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Reaction of Nitroxides with Sulfur Containing Compounds II [1]. Preparation of Nitroxides Bearing an Isothiocyanate Substituent in View of the Nitroxyl Group Reduction with Thiophosgene

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Summary. The reaction of thiophosgene with 2,2,6,6-tetramethylpiperidine-1-oxyl (used as a model nitroxyl radical) was examined. 2,2,6,6-Tetramethylpiperidine and 2,2,6,6-tetramethyl-1-hydroxypiperidine were identified as products. The reaction is not competitive with the reaction of thiophosgene with an amino group. Thus, three nitroxides with an isothiocyanate group were synthesized from thiophosgene and the nitroxides containing the amino substituent.

Keywords. Thiophosgene; Isothiocyanates; Nitroxides.

Introduction

The reaction of thiophosgene (**1**) [2–4] (and references cited therein) with compounds containing a primary amino group is the most important method for the synthesis of isothiocyanates [5–8] (and references cited therein). This basic method was applied for the synthesis of nitroxide radicals bearing an isothiocyanate group [9, 10a], however **1** may be suspected to reduce a nitroxyl group, as it is the case with a number of low valent sulfur containing compounds which are reported to be responsible for a reduction of nitroxides. Especially, many references can be found for compounds containing a sulfhydryl group (*e.g.* [11–16]) which are important in the biochemical environment. Most often, the corresponding hydroxylamines are reported as products. However, reductions of nitroxides to the corresponding amines were also described [1] (and references cited therein). Thus, **1** (as a compound susceptible to oxidation [17]) may also interfere with a nitroxyl group.

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We here report the results of the reaction of **1** with a nitroxyl group and with nitroxides containing a primary amino function, which may give the corresponding isothiocyanates.

Results and Discussion

Reaction of Thiophosgene (**1**) *with 2,2,6,6-Tetramethylpiperidine-1-oxyl* (**2**)

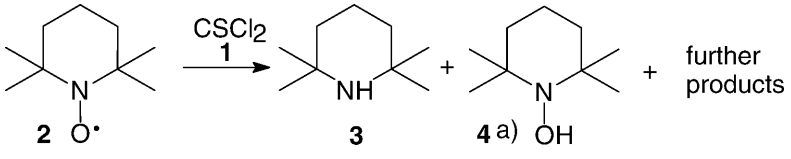
In order to investigate the reaction of **1** with the nitroxyl group, **2** – a radical without extra functional groups – was selected as model compound. The reaction of **1** with **2** was examined in benzene and dichloromethane as solvents. An excess of **1**, benzene with triethylamine as hydrogen chloride acceptor, and (to simulate conditions for isothiocyanate synthesis) two-phase systems: dichloromethane/aqueous sodium bicarbonate solution and dichloromethane/aqueous sodium hydroxide solution at ambient temperature were tested.

The course of the reaction was monitored by means of TLC, GLC, and GLC/MS. Strong darkening of the reaction mixtures and the complete decay of the radical **2** were observed after 8–10 hours. When benzene and an excess of **1** were used as solvents a black precipitate formed. After workup, analysis by means of GLC and GLC/MS revealed a strong peak for 2,2,6,6-tetramethylpiperidine (**3**) and – unexpectedly – the radical **2** again (Scheme 1). So, we assumed that 2,2,6,6-tetramethyl-1-hydroxypiperidine (**4**) is the true product of the reaction. Its re-oxidation (simply by air during workup of the reaction mixture) affords back radical **2** [10b, 18a, 19].

The presence of **4** in the reaction mixture was directly confirmed by comparison of the reaction mixtures with an authentic sample by means of TLC. The GLC results revealed, that the higher the starting ratio of **1**:**2**, the higher was the final ratio **3**:**4** (determined as the radical **2**), (Table 1, entries 1–6). Isolation of the products led to a mixture of **3** and the secondary formed radical **2**. The GLC analysis of this mixture allowed to estimate directly the yield of the amine **3** (Table 1, entries 7–9). When the process was carried out either with NaOH/H_2O/CH_2Cl_2 as base or in NEt_3/C_6H_6, the hydrolysis of **1** and the reaction of **1** with triethylamine, respectively, were observed, instead of the reaction of radical **2** with **1**.

