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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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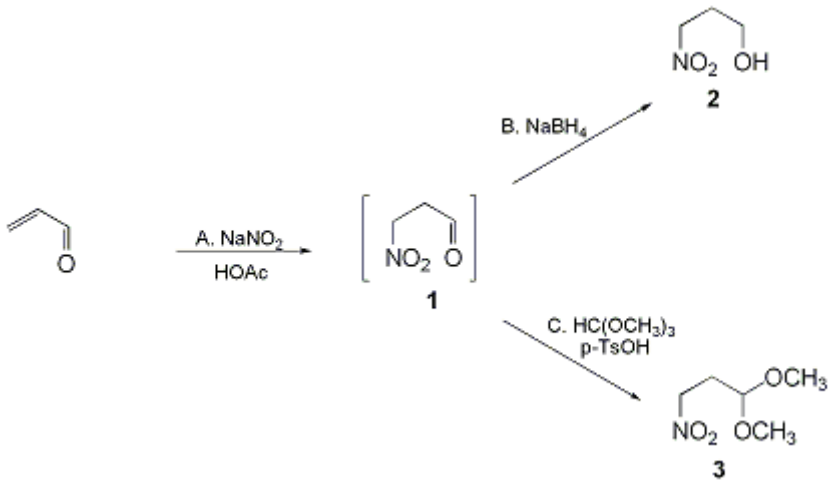
3-NITROPROPANAL, 3-NITROPROPANOL, AND 3-NITROPROPANAL DIMETHYL ACETAL

[Propanal, 3-nitro-; 1-Propanol, 3-nitro-; and Propane, 1,1-dimethoxy-3-nitro-]



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Checked by James P. Davidson and Stephen F. Martin.

1. Procedure

Caution! *Distillation of nitroalkanes in general should be conducted behind a safety shield. To avoid decomposition of distillation residues the distillation apparatus should be cooled to 0°C prior to ventilating with inert gas.*

A. 3-Nitropropanal **(1)**. A 1-L, round-bottomed flask equipped with a magnetic stirring bar, a 50-mL pressure-equalizing dropping funnel, and a Schlenk-type adapter to keep the reaction mixture under nitrogen (Note 1), is charged with 43.5 g (0.630 mol) of sodium nitrite (Note 2), 125 mL of water (Note 3), and 200 mL of tetrahydrofuran (Note 4). To the well-stirred solution at 0°C is added 33.4 mL (28.0 g, 0.500 mol) of acrolein (Note 5), then 31.5 mL (33.0 g, 0.550 mol) of acetic acid is added over a period of 30-45 min (Note 6). The reaction mixture is stirred at 0°C for another 3 hr. Then 250 mL of ethyl acetate (Note 7) and 100 mL of aqueous saturated sodium bicarbonate are added and the reaction mixture is transferred to a 1-L separatory funnel for complete neutralization, by thorough, but cautious shaking (CO_2 gas develops). The aqueous phase is separated and extracted with ethyl acetate (3 × 50 mL, (Note 7)). The organic layers are combined and washed with brine (3 × 20 mL), dried ($MgSO_4$, with stirring for 2 hr), filtered, and concentrated by rotary evaporation (20 mbar, 15 mm, 30°C). The yellow oil obtained is submitted to azeotropic distillation with toluene (2 × 50 mL, 20 mbar, 15 mm, 30° C) to remove residual water and acetic acid to give 46.0-47.0 g (89-91%) of **1** (Note 8), (Note 9). This material is used without further purification in parts **B** and **C**.

B. 3-Nitropropanol **(2)**. A 1-L, round-bottomed flask, equipped with a magnetic stirring bar and a Schlenk-type adapter (Note 1), is charged with 47.0 g (0.456 mol) of crude 3-nitropropanal and 450 mL of methanol (Note 10). To the stirred solution at −20°C (Note 11) is added 17.26 g (0.456 mol) of sodium borohydride (Note 12) in 10 portions over a period of 30 min; stirring at this temperature is continued for 1 hr. Methyl orange (0.1 mL of 0.1% solution in water) is added to the solution, followed by about 50 mL of 7.5 N hydrochloric acid in methanol (Note 13) until the suspension turns pink (Note 14). After stirring is continued at −20°C for another 30 min, the mixture is allowed to warm to room temperature over a period of 15 min and then concentrated by rotary evaporation (30°C, 20 mbar, 15

