Organic Chemistry

Nitrolysis of urethanes derived from secondary alcohols as a new method for the synthesis of secondary *N*-nitroamines

O. A. Luk'yanov, T. G. Mel'nikova, and M. E. Shagaeva*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 117913 Moscow, Russian Federation.
Fax: +7 (095) 135 5328

The reactions of dialkylurethanes $R^1{}_2NCOOR$ (RO is the residue of a secondary but not a primary alcohol) with nitrating reagents leads to the formation of the corresponding secondary *N*-nitroamines $R^1{}_2NNO_2$.

Key words: secondary urethanes, nitroamines, nitrolysis, nitrating reagents.

An important and rather common group of methods for the synthesis of secondary *N*-nitroamines is nitrolysis of secondary amides R_2N-X. A number of examples, in which the role of the leaving group X was played by the acid residues of aliphatic[1–3] and aromatic[4] carboxylic acids, alkyl-[5,6] and arylsulfonic acids,[6,7] and also sulfuric[8] and carbamic[1] acids, have been reported. One might suggest that reactions of secondary urethanes with nitrating reagents would follow a similar pathway. However, back in the previous century, it was shown[1] that nitration of urethanes R^1R^2NCOOR (R = Me or Et) occurs, at best, as the replacement of an alkyl group rather than the alkoxycarbonyl group by a nitro group. An attempt to replace the methoxycarbonyl group by a nitro group during nitrolysis of *N*-alkylimides was also unsuccessful.[9]

While analyzing the possible mechanisms of electrophilic substitution at the nitrogen atom, we arrived at the conclusion that transformation of the desired type could be attained by passing from secondary urethanes based on primary alcohols to urethanes based on secondary or tertiary alcohols. Therefore, we prepared a number of easily accessible *O*-isopropyl- and *O*-cyclopentylurethanes and studied their reactions with several nitrating reagents. As the nitrating reagents, we used concentrated HNO_3, its mixture with Ac_2O or concentrated H_2SO_4, and also nitronium tetrafluoroborate

Table 1. Yields of *N*-nitromorpholine (**2a**) (entries 1–6) and *N,N'*-dinitropiperazine (**2b**) (entries 7, 8) in the nitrolysis of secondary urethanes

Entry	Starting urethane	Nitrating reagent	Yield of *N*-nitroamine (%)
1	**1a**	HNO_3	53
2	**1a**	HNO_3/Ac_2O	46
3	**1a**	HNO_3/H_2SO_4	81
4	**1a**	NO_2BF_4	33[a], 47[b]
5	**1b**	HNO_3/H_2SO_4	58
6	**1b**	NO_2BF_4	25[a], 46[c]
7	**1c**	HNO_3/H_2SO_4	95
8	**1d**	HNO_3/H_2SO_4	61

[a] The excess of NTFB was 10%.
[b] The excess of NTFB was 50%.
[c] The excess of NTFB was 120%.

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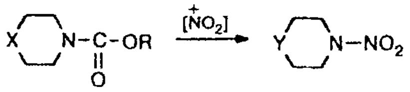
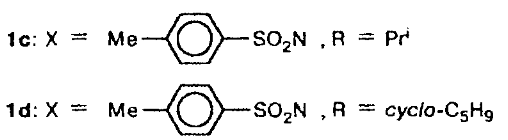
(NO_2BF_4, NTFB) (Table 1). It can be seen from Table 1 that urethanes based on secondary alcohols can be easily converted into secondary *N*-nitroamines in satisfactory yields.*



1a—d **2a,b**

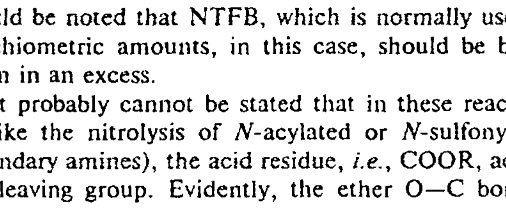
1a: X = O, R = Pr^i **2a**: Y = O
1b: X = O, R = *cyclo*-C_5H_9 **2b**: Y = NNO_2



1c: X = $Me-C_6H_4-SO_2N$, R = Pr^i
1d: X = $Me-C_6H_4-SO_2N$, R = *cyclo*-C_5H_9

The yields of the products depend on the structure of the secondary alcohol, the nature of the nitrating reagent, and the reaction conditions. Urethanes based on isopropyl alcohol are converted into *N*-nitroamines more smoothly than similar *O*-cyclopentyl derivatives. In the series of nitrating reagents, the highest yields were observed with a mixture of sulfuric and nitric acids. It should be noted that NTFB, which is normally used in stoichiometric amounts, in this case, should be better taken in an excess.

It probably cannot be stated that in these reactions (unlike the nitrolysis of *N*-acylated or *N*-sulfonylated secondary amines), the acid residue, *i.e.*, COOR, acts as the leaving group. Evidently, the ether O—C bond is cleaved synchronously with the N—C bond to give the secondary carbocation, which is thermodynamically much more stable. Hence, it becomes clear why urethanes based on primary alcohols do not enter into similar transformations.



