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1-Morpholino-2-nitroethylene as a precursor of nitroacetaldehyde in the synthesis of azolo[5,1-*c*][1,2,4]triazines

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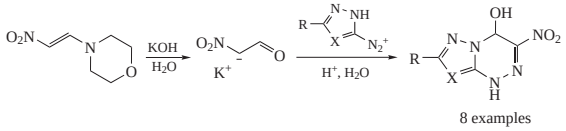
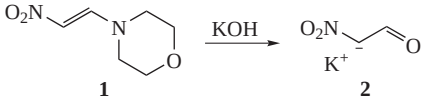
3-Nitro-4-hydroxy-1,4-dihydroazolo[5,1-*c*][1,2,4]triazines were obtained using nitroacetaldehyde potassium salt generated *in situ* from 1-morpholino-2-nitroethene.



Nitroacetaldehyde is a highly reactive compound and can be regarded as an actual building block containing both nucleophilic and electrophilic centers. This structural feature of nitroacetaldehyde is the reason of its extremely low stability. Therefore, the number of publications on the use of nitroacetaldehyde does not exceed ten. Nitroacetaldehyde is used in the synthesis of 1,2,4-triazolo[5,1-*c*][1,2,4]triazines,[1] quinolines and their precursors.[2,3] On the other hand, synthesis of complex natural polycyclic structures such as pyrrolizidine bases and (–)-rosmarinecine,[4,5] (–)-detoxinine,[6] (+)-castanospermine, (+)-6-epicastanospermine, (+)-australine, and (+)-3-epiaustraline[7,8] and aminocarbasugars[9,10] seems expedient with derivatives of nitroacetaldehyde. Thus, the development of simple and accessible methods of obtaining nitroacetaldehyde is an important objective of organic synthesis. Dimethylformamide dimethylacetal[11,12] or 2-*N*,*N*-dimethylamino-1-nitroethylene[13] are used for the synthesis of nitroacetaldehyde potassium salt. It seems implausible that nitromethane is used for producing nitroacetaldehyde.[2,3] Generation of nitroacetaldehyde potassium salt from 1-piperidino-2-nitroethylene is inconvenient.[14]

Here we propose a new efficient preparation and synthetic use of nitroacetaldehyde potassium salt *in situ*.† We used the most available aminonitroethylene, namely, 1-morpholino-2-nitroethene **1**, which was obtained by one-pot condensation of morpholine, triethyl orthoformate and nitromethane in high yield.[15–18] We have also demonstrated the successful use of both nitroacetaldehyde potassium salt and its *in situ* prepared solution‡ in the synthesis of 3-nitro-4-hydroxy-1,4-dihydroazolo[5,1-*c*][1,2,4]triazines which are of practical interest.[19]

Stirring compound **1** in an ethanolic solution with KOH (1.1 equiv.) followed by filtration affords nitroacetaldehyde potassium salt **2** in 98% yield (Scheme 1). Compound **2** was characterized by IR, ^{1}H, ^{13}C, ^{15}N NMR spectroscopy and elemental analysis. The absorption bands of salt **2** are not in common range in the IR spectrum, which is explained by the unusualness of structure and anionic form of the molecule. The ^{1}H NMR spectrum contains doublet at δ 6.31 ppm (CH–NO_2, ^3J 8.6 Hz) and the associated doublet of formyl group proton (δ 9.61 ppm, CH=O, ^3J 8.6 Hz). The ^{13}C NMR spectrum reveals two signals at δ 116.47 ppm (O_2N–C*H*K–CH=O) and at δ 181.55 ppm (O_2N–CHK–C*H*=O). ^{1}H–^{13}C and ^{1}H–^{15}N correlation can uniquely attribute the signals in the spectra to specific atoms. Thus, the proton signal at δ 6.31 ppm correlates with the only signal in the ^{15}N NMR spectrum as well as with the signal at δ 116.47 ppm in the ^{13}C NMR spectrum (HMQC). The decomposition temperature of salt **2** is 194–196 °C. Compound **2** is unstable in air and decomposes rather rapidly, but is sufficiently stable under argon.



