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Synthesis of nitric acid esters from alcohols in a dinitrogen pentoxide/carbon dioxide liquid system

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Organic nitric acid esters have been prepared in 89–98% yield by the nitration of the corresponding alcohols and polyols with N_2O_5 in liquid CO_2.

Nitric acid esters are used as components of high-energetic materials[1] and active ingredients of pharmaceuticals.[2] They are conventionally produced by O-nitration of alcohols with nitric acid,[3] nitric/sulfuric acid mixtures,[1(a),4] acetyl nitrate,[4(c),5] nitronium salts,[4(e),6] nitrogen oxides[7] and some other nitrating agents[8] in organic solvents or under neat conditions. Being performed in a large scale, these reactions are associated with safety and/or waste disposal problems caused by intensive heat evolution and by the presence of considerable amounts of organic nitrates in the acidic wastes and aqueous washings.[9]

A promising approach to address these issues is based on carrying out the nitration in an N_2O_5/CO_2 liquid system. Dinitrogen pentoxide is an extremely active and versatile nitrating agent which can be easily prepared in laboratory and industry by oxidation of available N_2O_4 with ozone.[10] According to the equation of this reaction (Scheme 1) nitric acid is formed as byproduct and it is recoverable for reuse.[7(g)] Inexpensive, non-toxic, incombustible and thermally stable compressed CO_2 is a suitable medium for various reactions of organic compounds.[11] The idea to combine N_2O_5 and CO_2 in nitration reactions affording high-energetic materials is not new.[12–14] This approach has been applied to the synthesis of some promising high-energetic nitric esters such as 3-methyl-3-oxetanemethyl nitrate and cyclodextrin nitrate. We expanded the area of using the N_2O_5/CO_2 liquid system to the synthesis of wider range of nitric esters, some of them having pharmaceutical application.

$$\mathrm{R(OH)}_n + 1.1n\,\mathrm{N_2O_5} \xrightarrow[\text{liquid CO}_2]{} \mathrm{R(ONO_2)}_n + \mathrm{HNO_3}$$

1a–l **2a–l**

Scheme 1 For the certain compounds, see Table 2.

At first, we examined the nitration of 1-hexanol **1c** feeding it to a solution of N_2O_5 in liquid CO_2 (55–75 bar) at 0 °C (procedure A)[†] (Table 1). The nitrate **2c** was generated in a yield of 90% when a 10 mol% excess of N_2O_5 was used and the reaction was carried out for 30 min (entry 2). Increasing of the nitrating agent amount (entry 3) or the reaction duration (entry 5) did not increase the yield.

Table 1 Nitration of model compound **1c** in the N_2O_5/CO_2 liquid system.[a]

Entry	N_2O_5 (equiv.)	Time/min	Isolated yield of **2c** (%)
1	1.0	30	75
2	1.1	30	90
3	1.5	30	89
4	1.1	15	87
5	1.1	60	90

[a] The reactions were carried out using 1-hexanol **1c** (8 mmol) and N_2O_5 (8–12 mmol) at 55–75 bar and 0 °C.

This procedure appeared to be applicable to the nitration of various alcohols **1a–d** and polyols **1f** and **1j**. In all cases the corresponding nitric esters **2a–d**, **2f** and **2j** were obtained in yields

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[†] Dinitrogen pentoxide was synthesized according to the published procedure.[15] Alcohols were provided by Acros Organics. Carbon dioxide (99.995%) was supplied by the Linde Gas (Russia). IR spectra were obtained on a Specord M-80 spectrometer in thin film on NaCl plates or in KBr pellets. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300 and 75 MHz for ^1H and ^{13}C, respectively) using TMS as the internal standard.