mm). The pink residue is treated with 85 g of ice and 450 mL of ethyl acetate (Note 7), then transferred to a 1-L separatory funnel. The organic layer is separated and washed with a mixture of 1 N aqueous potassium bicarbonate and brine (2 × 20 mL, 1:3). The aqueous layers are combined and extracted with ethyl acetate (2 × 100 mL, (Note 7)) as described above. The combined organic solutes are thoroughly dried ($MgSO_4$, stirring for 2 hr), filtered, and concentrated by rotary evaporation (20 mbar, 15 mm, 30°C). The residual yellow oil is purified by distillation (Note 8) in a Kugelrohr apparatus (air bath temperature: 70°C, 0.034 mbar, 0.02 mm; the product is collected by cooling with ice; duration of the distillation: ca. 90 min) to yield 34.3-34.8 g (73-74%; 65-66%, overall) of pure 3-nitropropanol as a pale yellow oil (Note 15).

C. 3-Nitropropanal dimethyl acetal **(3)**. A 1-L, round-bottomed flask, equipped with a magnetic stirring bar and a Schlenk-type adapter (Note 1), is charged with 47.0 g (0.456 mol) of crude 3-nitropropanal , 150 mL of methanol (Note 10) and 63.7 g (0.600 mol) of trimethyl orthoformate (Note 16). The stirred solution is cooled to 0°C, then 1.8 g of p-toluenesulfonic acid monohydrate (Note 17) is added and the mixture is stirred at room temperature for 4 hr (Note 18). After the volatile material is removed on a rotary evaporator (20 mbar, 15 mm, 30°C), the remaining dark liquid is neutralized with 30 mL of aqueous saturated sodium bicarbonate and diluted with 50 mL of ethyl acetate (Note 7). The mixture is transferred to a 500-mL separatory funnel, and the aqueous layer is separated and extracted with ethyl acetate (3 × 50 mL). The combined organic layers are washed with brine (2 × 20 mL), treated with $MgSO_4$ and 0.5 g of charcoal (Note 19), filtered, and concentrated by rotary evaporation (20 mbar, 15 mm, 30°C). The residual dark-yellow oil is purified by distillation (Note 8) in a Kugelrohr apparatus (air bath temperature: 55°C, 0.4 mbar, 0.3 mm); the product is collected by cooling with ice; duration of the distillation: ca. 90 min) to afford 46.2-48.2 g (68-71%; 63-65% overall) of pure 3-nitropropanal dimethyl acetal as a pale yellow oil (Note 20), (Note 21).