1 **2**

Scheme 1

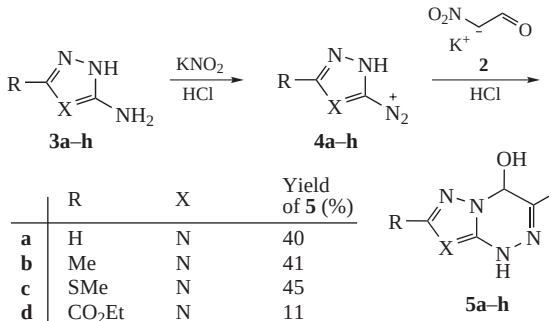
The advantage of the developed approach to salt **2** is that it can be used as obtained *in situ* by the treatment of nitroethene **1** with aqueous solution of KOH. This material readily reacts with azolyldiazonium salts **4** to afford azolotriazines **5** (Scheme 2) in 9–49% yield (*cf.* ref. 20). Low preparative yields are due to multistage purification of the product resulting in its significant loss. Azolotriazines **5a** and **5f** are crystallized as monohydrates.

Some azolotriazines **5a**,**b**,**d**,**e**,**h** are known, however the physical characteristics of the substances obtained by us do not correspond to previously reported.[20] Herein for compounds **5**, we provide sufficient spectral characteristics§ and X-ray data¶ (Figure 1), which clearly prove their structures.

Compounds **5** manifest two characteristic signals in their ^{1}H NMR spectra: δ 6.8–7.1 ppm corresponding to the 4-H atom

† *Nitroacetaldehyde potassium salt* **2**. 1-Morpholino-2-nitroethene **1** (6 g, 0.038 mol) was added to a solution of KOH (2.35 g, 0.042 mol) in EtOH (20 ml). The mixture was stirred at room temperature for 1 h, the precipitate was filtered, washed with ethanol and diethyl ether and dried. The product was stored under argon, yield 4.69 g (98%), white-pink powder, mp 194–196 °C (decomp.). ^{1}H NMR, δ: 6.31 (d, 1H, CH, *J* 8.6 Hz), 9.61 (d, 1H, CH, *J* 8.6 Hz). ^{13}C NMR, δ: 116.47 (CHK), 181.55 (CH=O). IR (ν/cm^{-1}): 557, 732, 765, 1022, 1197, 1261, 1346, 1376, 1450, 1593, 2337, 2377, 2877, 2957, 3105. Found (%): C, 18.74; H, 1.57; N, 10.84. Calc. for $C_2H_2NO_3K$ (%): C, 18.89; H, 1.59; N, 11.02.

‡ *Solution A. Nitroacetalehyde potassium salt (1 equiv.).* 1-Morpholino-2-nitroethene (1.58 g, 0.01 mol) was added to a solution of KOH (0.672 g, 0.012 mol) in water (15 ml) under cooling in the ice bath. The mixture was stirred until complete dissolution of the precipitate.



	R	X	Yield of **5** (%)
a	H	N	40
b	Me	N	41
c	SMe	N	45
d	CO_2Et	N	11
e	Ph	N	18
f	CF_3	N	25
g	2-thienyl	N	9
h	H	CCO_2Et	49

Scheme 2

of the triazine ring and the associated doublet of the OH group at δ 7.5–8.5 ppm, along with the signals of substituents R. Characteristic signals in the ^{13}C NMR spectra are observed at δ 70–74 ppm (C^4) and 130–150 ppm (C^3, C^7 and C^{8a}).

Azo coupling was performed in acidic medium to avoid the possible side reaction of diazoazoles **4** with morpholine. There are several ways of carrying out the reaction: addition of the solution of nitroacetaldehyde potassium salt to the diazoazole mixture containing excess acid to form morpholine salt or addition of diazoazole to a solution of nitroacetaldehyde formed after the addition of acid to the latter. In both cases the yields are close. The synthesis of azolotriazines **5** with a previously prepared salt **2** has no synthetic advantage over that with the nitroacetaldehyde potassium salt solution prepared *in situ*. Moreover, 1-morpholino-2-nitroethene **1** does not require special storage conditions unlike salt **2**.

