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A simple and convenient method for the synthesis of 1,3,5-triazine-nitrolic acids. The first X-ray investigation of *Z*-isomeric nitrolic acid

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Abstract: A simple and convenient method for the preparation of 2,4-disubstituted 1,3,5-triazine-nitrolic acids has been developed. The first example of nitrolic acid with *Z*-configuration was revealed by X-ray crystallographic analysis.

Keywords: 2,4-disubstituted 1,3,5-triazin-nitrolic acids; nitrosation; NO-donors; potassium 1,3,5-triazine dinitromethanide; *Z*-configuration of nitrolic acid.

Introduction

Due to its integral role in human physiology, deficiencies in nitric oxide (NO) biosynthesis have been linked to a number of disease states [1–3]. A wide range of NO-releasing compounds, such as organic nitrates, nitrites, oximes, nitrosamines, *N*-diazeniumdiolates, *S*-nitrosothiols, and furoxans, has emerged as potential therapeutic agents [1].

Although the nitrolic acids, R-C(=NOH)NO_2, has been known since a 1873 report from Meyer [4], NO-releasing molecules of this type are rare [1]. The first example of these is a 2005 report from Oresmaa and co-workers [5], who demonstrated that 1-R-imidazole nitrolic acids are potential NO donors. Efforts of our research group have focused on the development of 1,3,5-triazines bearing differ NO-releasing moieties [6]. Some time ago we described the synthesis and NO-releasing properties of 1,3,5-triazine-nitrolic acids [7]. The synthesis, however, was inefficient and we sought to develop an improved protocol in order to obtain more material for biological studies. In the previously reported approach [7], construction of the nitrolic acid moiety gave mixture of products that required laborious silica gel chromatography to obtain the desired product. Large scale synthesis using this technique was therefore problematic. The crystalline structures of the 1,3,5-triazinenitrolic acids have not so far been determined. However, in order to understand the chemical biology of 1,3,5-triazinenitrolic acids, a better knowledge of their structural features is needed.

This report describes the optimization of 1,3,5-triazine-nitrolic acids synthesis and the results of single-crystal X-ray diffraction studies.

Results and discussion

In our previous work [7], 1,3,5-triazine-nitrolic acids **2** were obtained in ca. 65% yields using column chromatography. The synthesis was based on a nitrosation reaction of potassium 1,3,5-triazine-dinitromethanide **1** and products 2 were accompanied by zwitter-ionic dinitromethyl derivatives **3** and furoxans **4** as byproducts (Scheme 1).

In this work, our initial investigations focused on the reaction of potassium 2-dimethylamino-4-methoxy-1,3,5-triazin-6-yl-dinitromethanide with N_2O_4 in an organic solvent to generate 2-dimethylamino-4-methoxy-1,3,5-triazin-6-yl-nitrolic acid. Optimization of the reaction stoichiometry (**1**:N_2O_4 from 1:0.8 to 1:5), solvent (CH_2Cl_2, $CHCl_3$, CCl_4, DCE, hexane, benzene, toluene, chlorobenzene, xylene, and their mixtures), temperature (from -5°C to +30°C) and reagent concentration (from 0.01 mmol/mL to 1 mmol/mL) highlighted that this process could be significantly improved, providing a convenient means for the preparation of 1,3,5-triazin-nitrolic acids in high yield. After extensive screening, it was determined that

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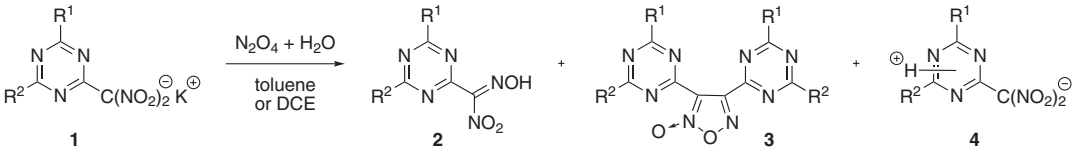

Scheme 1

potassium salts **1** (concentration of 0.5 mmol/mL) undergo a reaction with 1.2 equiv of N_2O_4 in hexane/toluene (1/10) in the presence of 1.8 equiv of H_2O at 8–10°C for 30 min to afford the desired nitrolic acids **2** in 78–93% isolated yields. The yields reflect the amount of products that precipitated directly from the reaction mixture as a fine powder. This modification resulted in a decrease in the yields of furoxanes and zwitter-ionic salts, and the desired products 2 were obtained in high purity. Moreover, the method allowed us to increase significantly the range of substituents R^1 and R^2 at the 1,3,5-triazine ring and synthesize some new nitrolic acids, which could not earlier be separated in pure form (Table 1).