n-*Hexyl nitrate* **2c**. *Procedure A*. A steel autoclave (25 cm^3) containing N_2O_5 (0.95 g, 8.8 mmol) was filled with liquid CO_2 (65 bar) and cooled to 0 °C. Then 1-hexanol **1c** (1 cm^3, 0.82 g, 8.0 mmol) was added by a syringe pump with a flow rate of 0.05 cm^3 min^{-1}. After the addition, reactor pressure was 75 bar. The reaction mixture was stirred for 30 min, CO_2 was then removed, and the residue was poured into ice water (50 ml). The product was extracted with CH_2Cl_2 (4 × 10 ml), the combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ (2 × 20 ml), water (25 ml) and dried over Na_2SO_4. Evaporation of the solvent afforded 1.06 g (90%) of compound **2c**. Nitric esters **2a**,**b**,**d**,**f**,**j** were synthesized similarly using 1.1 equiv. N_2O_5 per each hydroxy group of corresponding alcohol **1** (see Table 2). The physicochemical and spectral data of obtained nitro esters are below and identical to reported ones.

Procedure B. A steel autoclave (25 cm^3) containing 1-hexanol **1c** (1 cm^3, 0.82 g, 8 mmol) was filled with liquid CO_2 to a pressure of 60 bar and cooled to 0 °C. Then N_2O_5 (0.95 g, 8.8 mmol) dissolved in liquid CO_2 (~3.5 g) was added in ten portions. The pressure after the addition was 80 bar. The reaction mixture was stirred for 30 min, CO_2 was then removed, and the residue was poured into ice water (50 ml). *n*-Hexyl nitrate **2c** was isolated as described above. The yield of **2c** was 1.15 g (97%). Nitrate esters **2a**,**b**,**d–l** were synthesized similarly using 1.1 equiv. N_2O_5 per hydroxy group of alcohol **1** (see Table 2).

n-*Butyl nitrate* **2a**: bp 134 °C (lit.,[8(e)] 130–133 °C), n_D^{20} 1.4063. IR (NaCl, ν/cm^{-1}): 1626 (NO_2^{as}), 1270 (NO_2^{s}). ^1H NMR ($CDCl_3$) δ: 4.45 (t, 2H, CH_2ONO_2, *J* 6.7 Hz), 1.75–1.66 (m, 2H, CH_2), 1.50–1.40 (m, 2H, CH_2), 0.96 (t, 3H, Me, *J* 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 73.17, 28.71, 18.89, 13.52.

2-Butyl nitrate **2b**: bp 123 °C (lit.,[8(e)] 120–122 °C), n_D^{20} 1.4018. IR (NaCl, ν/cm^{-1}) 1625 (NO_2^{as}), 1260 (NO_2^{s}). ^1H NMR ($CDCl_3$) δ: 5.01 (q, 1H, $CHONO_2$, *J* 6.3 Hz), 1.77–1.59 (m, 2H, CH_2), 1.33 (d, 2H, CH_2, *J* 6.2 Hz), 0.97 (t, 3H, Me, *J* 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 82.44, 27.03, 17.75, 9.33.

n-*Hexyl nitrate* **2c**: bp 54–55 °C / 4 Torr (lit.,[8(d)] 51–53 °C / 4 Torr), n_D^{20} 1.4191. IR (NaCl, ν/cm^{-1}): 1630 (NO_2^{as}), 1270 (NO_2^{s}). ^1H NMR ($CDCl_3$) δ: 4.44 (t, 2H, CH_2ONO_2, *J* 6.6 Hz), 1.76–1.67 (m, 2H, CH_2), 1.42–1.31 [m, 6H, $(CH_2)_3$], 0.90 (t, 3H, Me, *J* 6.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 73.54, 31.34, 26.79, 27.37, 22.49, 13.94.

