The reaction of polyhalonitrosoarenes with 1-morpholinocyclohexene

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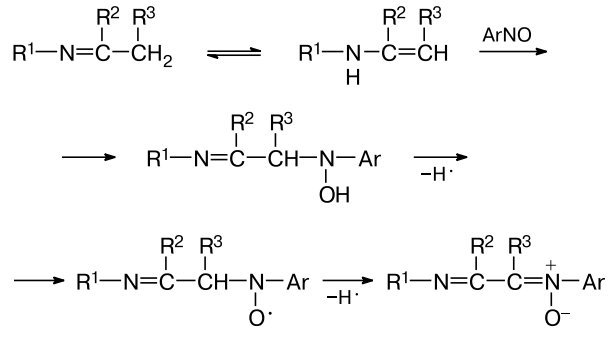
The addition of 1-morpholinocyclohexene to the nitroso group of polyhalonitrosoarenes gives *N*-(2-morpholinocyclohex-2-enyl)-*N*-(polyhalophenyl)hydroxylamines.

Key words: nitroso compounds, enamines, hydroxylamines, aromatic compounds, ene reaction.

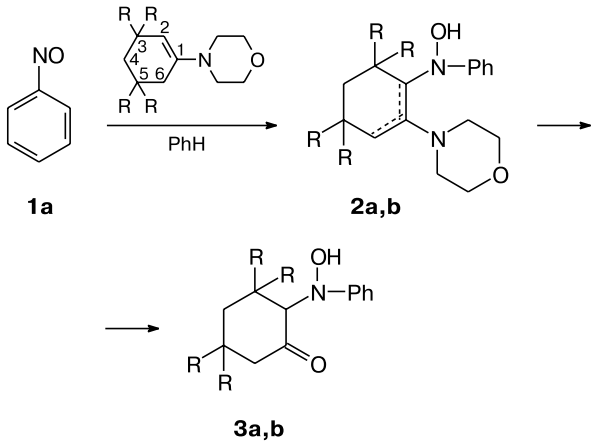
N,*N*-Disubstituted hydroxylamine derivatives are used to prepare nitrones[1] or aminoxyl radicals[2] and are of interest as biologically active compounds.[3] Despite the fact that the range of reactions giving rise to *N*,*N*-disubstituted hydroxylamines is fairly broad, versatile methods for their preparation have not been adequately developed. The reactions of *C*-nitroso compounds with carbanions or their precursors is an approach to the synthesis of *N*,*N*-disubstituted hydroxylamines.[3] A reaction of nitrosoarenes with imines,[4] which isomerize into enamines during the process, the latter then adding to nitrosoarenes is also known. Reactions of this type often do not stop after the formation of hydroxylamines but proceed further, resulting in the formation of aminoxyl radicals and nitrones (Scheme 1).

Scheme 1



Nitrosobenzene (**1a**) adds to cyclic enamines of the morpholinocyclohexene series[5] to afford adducts **2a,b** (Scheme 2) in which the position of the double bond has not been determined. Unsubstituted adduct **2a** was readily converted into ketone **3a** (see also Ref. 6), while tetramethyl-substituted derivative **2b** proved to be more stable.

Scheme 2



R = H (**a**), Me (**b**)

Later on,[7] adduct **4a** has been obtained in 40% yield by the reaction of pentafluoronitrosobenzene (**1b**) with 1-morpholinocyclohexene (Scheme 3).

This study describes the reactions of polyhalonitrosoarenes **1c—g** with 1-morpholinocyclohexene, attention being focused on verification of the product structures. Nitrosoarenes **1c—g** readily react with 1-morpholinocyclohexene in aprotic solvents at 20—25 °C to give colorless products **4b—f**, which precipitate during the reaction as crystals (Scheme 4, Table 1).