Three nitrolic acids and four their salts [5, 8–12] have been previously studied by X-ray crystallographic analysis and showed to have *E*-configuration of the hydroxyimino group in all cases.

X-ray crystallographic analysis of compound **2d** (Figure 1) surprisingly showed a *Z*-configuration of the hydroxyimino group rather than an *E*-form as would be expected from the literature data. An asymmetric unit cell contains one molecule of compound **2d**. Triazine ring is planar and the methoxy group is located in the plane of the ring. The morpholine fragment adopts a chair conformation. The hydroxyimino group of the nitrolic moiety is coplanar with the triazine ring while the nitro group appears to be nearly perpendicular to it: the C3-C4-N4-O2 torsion angle is 81.6(2)°. No intramolecular hydrogen bonds are observed. On the other hand, highly directed intermolecular O1-H1…N3 hydrogen bond (O-N 2.751(3) Å, H…N 1.90 Å, <NHO 177°) is formed between molecules related by the screw axis. Also, the O1…O4 close contact (2.744(3) Å) is observed that results in formation of layers parallel to the *bc* crystallographic plane.

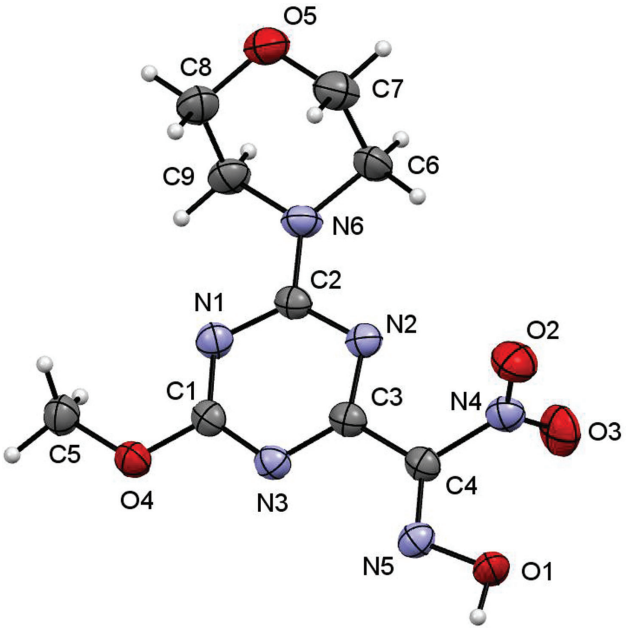

Figure 1 General view of the structure of compound **2d,** as derived from the X-ray diffraction analysis, with the atom numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

Table 1 Yields of 1,3,5-triazin-nitrolic acids **2a–n**.

Product[a,b]	R^1	R^2	Yield (%)[c]	
			Reported [7]	Modified
2a	OMe	NMe_2	72	92
2b	OMe	$N(CH_2)_4$	55	84
2c	OMe	$N(CH_2)_5$	68	85
2d	OMe	$N(CH_2CH_2)_2O$	75	91
2e	NMe_2	NMe_2	60	78
2f	$OC_6H_4NO_2$-p	NMe_2	57	81
2g	OMe	OMe	80	93
2i	OPr	OPr	68	82
2j	$OC_6H_4NO_2$-p	$N(CH_2)_5$	–	84
2k	OC_6H_4Br-p	$N(CH_2)_5$	–	79
2l	OCy	OCy	–	80
2m	OMe	$N(CH_2)_6$	–	92
2n	$OC_6H_4NO_2$-m	NEt_2	–	84

[a]The identity of products **2a–i** was confirmed by spectral comparison with authentic samples [7]. [b]Products **3** and **4** are minor impurities, see [7] for isolation and characterization. [c]Isolated yields.