Isothiocyanates with a Nitroxyl Group

The six- and five-membered cyclic nitroxides bearing a primary amino group were allowed to react with **1**. Reactions with sodium hydroxide (A) [9, 10a], $NaHCO_3/H_2O/CH_2Cl_2$ [20–22] (B), and NEt_3/C_6H_6 [23] (C) were tested.

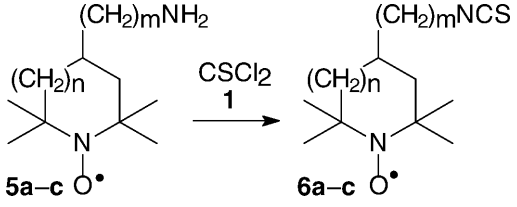


Scheme 1. [a] identified as starting radical **2** after re-oxidation by air

Table 1. Reaction of thiophosgene **1** with the radical **2**

Entry	**1**:**2** [mol/mol]	Solvent	**3**:**2**[a] (GLC)	Yield of **3** [%]
1	1:2	benzene	0.38	
2	1:1	benzene	0.53	
3	2:1	benzene	3.68	
4	1:2	CH_2Cl_2	0.46	
5	1:1	CH_2Cl_2	4.12	
6	2:1	CH_2Cl_2	17.2	
7	1:1	benzene		20
8	13:1	**1**		37
9	1:1	$NaHCO_3/H_2O/CH_2Cl_2$		23

[a] The radical **2** detected in the mixture of products after re-oxidation of **4**



#	n	m	Method	Yield of **6**/%
5, **6a**	1	0	A	54
			B	66
			C	67
5, **6b**	0	0	A	33
			B	72
			C	77
5, **6c**	0	1	A	33
			B	76
			C	63

Scheme 2

When the reactions were carried out below ambient temperature and quenched after several minutes, only the amino group reacted with **1**, whereas the nitroxyl group remained unchanged. If $NaOH/H_2O/CH_2Cl_2$ was used as base, the results were apparently worse – obviously due to hydrolysis of **1**. The synthesized nitroxides bearing an isothiocyanate group are presented in Scheme 2.

Conclusions

The synthesis of nitroxides bearing an isothiocyanate group can be efficiently performed by reaction of **1** with the amino group, both with $NaHCO_3/H_2O/CH_2Cl_2$ and NEt_3/C_6H_6 systems rather than in $NaOH/H_2O/CH_2Cl_2$.

Comparison of the reactions let us conclude that the relative reactivity of **1** towards reagents should be arranged in the order: **5a–c** $\sim$ NaOH > NEt_3 > **2** $\sim$ $NaHCO_3$. The reduction of the nitroxyl group does not take place under the given conditions.

Experimental Part

Methods

Melting points are uncorrected. TLC was done on silica gel with 254 nm fluorescent: Merck 5554, 5562. Visualization: UV 254 nm and I_2 vapour. Mobil phase for the evaluation of the radical **2** decay: benzene:ethyl acetate = 9:1. Column chromatography was done on silica gel: < 0.08 mm (Merck 7729), 60 G for TLC (Merck 7731), Serva for TLC (27185), Merck 1.09385.1000. Mobil phase: benzene:ethyl acetate = 95:5. GLC was recorded on a Varian 3300 gas chromatograph: DB1, $t_c = 90°C$ (3 min) ↗ (10°C/min) ↗ 260°C (5 min), $t_i = 260°C$, $t_d = 280°C$ (FID). GLC/MS was recorded on an AMD M-40 gas chromatograph with mass detector: HP5, $t_c = 50°C$ (3 min) ↗ (5°C/min) ↗ 220°C, $t_i = 240°C$. MS and IR data were determined using an AMD M-40 (EI, 70 eV) and FT IR Jasco 420 apparatus.

