Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2024, **34**, 398–400

Mendeleev Communications

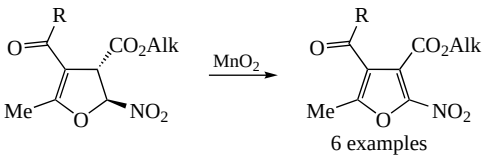
Nitrofuran-3-carboxylates: synthesis and structure

Kirill A. Gomonov,[a] Vasilii V. Pelipko,[a] Igor A. Litvinov,*[b] Stanislav I. Selivanov,[c] Ruslan I. Baichurin[a] and Sergey V. Makarenko*[a]

[a] *Herzen State Pedagogical University of Russia, 191186 St. Petersburg, Russian Federation. E-mail: kohrgpu@yandex.ru*
[b] *A. E. Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center of the Russian Academy of Sciences, 420088 Kazan, Russian Federation. E-mail: litvinov@iopc.ru*
[c] *Institute of Chemistry, St. Petersburg State University, 199034 St. Petersburg, Russian Federation. E-mail: nmr.group.spbu@gmail.com*

DOI: 10.1016/j.mencom.2024.04.027

Nitrofuran-3-carboxylates were obtained by selective oxidation of *trans*-2,3-dihydronitrofuran-3-carboxylates with manganese dioxide in toluene. The structure of nitrofuran-3-carboxylates was characterized by physicochemical methods, including X-ray diffraction analysis.



Keywords: nitrodihydrofurans, nitrofurans, oxidation, manganese dioxide, X-ray diffraction analysis.

Nitrofurans, a well-known class of compounds,[1–3] are currently still of interest[4–6] due to the wide range of their biological activity.[1–14] For example, some 5-nitrofuran-2-carbohydrazides are used as antibiotics[2,8] and demonstrate antimicrobial[1,3,5,8] and antiparasitic[9] activity. In addition, nitrofurans are used as anti-tuberculosis agents,[4,7,13,14] and 5-nitrofuran-2-carboxylates are active against HIV-1.[11,12]

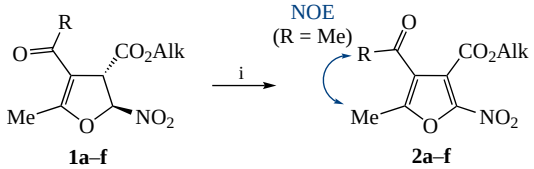
The main method for the preparation of 2(5)-nitrofurans containing various substituents is the nitration reaction,[15–19] a version of which in the form of *ipso*-nitration is used for the 2-nitro-5-acetylfuran[20] synthesis. Nitrofurans can be prepared by the condensation of 1,1,2-trichloro-2-nitroethene with β-dicarbonyl compounds,[22] or by the C–C bond selective oxidation of their nitro dihydro precursors with sodium nitrite.[23] It should be noted that the oxidation of the dihydro precursors (with manganese dioxide,[24–26] iodobenzodiacetate,[25] hypervalent iodine[27] or 2,3-dichloro-5,6-dicyanobenzoquinone[28–30]) is also used for the synthesis of furans, including nitrofurans.

Representatives of substituted nitrofuran-3-carboxylates are prepared using a few methods.[31–34] Thus, the condensation of 2-nitro-1-phenylethan-1-one with ethyl 3-nitropent-2-enoate affords ethyl 2-ethyl-4-nitro-5-phenylfuran-3-carboxylate.[31] The action of bases on a 3-nitropyridinium salt containing a strong electron-withdrawing substituent (2-$CF_3C_6H_4$), leads to ethyl 2-methyl-5-nitro-4-(2-trifluoromethylphenyl)furan-3-carboxylate.[32] Reaction of 5-methoxyfuroxano[3,4-*d*]pyrimidine with alkyl acetoacetates results in 2-methyl-5-nitrofuran-3-carboxylates.[33] Dimethyl 2-nitrofuran-3,4-dicarboxylates containing a 5-positioned aromatic substituent were obtained by nitration of furan-3,4-dicarboxylates.[34]

We herein suggest a method for nitrofuran-3-carboxylates synthesis by the selective oxidation of *trans*-2,3-dihydro-2-nitrofuran-3-carboxylates, the latter being readily available from the reaction of alkyl 3-bromo-3-nitroacrylates and aliphatic CH acids.[35] There are no literary analogies to the oxidation of nitrodihydrofurans with manganese oxide of similar structures containing a nitro group.