Conclusion

A simple and short protocol for a rapid assembly of 1,3,5-triazine-nitrolic acids is described. The products were isolated in good yields and with satisfactory purity after a simple filtration and washing after short reaction times. This approach is an improvement of the previously

described method as it does not require column chromatography, can be performed on a large scale, and allows facile isolation of the product as a stable and easily handled solid. The procedure may prove useful for the synthesis of a wide variety of new analogs. The first example of a nitrolic acid moiety of *Z*-configuration is also reported.

Experimental

All solvents and chemicals were reagent grade and used without further purification. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. FT-IR spectra were recorded on an Avatar 360 ESP spectrometer using KBr pellets. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a JEOL JNM ECX-400 spectrometer in acetone-d_6 as a solvent. Elemental analyses were performed on a Eurovector EA 3000 microanalyzer.

X-ray diffraction analysis

Single crystals of compound **2d**, suitable for X-ray analysis, were grown by slow cooling of an acetonitrile solution. Reflections for compound **2d** were collected on a SMART APEX2 difractometer [λ(Mo-Kα)] = 0.71073 Å, graphite monochromator, ω-scans) at 100 K. Collected data were analyzed by the SAINT and SADABS programs incorporated into the APEX2 program package [13]. The structure was solved by the direct methods and refined by the full-matrix least-squares procedure against F^2 in anisotropic approximation. All hydrogen atoms were placed in geometrically calculated positions and refined within a riding model. The refinement was carried out with the SHELXTL program [14].

Compound **2d** ($C_9H_{12}N_6O_5$): monoclinic, space group $P2_1/c$: a = 17.353(3)Å, b = 5.9450(10)Å, c = 12.761(2)Å, β = 110.882(3)°, V = 1230.0(4)Å^3, Z = 4, M = 284.25, d_{calc}= 1.535 g·cm^{-3}, μ = 0.127 mm^{-1}, $F(000)$ = 592, wR_2 = 0.1229, GOF = 1.008 for 2636 independent reflections with 2θ<54°, R_1= 0.0513 for 1749 reflections with $I>2\sigma(I)$.

CCDC 1062721 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

General procedure for 2

A solution of N_2O_4 (12 mmol, 1.1 g) in hexane (2 mL) was added dropwise to a suspension of potassium salt **1** (10 mmol) in a mixture of toluene (20 mL) and water (18 mmol, 0.32 mL) at room temperature. The resulting mixture was stirred for 30 min at 8–10°C, and the white solid formed (a mixture of the product **2** with KNO_3) was filtered off and washed with water (10 mL) and finally toluene (20 mL) to give desired product **2**. The yields are presented in Table 1.

2-(Piperidin-1-yl)-4-(4-nitrophenoxy)-1,3,5-triazin-6-yl-nitrolic acid (2j) Mp 143–145°C (dec); IR: 2950, 2933, 2858, 1604, 1583, 1554, 1515, 1500, 1481, 1448, 1421, 1382, 1365, 1332, 1288, 1234, 1162, 1135, 1118, 1049, 1006, 983, 929, 862, 852, 806, 786 cm^{-1}; ^{1}H NMR: δ 12.72 (s, 1H), 8.39–8.31 (m, 2H), 7.65–7.53 (m, 2H), 3.86–3.72 (m, 2H), 3.72–3.58 (m, 2H), 1.68 (ddd, 2H, J = 11.0, 5.8, 3.5 Hz), 1.57 (dtd, 4H, J = 16.9, 5.6, 2.8 Hz); ^{13}C NMR: δ 171.2, 165.6, 163.8, 157.8, 151.6, 146.1, 125.9, 123.6, 45.7, 45.3, 26.2, 26.1, 24.8. Anal. Calcd for $C_{15}H_{15}N_7O_6$: C, 46.28; H, 3.88; N, 25.18. Found: C, 46.19; H, 3.78; N, 25.08.