Table 2 Nitration of alcohols and polyols using procedures A and B.[a]

Starting alcohol	Nitric ester	*n*	Isolated yield of **2** (%)	
			Procedure A	Procedure B
n-Butanol **1a**	**2a**	1	91	94
Butan-2-ol **1b**	**2b**	1	85	91
n-Hexanol **1c**	**2c**	1	90	97
Cyclohexanol **1d**	**2d**	1	87	90
3-Methyl-3-oxetanemethyl alcohol **1e**	**2e**	1	—	95
Ethylene glycol **1f**	**2f**	2	85	96
1,3-Propylene glycol **1g**	**2g**	2	—	89
1,4-Butylene glycol **1h**	**2h**	2	—	93
Diethylene glycol **1i**	**2i**	2	—	98
Glycerol **1j**	**2j**	3	95	98
Pentaerythritol **1k**	**2k**	4	—	94
D-Mannitol **1l**	**2l**	6	—	91

[a] The reactions were carried out using an alcohol (8.0 mmol), N_2O_5 (8.8–52.8 mmol) at 60–80 bar and 0 °C for 30 min.

comparable with those reported in the literature[4(e),7(e),8(d),(e)] (Table 2, procedure A). Corresponding polynitrates **2f**,**j** were synthesized from polyols **1f** and **1j** in the presence of 2.2 or 3.3 equiv. of N_2O_5, respectively. However, the procedure A was not suitable to the nitration of poorly soluble in liquid CO_2 pentaerythritol **1k** and D-mannitol **1l**. Moreover, an excessive amount of nitrating agent at the reaction start may make the procedure explosion-risky in scaling-up experiments.

To overcome these problems, we examined a reverse mode of components mixing, gradually pressurizing the N_2O_5/CO_2 liquid system to a stirred solution (emulsion or suspension) of an alcohol in CO_2 (procedure B). The yields of nitrate esters **2a**–**j** prepared in this way were 3–11% higher than attained by the procedure A (Table 2). Unavailable by the procedure A pentaerythritol tetranitrate **2k** and D-mannitol hexanitrate **2l** were readily generated in 91–94% yields under proposed conditions.

In summary, an efficient procedure for O-nitration of alcohols by a dinitrogen pentoxide/carbon dioxide liquid system has been proposed. Due to a high heat capacity (*Cp* 6.35 J g^{-1} K^{-1} at 25 °C and a pressure of 64 bar,[19] *cf.* for dichloromethane *Cp* 1.70 J g^{-1} K^{-1} at 20 °C[20]), carbon dioxide effectively consumes the heat of exothermic nitration reaction and prevents uncontrollable processes to occur. Active ingredients **2j**,**k**,**l** of pharmaceuticals for curing cardiovascular diseases[21] have been synthesized in high yields by the developed method.

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Cyclohexyl nitrate **2d**: bp 78–79 °C / 18 Torr (lit.,[8(d)] 52–53 °C / 3 Torr), n_D^{20} 1.4546 (lit.,[16] 1.4560). IR (NaCl, ν/cm^{-1}): 1628 (NO_2^{as}), 1264 (NO_2^{s}). ^1H NMR ($CDCl_3$) δ: 4.98–4.90 (m, 1H, $CHONO_2$), 1.99–1.94 (m, 2H, CH_2), 1.81–1.72 (m, 2H, CH_2), 1.58–1.24 [m, 6H, $(CH_2)_3$]. ^{13}C NMR ($CDCl_3$) δ: 82.38, 29.81, 25.02, 23.52.

3-Methyl-3-(nitroxymethyl)oxetane **2e**: bp 39 °C / 4 Torr, n_D^{20} 1.4486. IR (NaCl, ν/cm^{-1}): 1634 (NO_2^{as}), 1270 (NO_2^{s}). ^1H NMR ($CDCl_3$) δ: 4.60 (s, 2H, CH_2ONO_2), 4.51 (d, 2H, CH_2O, *J* 6.2 Hz), 4.42 (d, 2H, CH_2O, *J* 6.2 Hz), 1.39 (s, 3H, Me). ^{13}C NMR ($CDCl_3$) δ: 79.24, 77.14, 38.55, 20.91.