In fact, the oxidation of nitrodihydrofuran-3-carboxylates **1a**–**f** with manganese dioxide in toluene at room temperature proceeds for 7 days and successfully completes with the formation of the corresponding nitrofuran-3-carboxylates **2a**–**f** in yields up to 57% (Scheme 1).† Attempts to obtain nitrofuran **2d** by nitration of ethyl 4-acetyl-5-methylfuran-3-carboxylate in acetyl nitrate,[35] both in the presence and in the absence of sulfuric acid, led to tarring of the reaction mass from which it was not possible to isolate the target product.

The structures of nitrofuran-3-carboxylates **2** were confirmed by ^{1}H, ^{13}C–{^{1}H}, ^{1}H–^{1}H NOESY, ^{1}H–^{13}C HMQC, HMBC NMR, IR, and UV spectroscopy. While nitrofuran dicarboxylates **2b**,**c**,**e**,**f** are individual, acetyl-containing nitrofuran carboxylates **2a**,**d** exist in the form of two conformers (NMR data, **2a′**/**2a′′** = 12 : 1 and **2d′**/**2d′′** = 17 : 1). The study of the obtained nitrofurans **2a**,**d** by the ^{1}H–^{1}H NOESY method with varying mixing times revealed the presence of a nuclear



1a–f **2a–f**

a R = Alk = Me
b R = OMe, Alk = Me
c R = OEt, Alk = Me
d R = Me, Alk = Et
e R = OMe, Alk = Et
f R = OEt, Alk = Et

Scheme 1 *Reagents and conditions*: i, MnO_2, PhMe, 18–20 °C, 7 days.

† *General procedure for the synthesis of nitrofuran-3-carboxylates* **2**. To a solution of the corresponding *trans*-2-nitro-2,3-dihydrofuran-3-carboxylate **1** (3.3 mmol) in toluene (40 ml), MnO_2 (0.26 mol) was added. The resulting mixture was stirred at 18–20 °C for 7 days. After filtration of MnO_2 and evaporation of the solvent, the oily residue was treated with hot hexane (40 ml). After cooling, the precipitate was filtered off to afford product **2** as a light-yellow crystals (or light-yellow oil for **2f**).

Overhauser effect (NOE) between the methyl group signals at the furan ring and the methyl protons of acetyl fragment for both major and minor conformers (see Scheme 1).

In the IR spectra of nitrofurans **2a–f**, the positions of the stretching vibration bands for the carbonyl group indicate that the acetyl group (1673–1684 cm^{-1}) in compounds **2a**,**d** and one of the ester groups (1722–1728 cm^{-1}) in compounds **2b**,**c**,**e**,**f** are coplanar with the furan ring and are in conjugation with its π-system,[36] while the ester group of all compounds **2a–f**, removed from conjugation, resonates in the higher frequency region (1744–1759 cm^{-1}). The absorption bands for the nitro group appear in the regions 1520–1531 cm^{-1} (ν_{as}) and 1354–1361 cm^{-1} (ν_s), characteristic of the conjugated nitro group.[21,22]

X-ray diffraction analysis of crystalline nitrofuran-3-carboxylates **2b** and **2d** (Figure 1)‡ showed that the ester group in the vicinal position to the nitro group is perpendicular to the furan ring plane [τ C(2)–C(3)–C(11)–O(12) = –91.6° (**2b**), τ C(2)–C(3)–C(10)–O(11) = 87.8° (**2d**)]. A structural feature of molecule **2d** is the proximity of the furan ring methyl group to the hydrogen atoms of the acetyl fragment; while in other furan-3-carboxylates,[35] a reversal of the acetyl fragment is observed [τ C(5)–C(4)–C(7)–O(8) = –38.2(2)°].