The method developed here markedly extends the potentialities of the synthesis of *N*-nitro derivatives. It appears to be especially attractive for a two-step transformation of tertiary amines into secondary *N*-nitroamines, because methods for the synthesis of secondary urethanes based on the interaction of tertiary amines with chloroformates are well developed.[10] To illustrate the foregoing, we carried out the following sequence of transformations.

$$TsN(CH_2CH_2Cl)_2 \xrightarrow{PhCH_2NH_2} \underset{\textbf{3}}{TsN(CH_2CH_2)_2NCH_2Ph} \longrightarrow$$

$$\xrightarrow{ROCOCl} \underset{\textbf{1}}{TsN(CH_2CH_2)_2NCOOR} \xrightarrow{HNO_3/H_2SO_4}$$

$$\longrightarrow \underset{\textbf{2b}}{O_2NN(CH_2CH_2)_2NNO_2}$$

R = Pr^i (**1c**), *cyclo*-C_5H_9 (**1d**)

Simultaneously, this scheme demonstrates the possibility of using this method to prepare poly-*N*-nitroamines.

Experimental

^1H NMR spectra were recorded on a Bruker WM-250 spectrometer (250.13 MHz). IR spectra were measured on a UR-20 instrument in pellets with KBr. TLC analysis was carried out using silica gel Silpearl UV 254 and a C_6H_6—AcOEt 2 : 1 mixture as the eluent. Melting points were determined on a Boetius type hot-stage apparatus.

***N*-Isopropyloxycarbonylmorpholine (1a)** was prepared from morpholine and isopropyl chloroformate according to a known procedure.[11] ^1H NMR ($CDCl_3$), δ: 1.23 (d, 6 H, CH_3, J = 6.5 Hz); 3.42 (m, 4 H, CH_2N); 3.62 (m, 4 H, CH_2O); 4.90 (m, 1 H, $\underline{CH}Me_2$).

***N*-Cyclopentyloxycarbonylmorpholine (1b)** was synthesized by analogy with **1a** from morpholine and cyclopentyl chloroformate, yield 65%, b.p. 135—137 °C (10 Torr), n_D^{21} 1.4812. ^1H NMR ($CDCl_3$), δ: 1.72 (m, 8 H, $(CH_2)_4$); 3.48 (m, 4 H, CH_2N); 3.62 (m, 4 H, CH_2O); 5.12 (m, 1 H, CH). Found (%): C, 60.41; H, 8.60. $C_{10}H_{17}NO_3$. Calculated (%): C, 60.28; H, 8.60.

***N*-Benzyl-*N'*-tosylpiperazine (3).** Bu_4NBr (0.2 g), Et_3N (5.6 mL, 0.04 mol), and $PhCH_2NH_2$ (2.2 mL, 0.02 mol) was added to a solution of $TsN(CH_2CH_2Cl)_2$ (6.0 g, 0.02 mol), prepared by a known procedure,[12] in 10 mL of DMF. The resulting mixture was heated to reflux; heating was continued for 3.0—3.5 h during which the temperature of the reaction mixture slowly increased from 90 °C to 130—135 °C. The hot mixture was poured in 50 mL of ice water, and the precipitate was filtered off, washed with H_2O, and dried in air to give 6.0 g of compound **3** (91%), m.p. 122—124 °C (EtOH) (*cf.* Ref. 13: m.p. 121—123 °C). ^1H NMR (DMSO-d_6), δ: 2.42 (s, 3 H, CH_3); 2.40 (m, 4 H, CH_2NCH_2); 2.86 (m, 4 H, $\underline{CH_2}NTs$); 3.45 (s, 2 H, $\underline{CH_2}Ph$); 7.25 (m, 5 H, C_6H_5); 7.45, 7.60 (both d, 2×2H, C_6H_4, J = 8.2 Hz).

***N*-Isopropyloxycarbonyl-*N'*-tosylpiperazine (1c).** Pr^iOCOCl (1.0 g, 0.008 mol) was added to a solution of **3** (1.32 g, 0.004 mol) in 30 mL of anhydrous MeCN, and the mixture was stirred at 20 °C for 2.5—3 h (until compound **3** disappeared, according to TLC). The precipitate of the by-product was filtered off, and the filtrate was concentrated *in vacuo*. The oily residue was extracted with hexane (2×5 mL) in order to remove $PhCH_2Cl$. The residual crystalline compound was dried in air to give 1.14 g of compound **1c** (87.7%), m.p. 119—120 °C (EtOH). ^1H NMR (DMSO-d_6), δ: 1.13 (d, 6 H, CH_3, J = 6.4 Hz); 2.42 (s, 3 H, CH_3); 2.84 (m, 4 H, $CH_2NC{=}O$); 3.42 (m, 4 H, CH_2NSO_2); 7.45, 7.62 (both d, 2×2 H, C_6H_4, J = 9.1 Hz). Found (%): C, 55.11; H, 6.74; S, 9.86. $C_{15}H_{22}N_2O_4S$. Calculated (%): C, 55.20; H, 6.79; S, 9.82.

