Acylation of aliphatic diamines with methyl nitroacetate

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N,N'-Bis(nitroacetyl)diamines were synthesized for the first time by the reaction of methyl nitroacetate with aliphatic diamines in H_2O or EtOH in the presence of pyridine or imidazole. In the case of 1,2-ethylenediamine, the *N*-mononitroacetyl derivative was isolated as an intermediate product.

Key words: methyl nitroacetate; *N,N'*-bis(nitroacetyl)diamines; aminolysis, nucleophilic catalysis.

Esters of nitroacetic acid are readily available and widely used in various chemical transformations.[1] The reactions of methyl nitroacetate (MNA) with aliphatic diamines were studied in the present work. A general method for the synthesis of hitherto unknown *N,N'*-bis(nitroacetyl)diamines (NADA) was proposed.

The procedure developed for obtaining nitroacetamides, heating MNA with excess aliphatic amines in protic solvents,[2,3] is not suitable for the synthesis of NADA. However, the target NADA can be obtained by the reaction of equivalent amounts of MNA with aliphatic diamines in water or EtOH in the presence of pyridine or imidazole as a catalyst (Schemes 1 and 2), though in low yields (Table 1). It should be noted that the synthesis of diamine **2a** fails to occur when Et_3N replaces pyridine.

Scheme 1

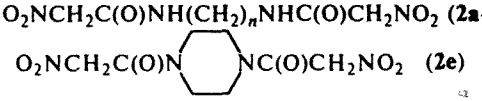
$$O_2NCH_2COOMe + NH_2(CH_2)_nNH_2 \xrightarrow{a} \underset{\text{MHA}}{} \rightarrow \underset{\textbf{1a–d}}{\bar{O}_2N{=}CHC(O)NH(CH_2)_n\overset{+}{N}H_3} \xrightarrow{b,\ c,\ d} O_2NCH_2C(O)NH(CH_2)_nNHC(O)CH_2NO_2$$

2a–d

n = 2, 4–6

Reagents and conditions: *a*. H_2O—Py, Δ; *b*. KOH; *c*. O_2NCH_2COOMe, Δ; *d*. HCl(aq).

Table 1. The characteristics of *N,N'*-bis(nitroacetyl)diamines $O_2NCH_2C(O)NH(CH_2)_nNHC(O)CH_2NO_2$ (**2a–d**) and



(**2e**)

Compound	n	Yield (%)	M.p./°C (decomp.)	Found / Calculated (%)			Molecular formula
				C	H	N	
2a	2	15	178–180	31.03 30.78	4.27 4.30	23.76 23.93	$C_6H_{10}N_4O_6$
2b	4	12	159–161	36.47 36.64	5.31 5.38	21.64 21.37	$C_8H_{14}N_4O_6$
2c	5	10	156–158	39.10 39.13	5.79 5.84	19.95 20.28	$C_9H_{16}N_4O_6$
2d	6	20	154–155	41.44 41.38	6.30 6.25	19.33 19.30	$C_{10}H_{18}N_4O_6$
2e	—	46	220–223	37.11 36.93	4.59 4.65	21.28 21.53	$C_8H_{12}N_4O_6$

