A Convenient Synthesis of *N*-Substituted 4-(Chloroalkylamino)-2,2,6,6-tetramethylpiperidine-1-oxyls

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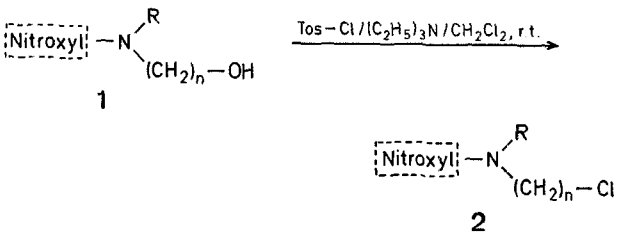
Many reactive derivatives of 2,2,6,6-tetramethylpiperidine-1-oxyl which are used directly or as building blocks in spin labeling have been synthesized and summarized in exhaustive reviews[1,2]. However, the synthesis of *N*-substituted 4-(chloroalkylamino)-2,2,6,6-tetramethylpiperidine-1-oxyls has not yet been published. These compounds are useful new nitroxyl key intermediates which can be used as alkylating agents in the synthesis of spin-labeled drug molecules since numerous pharmacologically active compounds have an aminoalkyl side chain. We have used 4-[*N*-methyl-*N*-(3-chloropropyl)-amino]-2,2,6,6-tetramethylpiperidine-1-oxyl **(2a)** in the synthesis of spin-labeled imipramine and chlorpromazine analogs[3].

Since most direct methods for the conversion of alcohols into the corresponding chlorides involve the use of strong acids they may not be applied to *N*-oxyl compounds, because in the presence of strong acids nitroxyls undergo a disproportionation reaction with loss of paramagnetism[4]. The reaction steps requiring acidic conditions must therefore be performed before the secondary amine or the hydroxylamine is oxidized to the nitroxyl[2].

We report here a simple one-pot conversion of a series of nitroxyl alcohols into the corresponding chlorides under conditions which do not affect the nitroxyl moiety.

In attempts to prepare tosylates of nitroxyl alcohols of the type **1** by a modification of a procedure for the synthesis of alkyl methanesulfonates[5], we found that stirring alcohols **1** with tosyl chloride and triethylamine in dichloromethane at room temperature resulted in excellent to moderate yields of the corresponding chlorides **2** which in most cases were T.L.C. pure and gave satisfactory analyses without further purification.

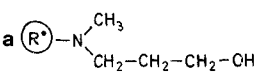
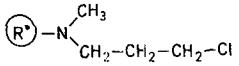
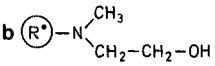
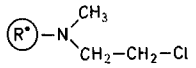
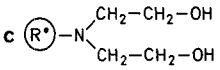
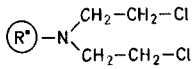
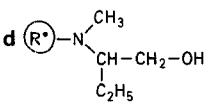
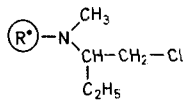
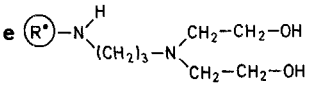
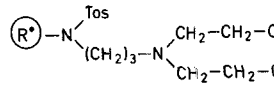
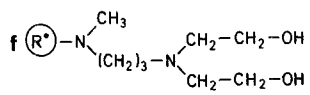
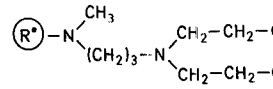


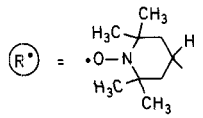
1 **2**

Melting points were determined on a Kofler hot stage microscope and are uncorrected. Microanalyses were performed using a Perkin Elmer 240C analyzer. Mass spectra were recorded on a CEC 21-110 B mass spectrometer. The I.R. spectra were run on a Perkin Elmer 257 instrument and were in accord with the structures given in Table 1. The E.S.R. spectra of compounds **1** and **2** were obtained from 10^{-4} molar solutions in chloroform using a Varian E 9 spectrometer and were characteristic triplets.

The nitroxyl alcohols **1a–f** were prepared by reductive amination of 4-oxo-2,2,6,6-tetramethylpiperidine-1-oxyl with the respective aminoalcohol using sodium cyanoborohydride as reducing agent and methylation of the secondary amine thus obtained with formaldehyde and sodium cyanoborohydride, as previously reported[6,7]. Compounds **1c–f** are new; they were characterized by microanalysis, mass, I.R., and E.S.R. spectrometry.

