# A Useful Protecting Group in the Preparation of Amino-nitroxides

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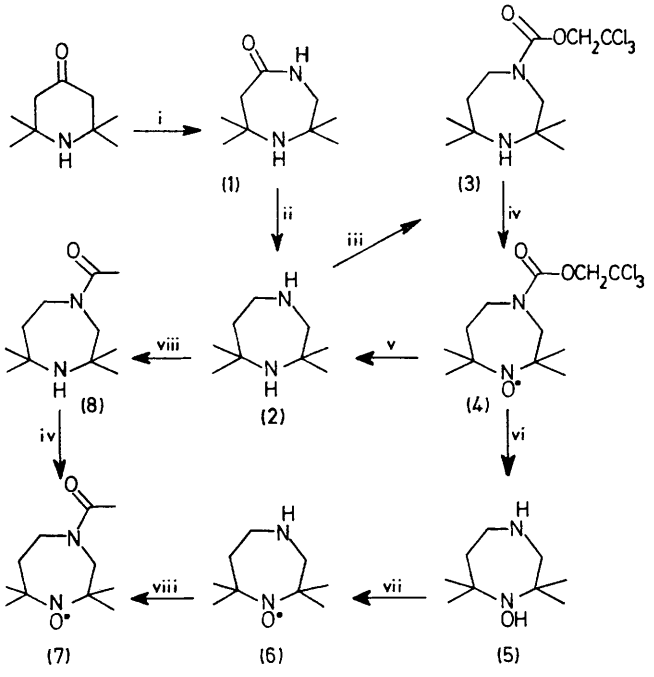
*Summary* β,β,β-Trichloroethoxycarbonyl, a useful amino protecting group, reacts selectively on the less hindered amino group of diamines; further oxidation of the hindered amino group and removal of the masking group leads to amino-nitroxides.

To prepare nitroxide radicals with an amino function, the hindered amino group of a diamine must be selectively oxidized. This selective oxidation cannot be achieved directly since the two amino groups are both reactive to oxidizing reagents. It is thus necessary to choose a protecting group unaffected by peracid oxidation and capable of removal under conditions which ensure survival of the nitroxide group or of its hydroxylamine. Protecting groups which must be removed under acidic conditions (in acidic medium the NO group may be transformed into a mixture of hydroxylamine and reactive immonium oxide salts[1]) or strong reductive conditions (*e.g.* Na in liquid $NH_3$ may reduce the NO function to secondary amine[2]) are therefore excluded.

For these reasons, we have chosen the β,β,β-trichloroethoxycarbonyl protecting group[3] which can be removed under mild reductive conditions ensuring its possible use with complex nitroxides. For instance, it is a useful protecting group in the synthesis of the cyclic amino-nitroxide (**6**) as follows. 2,2,7,7-Tetramethylhomopiperazine (**2**)† [$\nu_{max}$ (neat) 3310 $cm^{-1}$ (NH); δ($CDCl_3$, ref. $Me_4Si$) 1·08 (s, 2Me), 1·17 (s, 2Me), 1·65 (br, N*H*), 1·74 (m, $CH_2$-$CH_2$-N), 2·76 (s, $CH_2$-N), 2·90 (m, $CH_2$-$CH_2$-N)] is obtained by $LiAlH_4$ reduction (96% yield) of 2,2,7,7-

† Satisfactory elemental analysis and/or high resolution mass measurements have been obtained for all compounds.

tetramethyl-5-homopiperazinone (**1**).[4] β,β,β-trichloroethoxycarbonyl chloride in benzene, in the presence of $K_2CO_3$, acylates selectively the non-hindered amino group in (**2**)



i, Ref. 4; ii,$LiAlH_4$.$Et_2O$; iii, $ClCO_2CH_2CCl_3$, $C_6H_6$, $K_2CO_3$; iv, *m*-$ClC_6H_4CO_3H$, $Et_2O$ or $H_2O_2$—phosphotungstic acid; v, Zn(excess)–AcOH,$H_2O$, heat; vi, Zn dust, AcOH, $H_2O$,O °C; vii, $Ag_2O$, $Et_2O$; viii, $Ac_2O$.