In conclusion, we have developed a new effective and simple method for the synthesis of nitroacetaldehyde potassium salt and obtained new azolo[5,1-*c*][1,2,4]triazines using this reactant.

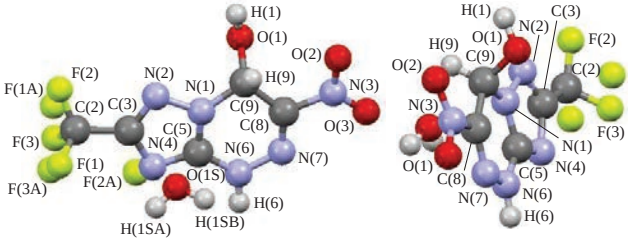


Figure 1 Molecular structure of **5f**.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.05.023.

References

1 V. L. Rusinov, A. Yu. Petrov, G. G. Aleksandrov and O. N. Chupakhin, *Chem. Heterocycl. Compd.*, 1994, **30**, 47 (*Khim. Geterotsikl. Soedin.*, 1994, **30**, 52).
2 X.-D. Ma, N. Qiu, B. Yang, Q.-J. He and Y.-Z. Hu, *Med. Chem. Commun.*, 2016, **7**, 297.
3 D. Qian, A. Q. Han, M. Hamilton and E. Wang, *Patent WO 2009/155527*, 2009 (*Chem. Abstr.*, 2009, **152**, 97479).
4 S. E. Denmark, A. Thorarensen and D. S. Middleton, *J. Org. Chem.*, 1995, **60**, 3574.
5 S. E. Denmark, A. Thorarensen and D. S. Middleton, *J. Am. Chem. Soc.*, 1996, **118**, 8266.
6 S. E. Denmark, A. R. Hurd and H. J. Sacha, *J. Org. Chem.*, 1997, **62**, 1668.
7 S. E. Denmark and E. A. Martinborough, *J. Am. Chem. Soc.*, 1999, **121**, 3046.
8 S. E. Denmark and J. J. Cottell, *J. Org. Chem.*, 2001, **66**, 4276.
9 S. E. Denmark and M. Juhl, *Helv. Chim. Acta*, 2002, **85**, 3712.
10 S. G. Zlotin, A. M. Churakov, O. A. Luk'yanov, N. N. Makhova, A. Yu. Sukhorukov and V. A. Tartakovsky, *Mendeleev Commun.*, 2015, **25**, 399.
11 T. Severin and H.-J. Böhme, *Chem. Ber.*, 1968, **101**, 2925.
12 H. Meerwein, W. Florian, N. Schön and G. Stopp, *Liebigs Ann. Chem.*, 1961, **641**, 1.
13 K. K. Babievskii, V. M. Belikov and N. A. Tikhonova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1970, **19**, 1096 (*Izv. Akad. Nauk SSSR, Ser. Khim.*, 1970, 1161).
14 C. D. Hurd and L. T. Sherwood, *J. Org. Chem.*, 1948, **13**, 471.
15 M. Faulques, L. Rene and R. Rover, *Synthesis*, 1982, 260.
16 N. Ono, *Sci. Synth.*, 2007, **33**, 359.
17 E. N. Gate, M. D. Threadgill, M. F. G. Stevens, D. Chubb, L. M. Vickers, S. P. Langdon, J. A. Hickman and A. Gescher, *J. Med. Chem.*, 1986, **29**, 1046.
18 N. S. Kondratyev, A. A. Zemtsov, V. V. Levin, A. D. Dilman and M. I. Struchkova, *Synthesis*, 2012, **44**, 2436.
19 V. L. Rusinov, E. N. Ulomskii, O. N. Chupakhin and V. N. Charushin, *Russ. Chem. Bull., Int. Ed.*., 2008, **57**, 985 (*Izv. Akad. Nauk, Ser. Khim.*, 2008, 967).
20 E. K. Voinkov, E. N. Ulomskiy, V. L. Rusinov, K. V. Savateev, V. V. Fedotov, E. B. Gorbunov, M. L. Isenov and O. S. Eltsov, *Mendeleev Commun.*, 2016, **26**, 172.
21 V. L. Rusinov, T. L. Pilicheva, O. N. Chupakhin, N. A. Klyuev and D. T. Allakhverdieva, *Chem. Heterocycl. Compd.*, 1986, **22**, 543 (*Khim. Geterotsikl. Soedin.*, 1986, **22**, 662).