2-(Piperidin-1-yl)-4-(4-bromophenoxy)-1,3,5-triazin-6-yl-nitrolic acid (2k) Mp 107–108°C (dec); IR: 2945, 2927, 2860, 1737, 1595, 1550, 1498, 1481, 1450, 1390, 1373, 1296, 1255, 1238, 1203, 1164, 1120, 1053, 1012, 975, 925, 852, 808 cm^{-1}; ^{1}H NMR: δ 7.65–7.56 (m, 2H), 7.28–7.19 (m, 2H), 3.81–3.73 (m, 2H), 3.68–3.59 (m, 2H), 1.67 (qt, 2H, J = 7.8, 3,1 Hz), 1.56 (dtd, 4H, J = 16.9, 5.6, 2.8 Hz); ^{13}C NMR: δ 171.5, 165.6, 163.8, 152.2, 151.6, 133.1, 124.7, 118.8, 45.5, 45.1, 26.2, 26.1, 24.9. Anal. Calcd for $C_{15}H_{17}N_6O_4Br$: C, 42.43; H, 4.11; N, 19.85. Found: C, 42.37; H, 4.13; N, 19.97.

2,4-Bis(cyclohexyloxy)-1,3,5-triazin-6-yl-nitrolic acid (2l) Mp 158–161°C (dec); IR: 2937, 2860, 1569, 1558, 1539, 1488, 1421, 1363, 1342, 1311, 1263, 1228, 1157, 1120, 1064, 1035, 1010, 995, 966, 891, 850, 821, 731 cm^{-1}; ^{1}H NMR: δ 12.99 (s, 1H), 5.08 (tt, 2H J = 9.1, 3.9 Hz), 2.01 (d, 2H J = 4.1 Hz), 1,79 (dt, 4H, J = 12.9, 4.1 Hz), 1.58 (dtd, 7H, J = 12.6, 9.6, 9.1, 3.5), 1.49–1.26 (m, 7H); ^{13}C NMR: δ 172.7, 165.2, 151.3, 77.9, 31.9, 25.96, 24.27. Anal. Calcd for $C_{16}H_{25}N_5O_5$: C, 51.38; H, 6.93; N, 19.13. Found: C, 51.38; H, 6.93; N, 19.06.

2-(Azepan-1-yl)-4-methoxy-1,3,5-triazin-6-yl-nitrolic acid (2m) Mp 86°C (dec); IR: 2919, 2848, 1581, 1546, 1519, 1475, 1438, 1373, 1288, 1255, 1151, 1058, 1018, 995, 842, 813 cm^{-1}; ^{1}H NMR: δ 12.66 (s, 1H), 3.94 (s, 3H), 3.84–3.76 (m, 2H), 3.76–3.68 (m, 2H), 1.80 (dt, 2H, J = 11.8, 6.5 Hz), 1.73 (dt, 2H, J = 9.8, 5.8 Hz), 1.55 (tt, 4H, J = 5.4, 3.1 Hz); ^{13}C NMR: δ 171.8, 166.2, 163.1, 151.9, 55.0, 47.9, 47.8, 27.9, 27.7. Anal. Calcd for $C_{11}H_{16}N_6O_4$: C, 44.59; H, 5.44; N, 28,36. Found: C, 44.49; H, 5.56; N, 28.28.

2-Diethylamino-4-(2-nitrophenoxy)-1,3,5-triazin-6-yl-nitrolic acid (2n) Mp 104°C (dec); IR: 3145, 3066, 2977, 2935, 2898, 2873, 2835, 2813, 1587, 1558, 1548, 1506, 1446, 1388, 1365, 1323, 1265, 1222, 1134, 1087, 1051, 975, 918, 860, 831 cm^{-1}; ^{1}H NMR: δ 12.76 (s, 1H), 8.20 (d, 1H, J = 7.3 Hz), 7.88 (t, 1H, J = 7.2 Hz), 7.69–7.48 (m, 2H), 3.57 (q, 2H, J = 7.0 Hz), 3.40 (q, 2H, J = 7.0 Hz), 1.12 (t, 3H, J = 7.0 Hz), 0.99 (t, 3H, J = 7.0 Hz); ^{13}C NMR: δ 171.1, 165.6, 163.6, 151.6, 145.8, 143.1, 136.1, 127.9, 126.3, 126.1, 43.3, 42.9, 12.9, 12.5. Anal. Calcd for $C_{14}H_{15}N_7O_6$: C, 44.57; H, 4.01; N, 25.99. Found: C, 44.44, H; 4.05; N, 25.97.

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