Starting Compounds

All commercially available chemicals were used as received. Thiophosgene (**1**) (98%) was manufactured in the Institute of Industrial Organic Chemistry. The radical **2** [18b, 24–26], as well as the samples of the amine **3** [27] and the hydroxylamine **4** [28] were obtained according to literature methods. 4-Amino-2,2,6,6-tetramethylpiperidine was either obtained from triacetonamine by oximation with hydroxylamine hydrochloride (18%) [24, 29], followed by reduction of the corresponding oxime with sodium in ethanol (80%) 18c, 30, 31], or purchased from Georganics (Slovakia) as well as received as a free sample from Degussa-Huels. 2,2,6,6-Tetramethyl-4-piperidinone-1-oxyl was synthesized by oxidation of triacetonamine with hydrogen peroxide and sodium carbonate (73%) [32, 33]. The starting aminonitroxides **5a–5c** were obtained in multi-step preparations from 2,2,6,6-tetramethyl-4-piperidinone (triacetonamine) according to reported methods with some modifications described below.

4-Amino-2,2,6,6-tetramethylpiperidine-1-oxyl (**5a**) [18d, 30, 34]

4-Amino-2,2,6,6-tetramethylpiperidine (117 g, 0.75 mol) dissolved in 340 cm^3 of diethyl ether was protected by acetylation with 236.6 g of acetic anhydride (adding dropwise at 5–10°C for 3.5 h) to give 197 g of 4-acetamido-2,2,6,6-tetramethylpiperidine acetate (mp 188–195°C). It was alkalized with 148.1 g of potassium carbonate in 1.42 dm^3 of H_2O at 25°C for 15 min, followed by oxidation with 284 cm^3 of 30% H_2O_2 in the presence of 14.2 g of sodium tungstate and 14.2 g of *EDTA*Na_2 for 73 h to give 150.8 g of 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxyl, which was directly hydrolyzed with 482.3 g of KOH in 1.32 dm^3 of H_2O under reflux and vigorous mechanical stirring for 29 h. Saturation of the solution with K_2CO_3, thorough extraction with about 1.5 dm^3 of diethyl ether, followed by fractional vacuum distillation afforded 63.3 g of **5a** (49%), bp 84–86°C/0.5 mm Hg; IR (film); $\bar{\nu} = 3360, 3280\ cm^{-1}$; MS is consistent with Refs. [35a, 36a].

2,2,5,5-Tetramethyl-3-carbamoylpyrrolidine-1-oxyl

Ring contraction of 2,2,6,6-tetramethyl-4-piperidinone-1-oxyl by *Favorski* rearrangement [37, 38]: A solution of 44.1 g of I_2 (0.1736 mol) in 882 cm^3 of benzene was added dropwise to a solution of 30.0 g of 2,2,6,6-tetramethyl-4-piperidinone-1-oxyl (0.1765 mol) and 29.7 g of KOH (0.53 mol) in 882 cm^3 of

25% aq. NH_3 at 25°C for 8 h. After workup, followed by crystallization from ethyl acetate, 17.3 g of 2,2,5,5-tetramethyl-3-carbamoylpyrrolidine-1-oxyl were obtained (53%), mp 168–170.5°C.

2,2,5,5-Tetramethyl-3-aminopyrrolidine-1-oxyl (**5b**)

Hofmann rearrangement of 2,2,5,5-tetramethyl-3-carbamoylpyrrolidine-1-oxyl with NaOBr [18e, 39, 40].

2,2,5,5-Tetramethyl-3-carbamoylpyrrolidine-1-oxyl (9.3 g, 0.05 mol) was added to a solution of 11.3 g of Br_2 (0.07 mol) and 12.1 g of NaOH in 130 cm^3 of H_2O at 5°C. The solution was stirred at 5°C for 2 h and at 70°C for 2 h. After workup, 4.13 g of **5b** were obtained (52%), bp 65.5–66°C/0.6 mm Hg (Refs. [18e, 39] 75–80°C/1 mm Hg); mp 44–46°C (Ref. [41] 34–35°C); IR (film): $\bar{\nu} = 3378$, 3312, 2970, 2929, 2870, 1464, 1361, 1106, 860 cm^{-1}; MS is consistent with Refs. [35b, 36b].