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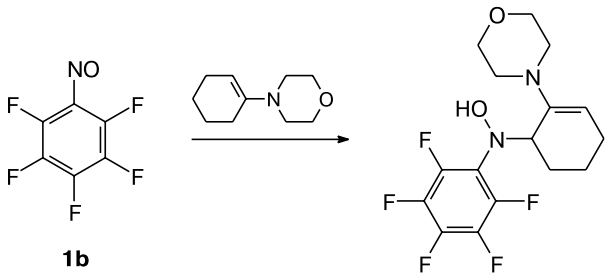
Table 1. Yields and properties of hydroxylamino derivatives **4b—f**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula
			C	H	N	
4b	74	155—158	56.37 55.99	5.80 5.87	8.27 8.16	$C_{16}H_{20}Cl_2N_2O_2$
4c	75	160—163	50.97 50.88	5.13 5.07	7.41 7.42	$C_{16}H_{19}Cl_3N_2O_2$
4d	76	165—170	37.96 37.60	3.83 3.75	5.53 5.48	$C_{16}H_{19}Br_3N_2O_2$
4e	65	165—168	41.12 41.19	3.97 4.10	5.92 6.00	$C_{16}H_{19}Br_2ClN_2O_2$
4f	72	157—160	42.49 42.69	4.25 4.25	6.15 6.22	$C_{16}H_{19}Br_2FN_2O_2$

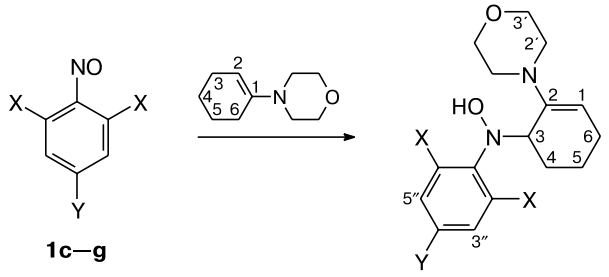
The position of the double bond in adducts **4b—f** follows unambiguously from ^{1}H NMR (the presence of two triplets for the protons for the =CH and N—CH fragments of the cyclohexene ring) (Table 2) and ^{13}C NMR data. For compound **4f**, two-dimensional spectra (COSY, HSQC, HMBC) were recorded and used to assign all ^{1}H and ^{13}C NMR signals. The presence of correlations between the hydroxyl proton and the C(3) and C(1″) atoms and between H(3) and C(1″) in the HMBC spectra confirms unambiguously the proposed structure.

The structures of compounds obtained in this study are consistent with published data[8] discussing the mechanism of reactions of nitroso compounds with alkenes and enols containing hydrogen atoms in the α-position with respect to the double bond. In our case, the process following the ene reaction mechanism can be represented by Scheme 5.

Scheme 3



Scheme 4



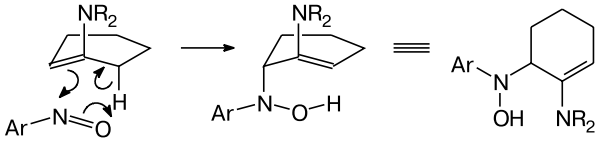
X = Cl, Y = H (**1c**, **4b**); X = Y = Cl (**1d**, **4c**); X = Y = Br (**1e**, **4d**); X = Br, Y = Cl (**1f**, **4e**); X = Br, Y = F (**1g**, **4f**)

Table 2. ^{1}H NMR data (δ (*J*/Hz)) for hydroxylamine derivatives **4b—f**

Compound	OH	H(3″), H(5″)	H(4″)	H(1) t	H(3) br.t	H_{eq}(3′), H_{eq}(5′)	H_{ax}(3′), H_{ax}(5′)	H_{eq}(2′), H_{eq}(6′)	H_{eq}(5)	H_{eq}(4) dd	H_{eq}(6)	H_{ax}(6)	H_{ax}(2′), H_{ax}(6′)	H_{ax}(5)	H_{ax}(4) t
						m					m				
4b	8.81 (s)	7.32 (d, *J* = 8.4)	7.15 (t, *J* = 8.4)	4.90 (*J* = 4.0)	4.32 (*J* = 2.5)	3.24	3.00	2.75	2.40	2.34 (*J* = 13.0, *J* = 2.5)	2.19	2.05	1.85	1.47	1.32 (*J* = 13.0)
4c	8.91 (s)	7.49 (s)	—	4.92 (*J* = 3.9)	4.24 (*J* = 2.6)	3.30	3.03	2.73	2.34	2.30 (*J* = 13.0, *J* = 2.6)	2.16	2.02	1.87	1.46	1.31 (*J* = 13.0)
4d	6.15 (br.s)	7.65 (s)	—	5.07 (*J* = 3.8)	4.51 (*J* = 2.9)	3.49	3.26	2.90		2.18—2.28*		2.07	2.12	1.53	1.45 (*J* = 13.0)
4e	8.88 (s)	7.70 (br.s)	—	4.93 (*J* = 4.0)	4.37 (*J* = 2.5)	3.33	3.05	2.79	2.40	2.35 (*J* = 13.0, *J* = 2.5)	2.22	2.04	1.90	1.47	1.32 (*J* = 13.0)
4f	8.70 (s)	7.50 (br.d, *J* = 7.8)	—	4.93 (*J* = 4.0)	4.39 (*J* = 2.5)	3.32	3.06	2.77	2.41	2.40 (*J* = 13.0, *J* = 2.5)	2.22	2.03	1.89	1.46	1.32 (*J* = 13.0)