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§ *3-Nitro-1,4-dihydro-1,2,4-triazolo[5,1-c][1,2,4]triazin-4-ol monohydrate* **5a**. *Method 1*. A solution of KNO_2 (0.936 g, 0.011 mol) in water (3 ml) was added portionwise to a mixture of 3-amino-1,2,4-triazole **3a** (0.84 g, 0.01 mol), water (3 ml), acetonitrile (2 ml) and 12 M HCl (4.6 ml, 0.055 mol) at –7 to –10 °C. The mixture was kept at this temperature for 10 min and the freshly prepared solution A (1.5 equiv.) was added. The mixture was kept at room temperature for 1 h. The precipitate was filtered, washed with cold acetonitrile–water (1:1) and dried in air. The product was purified by chromatography on silica gel (eluent, ethyl acetate), the most mobile fraction was separated, the solvent was removed to dryness. The residue was recrystallized from water, filtered and dried. Yield 0.808 g (32%).

Method 2. A solution of KNO_2 (0.936 g, 0.011 mol) in water (3 ml) was added portionwise to a mixture of 3-amino-1,2,4-triazole **3a** (0.84 g, 0.01 mol), water (3 ml), acetonitrile (2 ml) and 12 M HCl (3.3 ml, 0.04 mol) at –7 to –10 °C. The reaction mixture was kept at this temperature for 10 min and nitroacetalehyde potassium salt **2** (1.905 g, 0.015 mol) in water (10 ml) was added. The mixture was kept at room temperature for 1 h. Isolation and purification were carried out like in method 1. Yield 0.812 g (40%), pale yellow powder, mp 232–235 (decomp.). ^1H NMR, δ: 6.99 (d, 1H, CH, *J* 7.9 Hz), 8.03 (s, 1H, CH), 8.15 (d, 1H, OH, *J* 7.9 Hz), 13.38 (br.s., 1H, NH). ^{13}C NMR, δ: 72.50 (C^4), 142.29 (C^3), 146.03 (C^{8a}), 151.44 (C^7). DEPT-135 ^{13}C NMR, δ: 72.50 (C^4), 151.44 (C^7). IR (ν/cm^{-1}): 566, 657, 699, 751, 847, 904, 986, 1071, 1166, 1201, 1250, 1276, 1326, 1531, 1571, 1634, 2737, 2845, 3091, 3361, 3527. Found (%): C, 23.66; H, 2.89; N, 41.45. Calc. for $C_4H_4N_6O_3{\cdot}H_2O$ (%): C, 23.77; H, 2.99; N, 41.58.

¶ *Crystal data for* **5f**. $C_5H_5N_6F_3O_4$ (*M* = 270.13), monoclinic, space group $P2_1/n$, a = 11.430(12), b = 5.630(7) and c = 15.64(2) Å, β = = 103.10(10)°, V = 980(2) Å^3, μ(MoKα) = 1.714 mm^{-1}. Analysis was performed at 295(2) K on an Xcalibur 3 diffractometer by standard procedure (graphite monochromated MoKα radiation, ω-scanning). On the angles 4.36 < θ < 65.23° total of 7324 reflections were measured, 1660 unique reflections (R_{int} = 0.0390), 1507 reflections with $I > 2\sigma(I)$. The structure was solved and refined using the SHELXTL program package. The structure was defined by direct statistical methods and refined by full-matrix anisotropic approximation for F^2 for all non-hydrogen atoms with ShelXL program. The hydrogen atoms were localized by direct method and refined in the isotropic approximation. GOOF = 1.007, S = 1.038; final R values: R_1 = 0.0443, wR_2 = 0.1361 [$I > 2\sigma(I)$]; R_1 = = 0.0476, wR_2 = 0.1396 (all data). Residual electronic density max/min was 0.312/–0.247 eÅ^{-3}.

CCDC 1529899 contains 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.