tolerance and require an additional synthetic step for the preparation of the corresponding dipolar precursors.[13] An assembly of the 1,2,5-oxadiazole framework is usually accomplished via a dehydrative cyclization of tailor-made vicinal dioximes.[14] This process usually entails refluxing the precursor in a high-boiling solvent (100–150 °C) in the presence of a strong base, such as NaOH or KOH (Scheme 1b). However, such a method requires a multi-step preparation of dioxime precursors and usually suffers from harsh reaction conditions. These disadvantages preclude the presence of base-sensitive functional groups and stereocenters, elsewhere in the molecule.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 33.8, 55.1, 112.9, 116.4, 120.0, 126.6, 128.3, 128.8, 130.4, 134.0, 135.4, 149.6, 154.5, 159.5, 194.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{15}N_2O_3$: 295.0999; found: 295.1002.

Diethyl 2-Hydroxy-3-(4-phenyl-1,2,5-oxadiazol-3-yl)maleate (6o)

A mixture of *cis*- and *trans*-isomers; pale yellow solid; yield: 177 mg (89%); mp 138–139 °C; R_f = 0.78 (EtOAc–EtOH 3:1).

IR (KBr): 3434, 2986, 1734, 1670, 1450, 1372, 1267, 1105, 1031, 966, 862, 776 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.58 (t, *J* = 7.1 Hz, 3 H), 0.75 (t, *J* = 7.0 Hz, 1.5 H), 0.93 (t, *J* = 7.0 Hz, 3 H), 1.22 (t, *J* = 7.1 Hz, 1.5 H), 3.64 (q, *J* = 7.1 Hz, 1 H), 3.73 (q, *J* = 7.0 Hz, 2 H), 3.94 (q, *J* = 7.0 Hz, 2 H), 4.08 (q, *J* = 7.1 Hz, 1 H), 7.45–7.51 (m, 4.5 H), 7.75 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 13.5 (2 C), 14.1, 14.4, 57.0, 59.2, 59.7, 60.6, 82.5, 126.9, 127.3, 127.4, 127.6, 128.0, 128.6, 129.0, 129.4, 129.9, 130.4, 151.6, 154.5, 165.8, 166.9, 169.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}N_2O_6$: 333.1079; found: 333.1081.

Diethyl 2-Hydroxy-3-[4-(3-methoxyphenyl)-1,2,5-oxadiazol-3-yl]maleate (6p)

A mixture of *cis*- and *trans*-isomers; pale yellow solid; yield: 187 mg (86%); mp 101–102 °C; R_f = 0.74 (EtOAc–EtOH 3:1).

IR (KBr): 3434, 2986, 1726, 1660, 1535, 1468, 1368, 1257, 1002, 1035, 863, 781 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.85 (t, *J* = 7.1 Hz, 3 H), 1.00 (t, *J* = 7.1 Hz, 1.5 H), 1.23–1.29 (m, 4 H), 3.79 (s, 3 H), 3.82 (s, 1.5 H), 3.85 (q, *J* = 7.1 Hz, 2 H), 3.98 (q, *J* = 6.9 Hz, 1 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 4.22 (q, *J* = 6.9 Hz, 1 H), 7.08–7.17 (m, 1.5 H), 7.26–7.33 (m, 2.5 H), 7.44 (t, *J* = 7.8 Hz, 1.5 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 13.5, 13.7, 13.8,,13.9, 55.2, 55.4, 59.4, 61.1, 111.9, 112.9, 113.2, 116.1, 116.6, 116.8, 119.6, 120.2, 127.3, 130.3, 130.5, 148.5, 148.9, 154.2, 159.5, 164.8, 165.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{19}N_2O_7$: 363.1187; found: 363.1189.

Scale-Up Experiment for 1-Phenyl-2-(4-phenyl-1,2,5-oxadiazol-3-yl)ethanol (6d)

A solution of 4-phenylfuroxan (**1a**; 0.486 g, 3 mmol) in EtOH (10 mL) was added dropwise to a magnetically stirred solution of styrene (0.707 mL, 6 mmol) in H_2O (10 mL) at 20 °C. The resulting solution was stirred for 4 h at 20 °C and then a solution of KOH (0.34 g, 6 mmol) in EtOH (0.85 mL) was added. The reaction mixture was stirred for 40 min at 20 °C and concd HCl was added till pH 7. The resulting mixture was poured into H_2O (40 mL) and extracted with $CHCl_3$ (5 × 10 mL). The combined organic layers were dried (anhyd $MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on SiO_2 to afford **6d**; yield: 638 mg (80%).

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Supporting Information

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