2,2,5,5-Tetramethyl-3-(aminomethyl)pyrrolidine-1-oxyl (**5c**) [42, 43]

2,2,5,5-Tetramethyl-3-carbamoylpyrrolidine-1-oxyl (5.676 g, 30.7 mmol) was reduced with 7.32 g of $LiAlH_4$ (0.193 mol) (added in three 2.44 g portions in equidistant time intervals) in 800 cm^3 of anhydrous diethyl ether under reflux and vigorous magnetical stirring for 28 h. After workup, 5.3 g of **5c** (yellow oil) were obtained. The crude amine **5c** was purified by vacuum distillation (2.0 g, 38%), bp 84–7°C/0.8 mm Hg (Ref. [43] 55°C/0.1 mm Hg); IR (film): $\bar{\nu} = 3370$, 3303, 2971, 2929, 2867, 1463, 1362 cm^{-1}; MS: m/z (%) = 183 (2), 173 (12), 172 (30), 171 (100, M), 157 (38), 142 (6), 127 (6), 126 (16), 112 (8), 110 (6), 109 (22), 98 (3), 96 (2), 95 (8), 84 (5), 81 (7), 74 (18), 70 (42), 69 (12), 68 (10), 67 (13), 58 (12), 56 (15), 55 (13), 53 (9).

Reaction of Thiophosgene (**1**) *with 2,2,6,6-Tetramethylpiperidine-1-oxyl* (**2**)

a) In Benzene (Table 1, entry 7)

Thiophosgene (**1**) (0.115 g, 1 mmol, 77 mm^3) was added with a syringe to a solution of 0.1578 **2** of (1 mmol) in 1 cm^3 of benzene and the solution was allowed to stand at r.t. for 24 h. The precipitate (0.121 g) was filtered off, washed with acetone, and placed in a separatory funnel. A 20% aq. K_2CO_3 solution (1 cm^3) was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried with anh. $MgSO_4$, filtered, and the solvent was evaporated. A mixture of **3** and **2** (0.065 g, reddish oil) was obtained. The yield of the amine **3**, estimated according to GLC analysis, was 20%.

b) In an Excess of ***1*** (Table 1, entry 8)

The radical **2** (0.158 g, 1 mmol) was added to an excess of **1** (1.51 g, 13.1 mol, 1 cm^3) and the solution was allowed to stand at r.t. for 24 h. The precipitate was filtered off (0.1686 g), washed with acetone, and placed in a separatory funnel. The precipitate was alkalized as above providing 0.060 g of an oil (37% of **3** – estimated as above).

c) In the $NaHCO_3/H_2O/CH_2Cl_2$ System (Table 1, entry 9)

The radical **2** (0.3897 g, 2.5 mmol) dissolved in 1 cm^3 of CH_2Cl_2 was added to a mixture of 0.504 g of $NaHCO_3$, 1.25 cm^3 of H_2O, 1 cm^3 of CH_2Cl_2, and 0.302 g of **1** (2.624 mmol, 201 mm^3). The reaction mixture was vigorously stirred for 9 h at r.t., diluted with CH_2Cl_2, and then washed with sat. $NaHCO_3$ solution. The organic layer was dried with anh. $MgSO_4$. After filtration and evaporation, a dark crystalline mass (0.407 g) was obtained. The solid was triturated with benzene, then with benzene:ethyl

acetate 95:5, filtered, and placed in a separatory funnel. The precipitate was alkalized as above yielding 0.175 g of an oil (23% of **3** – estimated as above).