* This signal is a multiplet (3 H, H_{eq}(5), H_{eq}(4), H_{eq}(6)).

Scheme 5



In summary, our studies extended the scope of application of the rarely used reaction of enamines with nitrosoarenes.

Experimental

^{1}H NMR spectra were recorded on a Bruker DRX instrument (500 MHz) in $CDCl_3$ with Me_4Si as the internal standard. The reactions were monitored and the product purity was checked by TLC on Silufol UV-254 plates. The melting points were measured on a Boetius hot stage. The yields and physicochemical characteristics of the compounds are summarized in Tables 1 and 2.

The starting nitrosoarenes **1c—g** were synthesized by a known procedure,[9] 1-morpholinocyclohexene was also prepared by a reported procedure.[10]

***N*-(2,6-Dichlorophenyl)-*N*-(2-morpholinocyclohex-2-enyl)-hydroxylamine (4b).** 1-Morpholinocyclohexene (3.36 g, 0.02 mol) was added at ~20 °C over a period of 10 min to a solution of 2,6-dichloronitrosobenzene (**1c**) (3.52 g, 0.02 mol) in toluene (25 mL). The precipitated white crystals were filtered off, dried, and recrystallized from toluene.

***N*-(2-Morpholinocyclohex-2-enyl)-*N*-(2,4,6-trichlorophenyl)hydroxylamine (4c).** 1-Morpholinocyclohexene (3.36 g, 0.02 mol) was added at ~20 °C over a period of 5 min to a solution of 2,4,6-trichloronitrosobenzene (**1d**) (4.22 g, 0.02 mol) in acetone (20 mL). The precipitated white crystals were filtered off, dried, and recrystallized from toluene.

***N*-(2-Morpholinocyclohex-2-enyl)-*N*-(2,4,6-tribromophenyl)hydroxylamine (4d).** 1-Morpholinocyclohexene (1.68 g, 0.01 mol) was added at ~20 °C over a period of 7 min to a solution of 2,4,6-tribromonitrosobenzene (**1e**) (3.44 g, 0.01 mol) in acetone (15 mL). The precipitated white crystals were filtered off, dried, and recrystallized from toluene.

***N*-(2,6-Dibromo-4-chlorophenyl)-*N*-(2-morpholinocyclohex-2-enyl)hydroxylamine (4e).** 1-Morpholinocyclohexene (0.16 g, 0.001 mol) was added at ~20 °C over a period of 3 min to a solution of 2,6-dibromo-4-chloronitrosobenzene (**1f**) in acetone (5 mL). The precipitated white crystals were filtered off, dried, and recrystallized from toluene.

***N*-(2,6-Dibromo-4-fluorophenyl)-*N*-(2-morpholinocyclohex-2-enyl)hydroxylamine (4f).** 1-Morpholinocyclohexene (3.36 g, 0.02 mol) was added at ~20 °C over a period of 5 min to a solution of 2,6-dibromo-4-fluoronitrosobenzene (**1g**) (5.6 g, 0.02 mol) in acetone (20 mL). The precipitated white crystals were filtered off, dried, and recrystallized from toluene. ^{13}C NMR ($CDCl_3$), δ: 15.47 (C(5)); 24.63 (C(6)); 26.21 (C(4)); 50.54 (C(2′), C(6′)); 55.38 (C(3)); 65.83, 66.10 (C(3′), C(5′)); 113.70 (C(1)); 118.28 (C(2″), C(6″)), 121.11 (C(3″), C(5″)); 144.39 (C(2)); 157.81, 159.81 (C(1″), C(4″)).

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