2. Notes

1. The reaction mixture is kept under nitrogen passed through a Sicapent® (E. Merck) drying tube.
2. Sodium nitrite ($NaNO_2$) p.a. was obtained in 1-kg samples from Merck-Schuchardt, Hohenbrunn, Germany .
3. Smaller amounts of water decrease the yield of 3-nitropropanal. If absolute solvents and reagents are used, only 10% of the nitroaldehyde is obtained.
4. Tetrahydrofuran (THF) p.a. was purchased from Merck-Schuchardt, Hohenbrunn, Germany .
5. Acrolein p.a. from Merck-Schuchardt, Hohenbrunn, Germany was distilled prior to use through a 20-cm, silver-plated, Vigreux column with a 4-cm outer and 1.5-cm inner diameter (bp 52°C).
6. The reaction is carried out in the dark to avoid decomposition and side reactions. Acetic acid p.a. was obtained from Merck-Schuchardt, Hohenbrunn, Germany .
7. Ethyl acetate (technical grade) was purified by distillation. The checkers found that reagent grade ethyl acetate could be used without purification.
8. ***Caution!*** *See introductory warning.* The submitters report that **1** can be distilled in a Kugelrohr apparatus using a manifold with high-vacuum stopcocks (air bath temperature: 55°C, 0.001 mbar, 0.0007 mm); the product is collected by cooling with ice; duration of the distillation: ca. 90 min; ventilation with nitrogen should occur after ice-cooling of the distillation flask) to afford analytically pure, almost colorless **1** in 75% yield (GLC analysis: R_t = 7.1 min, content of **1** >99%, see (Note 9) for conditions). ***Explosion hazard!*** *Do not attempt to distill **1** unless 0.001 mbar (0.0007 mm) vacuum is available; the temperature of the bath should not exceed 60°C*. The checkers found that distillation of the product at 0.04 mbar (0.03 mm), 70°C gave 35-40% yield of **1** as a yellow oil, and that the distillation residues, even when cooled and ventilated with an inert atmosphere, were prone to violent decomposition.
9. GLC analysis is as follows: R_t = 7.1 min, content of **1** >95% [column PS 086/.32 mm × 20 m glass capillary, 86:14 dimethyl/phenyl silicone; on-column injection; program: T_1 = 40°C (1 min), rate 5° C/min, T_2 = 300°C; carrier gas: 0.4 bar (300 mm) H_2]. The content of **1** is >90% according to ^1H and ^{13}C NMR. The product thus obtained decomposes on storage and should be used for further transformations within a few days. The spectroscopic data of 3-nitropropanal are as follows: ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.5, 67.7, 197.2 ; ^1H NMR (500 MHz, $CDCl_3$) δ: 3.19 (t, 2 H, J = 6.0), 4.69 (t, 2 H, J = 6.0), 9.79 (s, 1 H) ; IR ($CHCl_3$) cm^{-1}: 2844, 1723, 1561, 1375 ; mass spectrum (CI) m/z 104.0350 [$C_3H_6NO_3$ (M+1) requires 104.0348] 104 (base), 86 .

10. Methanol p.a. was obtained from Merck-Schuchardt, Hohenbrunn, Germany .
11. The temperature of the isopropyl alcohol bath was monitored by a cold finger device TK-300, Fryka Kältetechnik, Germany.
12. Sodium borohydride ($NaBH_4$) was obtained in 100-g samples (>97%) from Fluka Feinchemikalien GmbH, Neu-Ulm, Germany .
13. Hydrogen chloride, passed through a Sicapent® (E. Merck) drying tube, was fed into 500 mL of methanol (Note 10) over a period of 15 min at 0°C. The titer of the solution (7.5 N) was determined by titration with 1.0 N sodium hydroxide, Titriplex Merck-Schuchardt, Hohenbrunn, Germany against phenolphthalein as indicator.
14. The checkers found that pH indicator paper (sensitivity +/− 1 pH unit) can also be used to monitor the acidity of the solution to pH 3.
15. GLC analysis (see (Note 9) for conditions): R_t = 8.3 min, content of **2** >98%. For further purification the submitters find that the product can be distilled under reduced pressure through a 35-cm, silver-plated Vigreux column with 6-cm outer and 2-cm inner diameter (bp = 65-67°C, 0.001 mbar, 0.0007 mm); purity from GLC analysis >99.5%). The spectroscopic data of 3-nitropropanol are as follows: ^{13}C NMR (125 MHz, $CDCl_3$) δ: 29.8, 58.9, 72.6 ; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.24 (tt, 2 H, J = 5.8, 6.8), 2.56 (bt, 1 H, J = 4.6), 3.73 (dt, 2 H, J = 4.6, 5.8), 4.55 (t, 2 H, J = 6.8) ; IR ($CHCl_3$) cm^{-1}: 3620, 3424, 2939, 2891, 1552, 1433, 1382 ; mass spectrum (CI) m/z 106.0503 [$C_3H_8NO_3$(M+1) requires 106.0504] 106 (base), 88 .
16. Trimethyl orthoformate (>97%) was obtained from Fluka Feinchemikalien GmbH, Neu-Ulm, Germany and distilled prior to use, bp 101°C.
17. p-Toluenesulfonic acid monohydrate (99%) was obtained from Fluka Feinchemikalien GmbH, Neu-Ulm, Germany.
18. The progress of the reaction was monitored by TLC: R_f (3-nitropropanal) = 0.35, R_f (3-nitropropanal dimethyl acetal) = 0.53, Kieselgel 60 F_{254}, Merck-Schuchardt, Hohenbrunn, Germany; eluent: ethyl acetate/hexane (3:7).
19. Charcoal p.a., obtained from Merck-Schuchardt, Hohenbrunn, Germany , was used to decolorize the dark brown solution.
20. GLC analysis (see (Note 9) for conditions): R_t = 12.9 min, content of **3** >99%. The spectroscopic data of 3-nitropropanal dimethyl acetal **3** are as follows: ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.5, 54.0, 71.2, 101.9 ; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.31 (dt, 2 H, J = 5.4, 6.8), 3.37 (s, 6 H), 4.46 (t, 2 H, J = 6.8), 4.48 (t, 1 H, J = 5.4) ; IR ($CHCl_3$) cm^{-1}: 2938, 2837, 1556, 1447, 1378 ; mass spectrum (CI) m/z 150.0761 [$C_5H_{12}NO_4$(M+1) requires 150.0766] 118 (base), 150 .
21. From **1**, various other acetals are available under standard conditions, cf. Section 3 (Discussion). For example, following the described procedure, submitters indicate that 3-nitropropanal diethyl acetal is prepared by reaction of 30.9 g (0.300 mol) of 3-nitropropanal , 53.4 g (0.360 mol) of triethyl orthoformate , and 1.0 g of p-toluenesulfonic acid monohydrate in 100 mL of ethanol ; yield: 44.5 g (84%). GLC analysis (see (Note 9) for conditions): R_t = 14.5 min, content >99.5%. The spectroscopic data of 3-nitropropanal diethyl acetal are as follows: ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.2, 31.5, 62.6, 71.4, 100.0 ; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.21 (t, 6 H, J = 7.0), 2.30 (dt, 2 H, J = 5.3, 6.8), 3.51 (dq, 2 H, J = 7.0, 9.3), 3.68 (dq, 2 H, J = 7.0, 9.3), 4.49 (t, 2 H, J = 6.8), 4.61 (t, 1 H, J = 5.3) .