***N*-Cyclopentyloxycarbonyl-*N'*-tosylpiperazine (1d).** C_5H_9OCOCl (0.99 g, 0.0066 mol) was added to a solution of **3** (1.97 g, 0.006 mol) in 40 mL of anhydrous MeCN, and the

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* Experimental conditions were not optimized.

mixture was stirred for 24 h at 20 °C. The product was isolated as described for **1c** to give 1.75 g of **1d** (87%), m.p. 129—130 °C (EtOH). ^{1}H NMR (DMSO-d_6), δ: 1.63 (m, 8 H, $(CH_2)_4$); 2.42 (s, 3 H, CH_3); 2.82 (m, 4 H, CH_2NCO); 3.42 (m, 4 H, CH_2NSO_2); 4.42 (m, 1 H, CH); 7.45, 7.62 (both d, 2×2 H, C_6H_4, J = 9.0 Hz). Found (%): C, 57.73; H, 6.94; S, 9.46. $C_{17}H_{24}N_2O_4S$. Calculated (%): C, 57.93; H, 6.86; S, 9.10.

Nitration of *N*-isopropyloxycarbonylmorpholine (1a) with conc. HNO_3. Urethane **1a** (0.4 g, 0.0023 mol) was added in portions to HNO_3 (*d* 1.5) (3 mL, 0.071 mol) with stirring and cooling to −20 to −25 °C. The reaction mixture was slowly heated to −8 °C, and kept for ~1 h at +5 °C (until gas evolution ceased) and for 45 min at 20—25 °C. Then the reaction mixture was poured onto 15 g of ice and extracted with CH_2Cl_2 (4×5 mL). The combined extracts were washed several times with H_2O, a 5% solution of $NaHCO_3$, and again with H_2O, and dried with Na_2SO_4. The solvent was evaporated *in vacuo*, and product **2a** was isolated by preparative chromatography on silica gel.

Nitration of *N*-isopropyloxycarbonylmorpholine (1a) with a mixture of conc. HNO_3 and Ac_2O. Nitric acid (*d* 1.5) (3 mL, 0.071 mol) and then urethane **1a** (0.4 g, 0.0023 mol) were added dropwise to Ac_2O (6.7 mL, 0.071 mol) with stirring and cooling by an ice—salt mixture. The reaction mixture was kept for 15 min at −8 °C and for 15 min at +5 °C. Then the temperature was raised to +15 °C and the mixture was stirred for ~15 min until gas evolution ceased, and poured onto 25 g of ice. The product was extracted with CH_2Cl_2 (5×5 mL), and the combined extracts were washed several times with H_2O, a 5% solution of $NaHCO_3$, and again with H_2O, and dried with Na_2SO_4. The solvent was evaporated *in vacuo*, and product **2a** was isolated by preparative chromatography on silica gel.

Nitration of urethanes 1a—d by a mixture of conc. HNO_3 and conc. H_2SO_4. A mixture of HNO_3 (*d* 1.5) (2.5 mL, 0.06 mol) and conc. H_2SO_4 (2.5 mL) was cooled to −25 to −30 °C, and the corresponding urethane **1a—d** (0.5 g) was added with vigorous stirring. The mixture was gradually heated until gas evolution began (−10 to 0 °C) and kept at this temperature until the intense gas evolution ceased (~15—30 min). Then the cooling bath was removed, and the reaction mixture was stirred for ~30 min at 20—25 °C and poured onto 50 g of ice. In the case of urethanes **1a,b**, the acidic aqueous solution was extracted with CH_2Cl_2 (5×5 mL), and the combined extracts were washed several times with H_2O, a 5% solution of $NaHCO_3$, and again with H_2O, and dried with Na_2SO_4. Evaporation of the solvent *in vacuo* gave **2a**, m.p. 51—54 °C (*cf.* Ref. 14: m.p. 52—54 °C (MeOH)). In the nitration of urethanes **1c,d**, after pouring the reaction mixture on ice, the white precipitate was filtered off, washed several times with H_2O, and dried in air to give **2b**, m.p. 212—215 °C (Ref. 15: m.p. 215 °C). The IR and ^{1}H NMR spectra of **2a** and **2b**, isolated after nitration, were identical to those of the authentic samples of *N*-nitromorpholine and *N,N'*-dinitropiperazine.[15]

Nitration of urethanes 1a,b with nitronium tetrafluoroborate. At −25 °C, urethane **1a,b** (0.005 mol) was added in portions with vigorous stirring to a suspension of NTBF in 25 mL of anhydrous MeCN, and the reaction mixture was kept at this temperature for 15—20 min. Then the cooling bath was removed, and the reaction mixture was allowed to warm up to ~20 °C, stirred for an additional 15—30 min, and poured in 25 mL of ice water. The product was extracted with CH_2Cl_2 (4×5 mL), and the combined extracts were washed several times with H_2O, and dried with Na_2SO_4. After removal of the solvent, product **2a** was isolated by TLC on silica gel.

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