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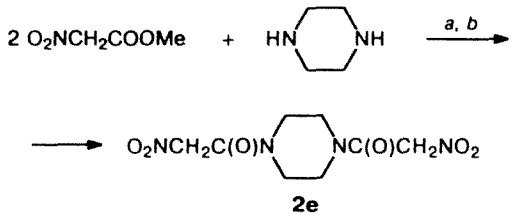
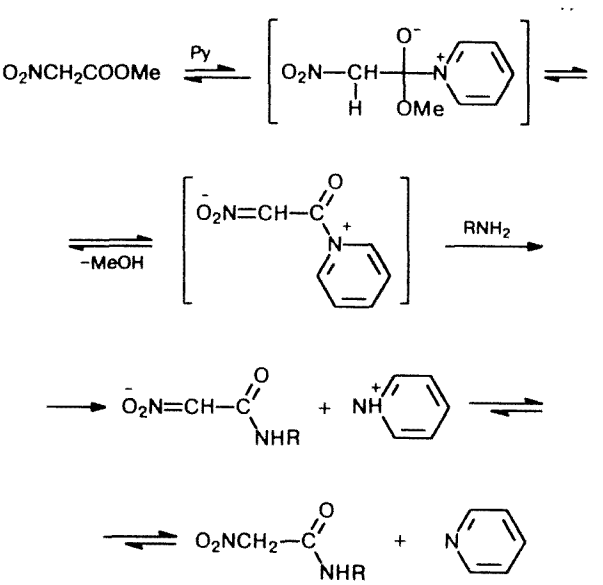
Scheme 2



2e

Reagents and conditions: *a*. EtOH—imidazole, Δ; *b*. HCl(aq).

Scheme 3



R = $-(CH_2)_nNH_2$, $-(CH_2)_nNHC(O)CH{=}NO_2^-$

The synthesis of products **2a—d** probably occurs through the formation of intermediate *N*-(nitroacetyl)diamines **1a—d**, which are zwitter ions. *N*-Nitroacetyl-1,2-ethylenediamine was isolated from the reaction mixture in the synthesis of NADA **2a** (see Experimental).

The aminolysis of MNA, which easily forms salts with aliphatic amines, seems to proceed smoothly only when there is an adequate amount of its nonionized form and of nonprotonated amino groups on the other reagent. The use of quite basic Et_3N probably leads to a significant decrease in the equilibrium concentration of free MNA, while in the absence of a catalyst the amine component exists predominantly in a nonreactive protonated form owing to the formation of salts with MNA. Only using weakly basic heterocyclic amines (pyridine or imidazole) allows one to fulfill the above-mentioned condition. In addition, it is known that pyridine and imidazole are capable of catalyzing nucleophilic substitution in anhydrides[4] and esters[5] of carboxylic acids containing a good leaving group. In the case of MNA, a compound with highly acidity of methylene protons, the highly nucleophugic neutral molecule of MeOH can be the leaving group (Scheme 3), rather than the weakly nucleophugic methoxide ion.

The structures of the NADA **2a—e** and intermediate **1a** obtained were established using heteronuclear NMR spectroscopy (Table 2) and confirmed by the data of elemental analysis (see Table 1). It should be noted that monoamide **1a** is markedly soluble in water, significantly less soluble in MeOH, and is almost insoluble in other organic solvents, which confirms its zwitter-ionic structure.

N,N'-Bis(nitroacetyl)diamines **2a—e** are rather stable crystalline compounds soluble in DMF and DMSO, and poorly soluble in other organic solvents. They are not soluble in water, but are soluble in dilute aqueous NaOH, KOH, and NH_3 solutions (due to salt formation), from which they easily precipitate, when acidified.

Table 2. The parameters of the ^1H, ^{13}C, and ^{14}N NMR spectra of compounds **2a—e**

Compound	δ ^1H				δ ^{13}C				δ ^{14}N
	CH_2N (4 H)	CH_2NO_2 (s, 4 H)	NH (br.m, 2 H)	other signals	CH_2N	CH_2NO_2	C=O	other signals	($\Delta\nu_{1/2}$/Hz), NO_2
2a	3.39 (br.s)	5.22	8.44	—	40.42	78.24	161.25		−7 (300)
2b	3.12 (m)	5.26	—	1.44 (br.m, $(CH_2)_2$)	38.86	78.74	161.38	26.25 ($(CH_2)_2$)	−5 (400)
2c	3.13 (m)	5.28	8.47	1.31 (m, CH_2); 1.45 (m, $(CH_2)_2$)	39.10	78.55	161.07	23.48 (CH_2); 28.23 ($(CH_2)_2$)	−4 (250)
2d	3.13 (m)	5.28	8.47	1.29 (m, $(CH_2)_2$); 1.44 (m, $(CH_2)_2$)	38.94	78.59	161.08	25.91 ($(CH_2)_2$); 28.61 ($(CH_2)_2$)	−5 (260)
2e*	3.48 (m)	5.81; 5.83	—	—	41.10; 41.30; 43.98; 44.22	78.06	160.80	—	−8 (900)