leading to the amino carbamate (**3**) (93% yield) [$\nu_{max}$ (neat) 3340 (NH), 1720 $cm^{-1}$ (CO); δ($CDCl_3$, ref. $Me_4Si$)‡ 1·16 (s, 4Me), 1·85 (m, $CH_2$-$CH_2$-N), 3·49 (s, $CH_2$-N), 3·62 (m, $CH_2$-$CH_2$-N), 4·77 (d, well resolved, N-CO-O-$CH_2$-$CCl_3$)]. Compound (**3**) is readily oxidized either by $H_2O_2$–phosphotungstic acid or by *m*-chloroperbenzoic acid (MCPA), to the protected nitroxide (**4**) (87% yield) [$\nu_{max}$ (neat) 1725 $cm^{-1}$ (CO); $\lambda_{max}$ (MeOH) 227 (ε 2800), 245 sh (1930), 444 (8·2), $\lambda_{max}$ ($C_6H_{12}$) 228 (ε 2800), 245sh (1950), 465 nm (8·1); δ ($CDCl_3$, ref. $Me_4Si$)‡ of the corresponding hydroxylamine,§ 1·14 (s, 4Me), 1·88 (m, $CH_2$-$CH_2$-N), 3·48 (s, $CH_2$-N), 3·62 (m, $CH_2$-$CH_2$-N), 4·77 (d, well resolved, N-CO-O-$CH_2$-$CCl_3$); e.s.r. ($CH_2Cl_2$) $a_N$ = 15·7 G]. The β,β,β-trichloroethoxycarbonyl group in (**4**) is easily removed with zinc dust (1·5 Zn $mol^{-1}$) in acetic acid–water (2 : 1) at 0°C and the amino hydroxylamine (**5**) [m.p. 92 °C; $\nu_{max}$ (nujol) 3300—3100 $cm^{-1}$ (NH,NOH); δ ($CDCl_3$, ref. $Me_4Si$) 1·17 (s, 2Me), 1·23 (s, 2Me), 1·72 (m, $CH_2$-$CH_2$-N), 2·75 (s, N-$CH_2$), 2·92 (m, $CH_2$-$CH_2$-N)] is obtained (92% yield).¶ The hydroxylamine group in compound (**5**) is quantitatively oxidized by silver(I) oxide in diethyl ether, the amino group being untouched. The resulting amino nitroxide (**6**) [$\nu_{max}$ (neat) 3320 $cm^{-1}$ (NH); $\lambda_{max}$ ($C_6H_{12}$) 452 (ε 9·1), 236 (2420), $\lambda_{max}$ (MeOH) 430 (8·4), 235 nm (2560); e.s.r. ($CH_2Cl_2$) $a_N$ = 15·4 G] has been characterized by its *N*-acetyl derivative (**7**) (78% yield) [m.p. 42 °C; $\nu_{max}$ (nujol) 1640 $cm^{-1}$ (CO); δ ($CDCl_3$, ref $Me_4Si$)‡ of the corresponding hydroxylamine,§ 1·16 (m, 4Me), 1·82 (m, $CH_2$-$CH_2$-N), 2·13 (d, well resolved, CO-*Me*), 3·60 (m, $CH_2$-N-$CH_2$); e.s.r. ($CH_2Cl_2$) $a_N$ = 15·6 G] which can be prepared independently from the diamine (**2**), by selective acylation of the non-hindered amino group (89% yield) followed by oxidation ($H_2O_2$ or MCPA, 81% yield) of the intermediate (**8**) [$\nu_{max}$ (neat) 3330 (NH), 1635 $cm^{-1}$ (CO); δ ($CDCl_3$, ref. $Me_4Si$)‡ 1·09 (m, 4Me), 1·80 (m, $CH_2$-$CH_2$-N), 2·15 (d, CO-*Me*), 3·60 (m, $CH_2$-$CH_2$-N-$CH_2$)].

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‡ In $^1H$ n.m.r., restricted rotation of the β,β,β-trichloroethoxycarbonyl group in (**3**) (60 MHz, coalescence temperature 46 °C) and in the hydroxylamine corresponding to (**4**) has been observed. Restricted rotation of the *N*-acetyl group has also been observed in (**8**) (60 MHz, coalescence temperature 100 °C) and in the hydroxylamine corresponding to (**7**).

§ In order to be characterized by high resolution $^1H$ n.m.r., the nitroxides are transformed into the corresponding hydroxylamines according to the procedure described in ref. 5.

¶ If this reaction is carried out with a large excess of zinc dust, at 70 °C, the starting diamine (**2**) is obtained, the hindered hydroxylamine group being reduced to the amine. The reduction of the nitroxide group in compound (**4**) was not unexpected.[2,6]


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