‡ Crystals of compounds **2b** and **2d** were obtained by slow evaporation of a hexane solution. The X-ray diffraction study was performed on a Bruker D8 QUEST automatic three-circle diffractometer at 105 K [graphite monochromator, λ(MoKα) = 0.71073 Å, ω- and φ-scan with a step of 0.5°] at the Distributed Spectral-Analytical Center of Shared Facilities for Study of Structure, Composition and Properties of Substances and Materials of The FRC Kazan Scientific Center of RAS. Single crystals of a suitable size were glued to the top of a glass fiber in a random orientation. The preliminary unit cell parameters were determined using three runs at different φ angle positions with 12 frames per run (φ-scan technique). The X-ray diffraction data were collected and indexed, and the unit cell parameters were determined and refined using the APEX2 software package.[41] The empirical absorption correction based on the crystal shape and an additional spherical correction were applied, and systematic errors were corrected using the SADABS software.[37] The structures were solved by direct methods using the SHELXT-2014/5 program package[38] and refined by the full-matrix least squares method based on F^2 using the SHELXL-2018/3 program package[39] as implemented in WinGX-2020.1.[40] Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were positioned geometrically and refined using a riding model. Intermolecular interactions were analyzed and the figures were generated with the PLATON[42] and Mercury 2020.3[43] programs, respectively.

Crystal data for **2b**. $C_9H_9NO_7$, M = 243.17, triclinic, space group $P\bar{1}$ (no. 2), 100 K, a = 7.7836(4), b = 8.5623(4) and c = 8.7753(4) Å, α = 82.783(2)°, β = 76.963(2)°, γ = 67.3940(10)°, Z = 2, V = 525.49(4) $Å^3$, d_{calc} = 1.537 g cm^{-3}, F(000) = 252. The intensities of 26117 reflections were measured [ω-scans, μ(MoK$_\alpha$) = 0.136 mm^{-1}, 5.158° ⩽ 2θ ⩽ 63.998°]. After merging of equivalents and absorption correction, 3655 unique reflections (R_{int} = 0.0515) were used for the structure solution and refinement. Final R factors: R_1 = 0.0409 [$I \geqslant 2\sigma(I)$], wR_2 = 0.1109 (all reflections), GOF = 1.016. The residual electron density extremums were –0.23 and 0.58 e $Å^{-3}$.

Crystal data for **2d**. $C_{10}H_{11}NO_6$, M = 241.20, triclinic, space group $P\bar{1}$ (no. 2), 100 K, a = 7.8477(4), b = 7.9224(4) and c = 10.1121(5) Å, α = 112.6770(10)°, β = 93.841(2)°, γ = 106.8840(10)°, Z = 1, V = 543.57(5) $Å^3$, d_{calc} = 1.474 g cm^{-3}, F(000) = 252.0. The intensities of 43417 reflections were measured [ω-scans, μ(MoK$_\alpha$) = 0.124 mm^{-1}, 6.37° ⩽ 2θ ⩽ 63.998°]. After merging of equivalents and absorption correction, 3745 unique reflections (R_{int} = 0.0683) were used for the structure solution and refinement. Final R factors: R_1 = 0.0406 [$I \geqslant 2\sigma(I)$], wR_2 = 0.1210 (all reflections), GOF = 1.046. The residual electron density extremums were –0.28 and 0.61 e $Å^{-3}$.

CCDC 2295211 (for **2b**) and 2295213 (for **2d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

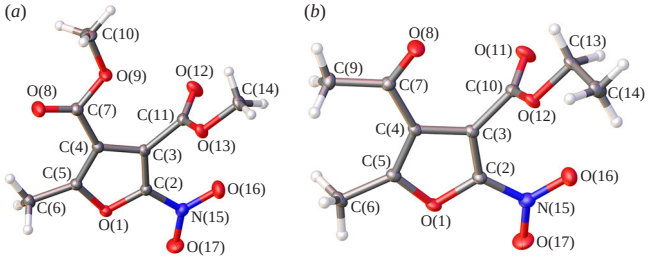


Figure 1 Geometry of (*a*) molecule **2b** and (*b*) molecule **2d** in the crystals. Ellipsoids of anisotropic displacements are shown with 50% probability.

In summary, we have suggested a convenient synthesis of nitrofuran-3-carboxylates by the oxidation of *trans*-2,3-dihydro-2-nitrofuran-3-carboxylates with MnO_2 in toluene. The structures of dimethyl 2-methyl-5-nitrofuran-3,4-dicarboxylate **2b** and ethyl 4-acetyl-5-methyl-2-nitrofuran-3-carboxylate **2d** have been characterized by single crystal X-ray diffraction analysis.