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995 and "Neue Datenblätter für gefährliche Arbeitsstoffe nach der Gefahrstoffverordnung", Welzbacher, U. (Ed.); WEKA Fachverlage, Kissing, 1991.

3. Discussion

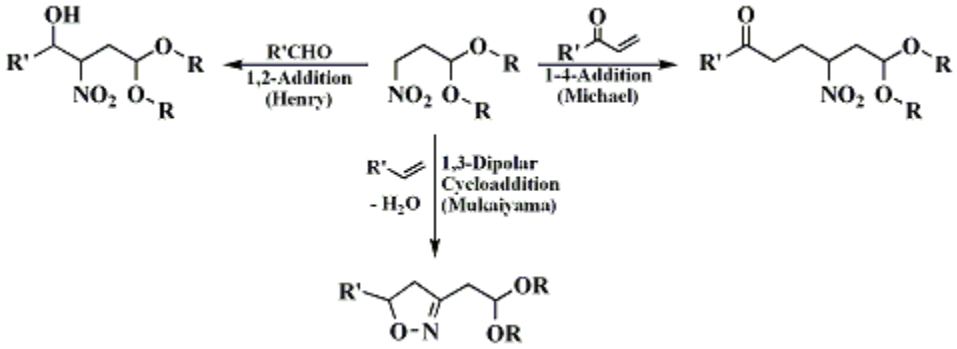
This procedure describes the preparation of 3-nitropropanal, **1**, employing the rarely encountered 1,4-addition of ambident nitrite ion with its "softer" N-atom,[2] and further transformations of **1**, as reported earlier.[3] A similar preparation of 3-nitrobutanal from crotonaldehyde (3-butenal) is known,[4] as well as analogous additions to α,β-enones.[2] The reduction of **1** to the alcohol **2**, originally carried out with borane-dimethyl sulfide (BMS),[3] is now more conveniently and economically done with sodium borohydride. The acetalization of **1** to yield the dimethyl acetal **3** is based on our earlier report.[3]

Two further preparations of 3-nitropropanal **1** have been claimed in the literature: by treatment of 1-chloro-3-nitro-2-propanol with potassium hydroxide ,[5] and by reaction of the 4-isopropyl-2-oxazolin-5-one anion with nitroethene .[6] These alternate methods are less suited and less economic for the preparation of 3-nitropropanal **1** on a multigram scale.