Table 1. 4-(Chloroalkylamino)-2,2,6,6-tetramethylpiperidine-1-oxyls (**2**) from the corresponding Nitroxyl Alcohols (**1**)

Educt **1**		equiv of Tos-Cl/$(C_2H_5)_3N$	Product **2**		
Formula[a]	m.p. [°C]	used	Formula[a]	Yield[b] [%]	m.p. [°C]
a 	77–79°[c]	1.5		81	38–40°
b 	29–30°[c]	1.5		45[d]	oil
c 	oil	3.0		50	65–67°
d 	oil	1.5		67	53–55°
e 	semisolid	4.5		30	83–85°
f 	55–57°	3.0		28[d]	semisolid

[a] 

[b] Yield of isolated pure product.

[c] m.p. not reported in Ref.[7].

[d] Purified by column chromatography on silica gel using chloroform/methanol (9/1) as eluent.

[e] Tos =

Table 2. Spectral Data of Compounds **1c–f** and **2a–f**

Compound	Molecular Formula[a]	M.S. *m/e*	I.R.[b] (film; KBr for **2a, c, d, e**) ν [cm^{-1}]	E.S.R. (3 lines) a_N (mT)
1c	$C_{13}H_{27}N_2O_3$ (259.4)	260 $(M+1)^{+c}$	3400, 2930, 1460, 1375, 1360, 1240, 1215, 1180, 1045	1.5
1d	$C_{14}H_{29}N_2O_2$ (257.4)	257 $(M)^+$	3430, 2960, 1455, 1370, 1355, 1240, 1215, 1175, 1050	1.5
1e	$C_{16}H_{34}N_3O_3$ (316.5)	317 $(M+1)^{+c}$	3350, 2940, 1465, 1380, 1365, 1250, 1185, 1050	1.5
1f	$C_{17}H_{36}N_3O_3$ (330.5)	331 $(M+1)^{+c}$	3395, 2930, 1455, 1375, 1360, 1240, 1215, 1175, 1040	1.5
2a	$C_{13}H_{26}ClN_2O$ (261.8)	261 $(M)^+$	2935, 1465, 1430, 1360, 1330, 1240, 1220, 1175, 765, 650	1.5
2b	$C_{12}H_{24}ClN_2O$ (247.8)	247 $(M)^+$	2970, 1460, 1375, 1360, 1330, 1240, 1215, 1175, 735	1.5
2c	$C_{13}H_{25}Cl_2N_2O$ (296.3)	296 $(M+1)^{+c}$	2985, 1465, 1435, 1375, 1360, 1330, 1240, 1205, 1175, 735, 715, 650	1.5
2d	$C_{14}H_{28}ClN_2O$ (275.9)	275 $(M)^+$	2970, 1460, 1380, 1365, 1250, 1220, 1195, 1185, 1035, 810, 705	1.5
2e	$C_{23}H_{38}Cl_2N_3O_3S$ (507.6)	507 $(M+1)^{+c}$	2975, 1600, 1465, 1345, 1305, 1250, 1165, 1115, 1095, 720, 685, 660	1.5
2f	$C_{17}H_{34}Cl_2N_3O$ (367.4)	367 $(M+1)^{+c}$	2930, 1455, 1375, 1360, 1325, 1295, 1240, 1215, 1175, 720, 660	1.5

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.39; H, ±0.29; N, ±0.29. Exception: **1c**, C, −0.48.

[b] Only the most intense absorption bands are listed. In the region $\nu = 3000–2700\ cm^{-1}$, only the peak with the highest intensity is given.

[c] M^+ is also present but its intensity is less than that of $(M+1)^+$.

4-[*N*-Methyl-*N*-(3-chloropropyl)-amino]-2,2,6,6-tetramethylpiperidine-1-oxyl (2a); Typical Procedure:

To a stirred solution of 4-[*N*-methyl-*N*-(3-hydroxypropyl)-amino]-2,2,6,6-tetramethylpiperidine-1-oxyl (**1a**; 2.43 g, 10 mmol) in dry dichloromethane (50 ml) *p*-toluenesulfonyl chloride (2.68 g, 15 mmol) and dry triethylamine[5] (2.1 ml, 15 mmol) are added. Stirring is continued for 48 h at room temperature. After evaporation of the solvent, ether (50 ml) is added to the residue and the resultant mixture is transferred to a separatory funnel. It is washed with water (2 × 50 ml) and extracted with 1 normal hydrochloric acid (50 ml). The acidic solution is washed with ether (50 ml), then made alkaline with sodium carbonate, and extracted with ether (4 × 25 ml). The etheral solution is dried with potassium carbonate, filtered, and evaporated in vacuo. Product **2a** is obtained as a red oil which crystallizes on standing; yield: 2.11 g (81%); m.p. 38–40°C.

Acknowledgements are due to Mrs. M. Kastelic and to the Department of Chemistry, E. Kardelj University, for microanalyses.

Received: June 27, 1983

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