* A mixture of two rotamers (~1 : 1), which occur due to decelerated rotation about the amide C(O)N bond.

Experimental

^1H, ^{13}C, and ^{14}N NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13, 75.5, and 21.5 MHz, respectively) in DMSO-d_6 at 27 °C with $SiMe_4$ as the internal standard (^1H and ^{13}C) and with $MeNO_2$ as the external standard (^{14}N).

***N*-Nitroacetyl-1,2-ethylenediamine (1a).** Methyl nitroacetate (2.68 g, 22.5 mmol) was added to a solution of 1,2-ethylenediamine (1.35 g, 22.5 mmol) in 5.63 mL of 50% aqueous pyridine and refluxed for 45 min. The mixture was cooled, and the precipitated product **1a** was filtered off, washed with cooled MeOH (3×10 mL), and dried. The yield of compound **1a** was 1.65 g (50%), m.p. 140—142 °C (decomp.). ^1H NMR (D_2O, with MeCN as the internal standard [δ 1.95]), δ: 3.08 (t, 2 H, CH_2, $^3J_{H,H}$ = 6.0 Hz); 3.52 (t, 2 H, CH_2); 6.40 (s, $C\underline{H}=NO_2^-$)*. ^{13}C NMR, δ: 36.93 (CH_2); 39.97 (CH_2); 109.87 ($\underline{C}H=NO_2^-$); 166.74 (C=O). ^{14}N NMR, δ: −45 ($CH=\underline{N}O_2^-$, $\Delta\nu_{1/2}$ = 350 Hz); −353 ($CH_2\underline{N}H_3^+$, $\Delta\nu_{1/2}$ = 130 Hz). Found (%): C, 32.41; H, 6.20; N, 28.68. $C_4H_9N_3O_3$. Calculated (%): C, 32.65; H, 6.17; N, 28.56.

Synthesis of *N,N'*-bis(nitroacetyl)diamines 2a—d (general procedure). An equimolar amount of MNA was added to a solution of diamine in 50% aqueous pyridine (~4 mmol mL^{-1}) and refluxed for 45 min. The mixture was cooled, then KOH (1.5 eqviv.) and extra MNA (1 equiv.) were added with stirring, and refluxed for 1.5—1.75 h. After the mixture was cooled and concentrated *in vacuo*, the residue was dissolved in a minimum amount of water and slowly, with cooling (0—10 °C), acidified with 15% aqueous HCl to pH 2—3. The precipitate of products **2a—d** was separated by filtering, washed with aqueous HCl (pH 2—3) and H_2O_2, and twice washed with small portions of cooled MeOH, and dried. The main characteristics of compounds **2a—d** are given in Tables 1 and 2.

* Integral intensity is reduced owing to exchange with D_2O.

***N,N'*-Bis(nitroacetyl)piperazine (2e).** A solution of piperazine (1.50 g, 17.4 mmol), MNA (5.45 g, 45.8 mmol), and imidazole (2.40 g, 34.8 mmol) in 5 mL of EtOH was refluxed for 1.5 h, then cooled, and the EtOH was concentrated *in vacuo*. The residue was dissolved in a minimum amount of water and acidified with care with 15% aqueous HCl to pH 2—3. The precipitate that formed was filtered off, washed with aqueous HCl (pH 2—3) and water, and then twice washed with small portions of cooled MeOH, and dried. The yield and characteristics of the product are given in Tables 1 and 2.

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