Procedures for the preparation of the acetals of 3-nitropropanal **1** [7] [8] [9] [10] have been reported from acrolein, by addition of hydrogen bromide in the presence of the corresponding alcohol (diol)[11] followed by bromide/nitrite exchange.[12] 3-Nitropropanol has been obtained similarly from 3-iodo- or 3-bromopropanol with silver nitrite [13] [14] and by reduction of 3-nitropropionic acid with diborane ,[15] or better, with borane-dimethyl sulfide (BMS).[3] The use of 3-nitropropionic acid as a starting material is hampered by the fact that the common precursor, β-propiolactone, is toxic and mutagenic (LD_{L0} 50 mg, oral, rat; carcinogenic group III, <1-0.1%);[16] its fumes or aerosols inflame the skin, and on inhalation it can produce pulmonary edema.[17]

Aliphatic nitro compounds are versatile building blocks and intermediates in organic synthesis,[18] [19] [20] [21,22] [23] [24] [25] cf. the overview given in the *Organic Syntheses* preparation of nitroacetaldehyde diethyl acetal.[26] For example, Henry and Michael additions, respectively, lead to 1,2- and 1,4-difunctionalized derivatives.[18,19,20,21,22,23,24,25,26,27,28] [29] [30] 1,3-Difunctional compounds, such as amino alcohols or aldols are accessible from primary nitroalkanes by dehydration/1,3-dipolar nitrile oxide cycloaddition with olefins (Mukaiyama reaction),[31] followed by ring cleavage of intermediate isoxazolines by reduction or reduction/hydrolysis.[32] [33] [34] [35] [36] [37] [38,39] [40] [41]

For synthesis of more complex target molecules by these strategies, nitroalkanes with additional O-functions are often required. Specifically, the above CC-forming additions lead to a variety of 1,3,4-, 1,3,5- and 1,3,6-functionalized structures, as shown with **3** (or nitropropyl ethers, from **2**).



Examples for the use of acetals such as **3**, of 3-nitropropanal **(1)**, and of 3-nitropropanol **(2)** or its O-protected derivatives are given in the references.[42] [43] [44,45] [46] [47] [48] [49,50] [51] [52] [53] A recent, notable application from this group is a short, high-yield synthesis of L-acosamine,[54] the arabino isomer of 3-amino-2,3,6-trideoxyhexoses that form part of many antitumor aminoglycoside antibiotics.[55]

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3-Nitropropanal:
Propanal, 3-nitro- (9); (58657-26-4)

3-Nitropropanol:
1-Propanol, 3-nitro- (8,9); (25182-84-7)

3-Nitropropanal dimethyl acetal:
Propane, 1,1-dimethoxy-3-nitro- (10); (72447-81-5)

Sodium nitrite:
Nitrous acid sodium salt (8,9); (7632-00-0)

Acrolein (8):
2-Propenal (9); (107-02-8)

Sodium borohydride;
sodium tetrahydroborate:
Borate(1−), tetrahydro-, sodium (8,9); (16940-66-2)

Methyl orange:
Benzenesulfonic acid, p-[[p-(dimethylamino)phenyl]azo]-, sodium salt (8);
Benzenesulfonic acid, 4-[[4-(dimethylamino)phenyl]azo]-, sodium salt (9); (547-58-0)

Trimethyl orthoformate:
Orthoformic acid, trimethyl ester (8);
Methane, trimethoxy- (9); (149-73-5)

p-Toluenesulfonic acid monohydrate (8);
Benzenesulfonic acid, 4-methyl-, monohydrate (9); (6192-52-5)

3-Nitropropanal diethyl acetal:
Propane, 1,1-diethoxy-3-nitro- (12); (107833-73-8)

Triethyl orthoformate:
Orthoformic acid, triethyl ester (8);
Ethane, 1,1',1''-[methylidynetris(oxy)]tris- (9); (122-51-0)