The research was supported by an internal grant of the Herzen State Pedagogical University of Russia (project no. 3VG). The X-ray diffraction study was financially supported within the framework of the state assignment for the Federal Research Center 'Kazan Scientific Center of the Russian Academy of Sciences'.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.04.027.

References

1 M. L. Grayson and M. Whitby, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs*, 6th edn., eds. M. L. Grayson, S. Cosgrove, S. Crowe, W. Hope, J. McCarthy, J. Mills, J. W. Mouton and D. Paterson, CRC Press, London, 2010, vol. 1, pp. 1195–1204.
2 M. Vass, K. Hruska and M. Franek, *Vet. Med. (Prague, Czech Repub.)*, 2008, **53**, 469.
3 G. L. Kedderis and G. T. Miwa, *Drug Metab. Rev.*, 1988, **19**, 33.
4 A. Wang, Y. Yang, Y. Jun, B. Wang, K. Lv, M. Liu, H. Guo and Y. Lu, *Bioorg. Med. Chem.*, 2018, **26**, 2073.
5 A. V. Beliatskaya, I. M. Kashlikova, A. O. Elagina, I. I. Krasnyuk, Jr., I. I. Krasnyuk and O. I. Stepanova, *Drug Dev. Regist.*, 2019, **8**, 38.
6 Ł. Popiołek, B. Rysz, A. Biernasiuk and M. Wujec, *Chem. Biol. Drug Des.*, 2020, **95**, 260.
7 H. A. K. Abdel-Aziz, W. M. Eldehna, M. Fares, T. Elsaman, M. M. Abdel-Aziz and D. H. Soliman, *Biol. Pharm. Bull.*, 2015, **38**, 1617.
8 B. L. Edhlund, W. A. Arnold and K. McNeill, *Environ. Sci. Technol.*, 2006, **40**, 5422.
9 S. Meymandi, S. Hernandez, S. Park, D. R. Sanchez and C. Forsyth, *Curr. Treat. Options Infect. Dis.*, 2018, **10**, 373.
10 R. R. Zorzi, S. D. Jorge, F. Palace-Berl, K. F. M. Pasqualoto, L. de Sá Bortolozzo, A. M. de Castro Siqueira and L. C. Tavares, *Bioorg. Med. Chem.*, 2014, **22**, 2844.
11 H. Fuji, E. Urano, Y. Futahashi, M. Hamatake, J. Tatsumi, T. Hoshino, Y. Morikawa, N. Yamamoto and J. Komano, *J. Med. Chem.*, 2009, **52**, 1380.
12 H. Yanagita, S. Fudo, E. Urano, R. Ichikawa, M. Ogata, M. Yokota, T. Murakami, H. Wu, J. Chiba, J. Komano and T. Hoshino, *Chem. Pharm. Bull.*, 2012, **60**, 764.
13 M. Krasavin, A. Shetnev, V. Panova, S. Ivanovskyi, S. Kalinin, T. Vinogradova, V. Sharoyko and P. Yablonsky, *Mendeleev Commun.*, 2022, **32**, 452.
14 E. V. Verbitskiy, S. A. Baskakova, D. V. Belyaev, G. L. Rusinov, V. N. Charushin, D. V. Vakhrusheva and N. I. Eremeeva, *Mendeleev Commun.*, 2021, **31**, 210.
15 H. N. C. Wong, X. Hou, K. Yeung and H. Huang, in *Modern Heterocyclic Chemistry*, eds. J. Alvarez-Builla, J. J. Vaquero and J. Barluenga, Wiley, Weinheim, 2011, pp. 533–592.
16 G. Aridoss and K. K. Laali, *J. Org. Chem.*, 2011, **76**, 8088.