Ethylene glycol dinitrate **2f**: bp 71–72 °C / 4 Torr (lit.,[16] 63–64 °C / 1.5 Torr), n_D^{20} 1.4475 (lit.,[16] 1.4480). IR (NaCl, ν/cm^{-1}): 1640 (NO_2^{as}), 1270 (NO_2^{s}). ^1H NMR ($CDCl_3$) δ: 4.76 (s, 4H, CH_2ONO_2). ^{13}C NMR ($CDCl_3$) δ: 68.23.

1,3-Propylene glycol dinitrate **2g**: bp 67 °C / 4 Torr (lit.,[16] 65 °C / 1 Torr), n_D^{20} 1.4485. IR (NaCl, ν/cm^{-1}): 1633 (NO_2^{as}), 1268 (NO_2^{s}). ^1H NMR ($CDCl_3$) δ: 4.58 (t, 4H, CH_2ONO_2, *J* 6.1 Hz), 2.23–2.13 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 68.86, 24.89.

1,4-Butylene glycol dinitrate **2h**: bp 104–105 °C / 4 Torr (lit.,[17] 89–90 °C / 2 Torr), n_D^{20} 1.4515. IR (NaCl, ν/cm^{-1}): 1621 (NO_2^{as}), 1260 (NO_2^{s}). ^1H NMR ($CDCl_3$) δ: 4.50 (s, 4H, CH_2ONO_2), 1.88 (s, 4H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 72.19, 23.37.

Diethylene glycol dinitrate **2i**: bp 132 °C / 4 Torr (lit.,[17] 94–95 °C / 1 Torr), n_D^{20} 1.4525. IR (NaCl, ν/cm^{-1}): 1636 (NO_2^{as}), 1281 (NO_2^{s}). ^1H NMR ($CDCl_3$) δ: 4.61 (t, 4H, CH_2ONO_2, *J* 4.4 Hz), 3.78 (t, 4H, CH_2O, *J* 4.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 71.87, 67.45.

Glyceryl trinitrate (nitroglycerin) **2j**: bp 141–142 °C / 4 Torr (lit.,[16] 108–110 °C / 1 Torr), n_D^{20} 1.4725 (lit.,[16] 1.4730). IR (NaCl, ν/cm^{-1}): 1640 (NO_2^{as}), 1270 (NO_2^{s}). ^1H NMR ($CDCl_3$) δ: 5.57–5.51 (m, 1H, $CHONO_2$), 4.84 (dd, 2H, CH_2ONO_2, J_{AA} 13.0 Hz, J_{AB} 3.8 Hz), 4.68 (dd, 2H, CH_2ONO_2, J_{AA} 13.0 Hz, J_{AB} 5.9 Hz). ^{13}C NMR ($CDCl_3$) δ: 74.75, 68.12.

Pentaerythritol tetranitrate **2k**: mp 141–142 °C (lit.,[2(b)] 142.2 °C). IR (KBr, ν/cm^{-1}): 1658 (NO_2^{as}), 1288 (NO_2^{s}). ^1H NMR (DMSO-d_6) δ: 4.70 (s, 8H, CH_2ONO_2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 70.30, 40.86.

D-Mannitol hexanitrate **2l**: mp 111–112 °C (lit.,[18] 112 °C). IR (KBr, ν/cm^{-1}): 1658 (NO_2^{as}), 1273 (NO_2^{s}). ^1H NMR ($CDCl_3$) δ: 6.18–6.08 (m, 2H, $CHONO_2$), 6.07–5.97 (m, 2H, $CHONO_2$), 5.12 (dd, 2H, CH_2ONO_2, J_{AA} 13.1 Hz, J_{AB} 3.2 Hz), 4.91 (dd, 2H, CH_2ONO_2, J_{AA} 13.1 Hz, J_{AB} 5.7 Hz). ^{13}C NMR (DMSO-d_6) δ: 77.12, 76.70, 68.79.

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