2,2,6,6-Tetramethyl-4-isothiocyanatopiperidine-1-oxyl (**6a**)

Procedure A with $NaOH/H_2O/CH_2Cl_2$

Thiophosgene (**1**) (0.302 g, 2.62 mmol, 200 mm^3) was added dropwise with a syringe to 0.438 g of **5a** (2.56 mmol) dissolved in 10 cm^3 of a 5% NaOH solution at 5–7.5°C for 10 min. An exotermic process was observed and the resulting mixture was stirred for 10 min. The precipitate[1] (0.613 g) was removed by filtration and dried under vacuum to give 0.362 g of the raw product. It was subjected to column chromatography to yield 0.293 g of **6a** (54%), mp 125.5–127.5°C (Refs. [9, 10a] 127–128°C, Ref. [44] 131–132°C); IR (film): $\bar{\nu} = 2187, 2126\,cm^{-1}$; MS: m/z (%) = 214 (4), 213 (14, M), 199 (4), 198 (3), 183 (5), 154 (12), 140 (10), 128 (12), 127 (9), 126 (12), 124 (11), 112 (17), 109 (7), 100 (11), 98 (6), 92 (6), 85 (4), 81 (6), 78 (8), 74 (7), 72 (7), 69 (100), 56 (11), 55 (12), 53 (7), 41 (45).

2,2,5,5-Tetramethyl-3-isothiocyanatopyrrolidine-1-oxyl (**6b**; $C_9H_{15}N_2OS$)

Procedure C with NEt_3/C_6H_6

Thiophosgene **1** (0.279 g, 2.43 mmol, 185 mm^3) in 1 cm^3 of benzene (dried azeotropically) was added dropwise with a syringe to the solution of 0.363 g of **5b** (2.31 mmol) and 0.68 cm^3 of triethylamine in 5 cm^3 of benzene at 10–17°C with vigorous stirring. The mixture was stirred at 20°C for 5 min and the precipitate of triethylamine hydrochloride was filtered off and thoroughly washed with benzene. The benzene filtrate was washed with sat. $NaHCO_3$ solution, the aq. phase was extracted with $2 \times 3\,cm^3$ of benzene, and the organic layers were dried with anh. $MgSO_4$, filtered, and the solvent was evaporated. The residue was subjected to column chromatography to give 0.356 g of **6b** (77%); IR (film): $\bar{\nu} = 2098\,cm^{-1}$; MS: m/z (%) = 200 (1), 199 (11, M), 185 (2), 169 (2), 167 (3), 154 (4), 149 (5), 140 (2), 139 (3), 126 (15), 113 (60), 112 (19), 111 (14), 110 (7), 100 (24), 99 (9), 98 (15), 95 (12), 92 (6), 90 (4), 84 (13), 83 (8), 80 (18), 78 (5), 74 (14), 69 (48), 67 (16), 58 (20), 57 (14), 56 (86), 55 (100), 53 (22), 43 (32).

2,2,5,5-Tetramethyl-3-(isothiocyanatomethyl)pyrrolidine-1-oxyl (**6c**)

Procedure B with $NaHCO_3/H_2O/CH_2Cl_2$

Amine **5c** (0.375 g, 2.19 mmol) dissolved in 0.5 cm^3 of CH_2Cl_2 was added dropwise with vigorous stirring to the mixture of 0.493 g of $NaHCO_3$, 1.25 cm^3 of H_2O, 1 cm^3 of CH_2Cl_2, and 0.297 g of **1** (2.58 mmol, 197 mm^3) at 10–15°C. The mixture was stirred at r.t. for 5 min, CH_2Cl_2 (5 cm^3) and 5 cm^3 of H_2O were added, and the aq. layer was extracted with $3 \times 2\,cm^3$ of CH_2Cl_2. The organic layer was dried with anh. $MgSO_4$, filtered, and the solvent was evaporated. The dark-yellow oil (0.463 g) was subjected to column chromatography to give 0.353 g of **6c** (76%), mp 33–6°C (Ref. [44] 36–7°C); IR (film): $\bar{\nu} = 2080\,cm^{-1}$; MS: m/z (%) = 214 (2), 213 (14, M), 199 (1), 183 (5), 140 (4), 109 (3), 100 (3), 81 (5), 74 (13), 69 (100), 56 (9), 55 (10), 41 (37).

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[1] In the case of **6b** and **6c**, synthesis according to procedure **A** gave no precipitate. Thus, the reaction mixture was extracted with CH_2Cl_2

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