17 R. Calvo, K. Zhang, A. Passera and D. Katayev, *Nat. Commun.*, 2019, **10**, 3410.
18 T. T. Pham, A. C. Lindsay, S. W. Kim, L. Persello, X. Chen, N. Yan and J. Sperry, *ChemistrySelect*, 2019, **4**, 10097.
19 G. A. Gamov, A. N. Kiselev, A. E. Murekhina, M. N. Zavalishin, V. V. Aleksandriiskii and D. Yu. Kosterin, *J. Mol. Liq.*, 2021, **341**, 116911.
20 K. Zhang, A. Budinská, A. Passera and D. Katayev, *Org. Lett.*, 2020, **22**, 2714.
21 L. I. Deiko, V. A. Buevich, V. S. Grineva and V. V. Perekalin, *Chem. Heterocycl. Compd.*, 1975, **11**, 1002 (*Khim. Geterotsikl. Soedin.*, 1975, 1148).
22 V. A. Buevich, L. I. Deiko and V. V. Perekalin, *Chem. Heterocycl. Compd.*, 1977, **13**, 244 (*Khim. Geterotsikl. Soedin.*, 1977, 311).
23 D. Becerra, W. Raimondi, D. Dauzonne, T. Constantieux, D. Bonne and J. Rodriguez, *Synthesis*, 2017, **49**, 195.
24 X. Bao, J. Rodriguez and D. Bonne, *Chem. Sci.*, 2020, **11**, 403.
25 V. S. Raut, M. Jean, N. Vanthuyne, C. Roussel, T. Constantieux, C. Bressy, X. Bugaut, D. Bonne and J. Rodriguez, *J. Am. Chem. Soc.*, 2017, **139**, 2140.
26 Z. Yang, M. Fan, R. Mu, W. Liu and Y. Liang, *Tetrahedron*, 2005, **61**, 9140.
27 S. C. Lu, P. R. Zheng and G. Liu, *J. Org. Chem.*, 2012, **77**, 7711.
28 F. Garzino, A. Méou and P. Brun, *Helv. Chim. Acta*, 2002, **85**, 1989.
29 F. Garzino, A. Méou and P. Brun, *Helv. Chim. Acta*, 2011, **94**, 18.
30 M. Pohmakotr, A. Issaree, L. Sampaongoen, P. Tuchinda and V. Reutrakul, *Tetrahedron Lett.*, 2003, **44**, 7937.
31 R. Ballini, S. Gabrielli and A. Palmieri, *Synlett*, 2010, 2468.
32 O. D. Mitkin, R. V. Kombarov and M. A. Yurovskaya, *Tetrahedron*, 2001, **57**, 1827.
33 G. Ya. Remennikov, V. V. Pirozhenko, S. I. Vdovenko and S. A. Kravchenko, *Chem. Heterocycl. Compd.*, 1997, **33**, 879 (*Khim. Geterotsikl. Soedin.*, 1997, 1001).
34 A. F. Oleinik, E. V. Adamskaya and K. Yu. Novitskii, *Chem. Heterocycl. Compd.*, 1982, **18**, 337 (*Khim. Geterotsikl. Soedin.*, 1982, 453).
35 K. A. Gomonov, V. V. Pelipko, I. A. Litvinov, R. I. Baichurin and S. V. Makarenko, *Mendeleev Commun.*, 2023, **33**, 11.
36 E. Pretsch, P. Bühlmann and C. Affolter, *Structure Determination of Organic Compounds*: *Tables of Spectral Data*, Springer, Berlin, Heidelberg, 2009.
37 G. M. Sheldrick, *SADABS*, University of Göttingen, Germany, 2004.
38 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Adv.*, 2015, **71**, 3.
39 G. M. Sheldrick, *Acta Crystallogr., Sect. C: Struct. Chem.*, 2015, **71**, 3.
40 L. J. Farrugia, *J. Appl. Crystallogr.*, 2012, **45**, 849.
41 *APEX2 (Version 2.1), SAINTPlus, Data Reduction and Correction Program (Version 7.31A), Bruker Advanced X-ray Solutions*, Bruker AXS Inc., Madison, WI, 2006.
42 A. L. Spek, *Acta Crystallogr., Sect. D: Biol. Crystallogr.*, 2009, **65**, 148.
43 C. F. Macrae, I. Sovago, S. J. Cottrell, P. T. A. Galek, P. McCabe, E. Pidcock, M. Platings, G. P. Shield, J. S. Stevens, M. Towler and P. A. Wood, *J. Appl. Crystallogr.*, 2020, **53**, 226.

Received: 26th December 2023; Com. 23/7353