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Water-soluble aminoxyls (nitroxides): 2-methyl-2-[(*N*-(4-*tert*-butylphenyl)oxyl]propanesulfonate and (1-oxyl-2,5,5-trimethylpyrrolidin-2-yl)methanesulfonate

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Two charged aminoxyls, ammonium (1-oxyl-2,5,5-trimethylpyrrolidin-2-yl)methanesulfonate and ammonium 2-methyl-2-[(*N*-(4-*tert*-butylphenyl)oxyl]propanesulfonate, obtained by methods easily adaptable to the preparation of various other aminoxyls are totally soluble in water but are partially associated in other solvents.

The usual piperidine and pyrrolidine aminoxyls are in general sufficiently soluble in water for some uses, such as spin-labeling[1] or dynamic nuclear polarization in biological fluids.[2] They are not soluble enough in water in nitroxide-mediated controlled free-radical polymerization (NMCRP)[3] of hydrophilic monomers,[4] where co-solvents have been used.[5]

Their solubility in water may be increased by introduction of charged substituents.[6] In particular, if these groups are close to the aminoxyl function, they may also induce inductive and steric effects different from those of the usual nitroxides. Since the effectiveness of one of the most successful mediators[7] for NMCRP has been attributed to these effects,[8] it could be interesting to test the behavior of such molecules in NMCRP in water. Carboxylate[9] and ammonium[10] aminoxyls of this type have been reported but, to our knowledge, no sulfonate salts.

We have prepared the sulfonate derivatives **1a**† , **1b**† (Scheme 1) and **2a**†, **2b**† (Scheme 2) in which the sulfur atom is separated from the aminoxyl nitrogen by three and four bonds respectively.

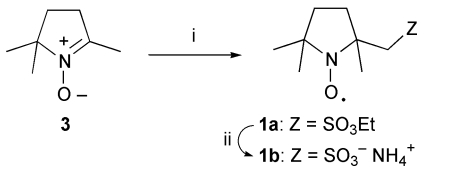
Following a general procedure for the preparation of sulfonate esters,[11] **1a** was prepared by addition of 2,5,5-trimethyl-1-pyrroline *N*-oxide (**3**)[12] to a solution of α-lithio methanesulfonate; formation of the expected hydroxylamine was not observed, probably because of its direct oxidation during work up. **1a** was isolated in 7% yield after chromatography (Scheme 1). Although the yield is quite low, this reaction provides a rapid and easy access to **1a**. Boiling methanolic ammonia[13] converted **1a** to the sulfonate salt **1b** in 46% yield. **1b** dissolves readily in cold water and in methanol.

For the preparation of **2a** and **2b**, a Strecker[14] reaction with 4-*tert*-butylaniline **4** and acetone gave (90%) the α-aminonitrile **5**, converted[15] by concentrated sulfuric acid, at room temperature to the amide **6** (89%), and then at 105 °C in methanol with TsOH to the methyl ester **7** (68%). Following Weinreb *et al.*,[16] **7** gave **8** (68%), reduced by $LiAlH_4$ in THF to the aldehyde **9** (82%). The unsaturated sulfonate ester **10** (75%), obtained by the method of Ghosez *et al.*[17] was then reduced by $NaBH_4$ to the saturated sulfonate ester **11**† (61%) in ethanol, at room temperature. Oxidation with *m*-CPBA in CH_2Cl_2 (Scheme 2) gave the new aminoxyl **2a** (90%) which was converted in boiling methanolic ammonia to **2b** (85%). **2b** was found to be soluble in water at a concentration greater than 400 mM.

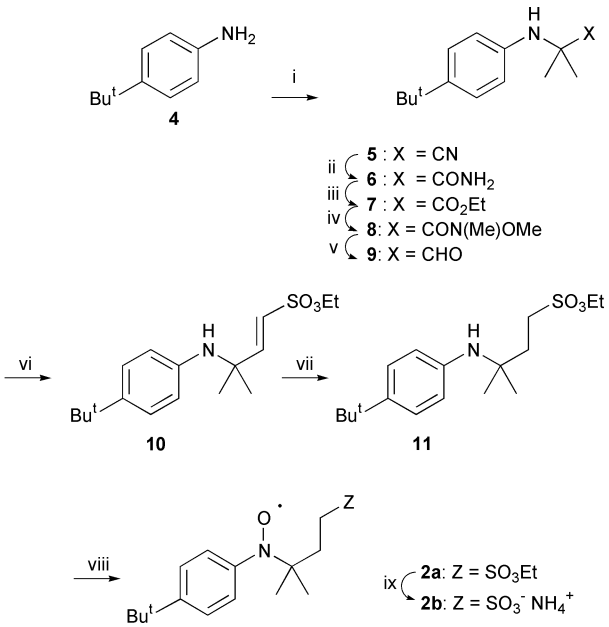
If these highly water-soluble nitroxides happen to possess a sufficiently low toxicity, they could also find some use as contrast agents or probes for *in vivo* magnetic resonance (NMR,[18] ESR[19] or PEDRI[20]) imaging.

Solutions (10^{-4} M) of **1b** and **2b** in water display the typical EPR spectra, the centre of each line being situated on the base-line. At the same concentration in ethanol, the spectrum is different: the centres of the two outer lines are above and below the base-line respectively, and the upper extremity of the three lines show an apparent decrease towards high field. As shown by spectral simulation, this apparent imbalance in the derivative spectrum is due to a broad absorption-line superimposed onto the three-line spectrum. This broad line can be attributed to the presence of a supplementary species with a large volume and/or strong spin–spin dipolar interactions,[21] *i.e.* a dimer or a larger aggregate, in equilibrium with the monomeric anions. On the spectrum of **2b** at the same concentration in CH_2Cl_2, the broad line is more apparent, indicating a higher concentration of these condensed species. Thus, at 10^{-4} M, these organic salts are not totally dissociated in solvents less polar than water, even if their solutions are totally limpid. They do not dissolve in a solvent of lower polarity such as Et_2O.

In principle, various sulfonated nitroxides can be obtained from other nitrones or other primary amines by the two schemes used here; in addition, the intermediate secondary amines



Scheme 1 *Reagents and conditions*: i, $LiCH_2SO_3Et$, THF, −50 °C, 2 h, 7%; ii, NH_3, MeOH, reflux, 46%.



Scheme 2 *Reagents and conditions*: i, AcOH, KCN, Me_2CO, 20 °C, 2 h, 90%; ii, H_2SO_4, 20 °C, 48 h, 89%; iii, TsOH, MeOH, sealed tube, 105 °C, 36 h, 68%; iv, Me_3Al, MeN(H)OMe.HCl, benzene, 69 °C, 14 h, 68%; v, $LiAlH_4$, THF, −78 °C, 4 h, 83%; vi, $(EtO)_2P(O)CH(Li)SO_3Et$, THF, from −78 °C to 20 °C, 18 h, 75%; vii, $NaBH_4$, EtOH, 20 °C, 2 h, 62%; viii, *m*-CPBA, CH_2Cl_2, 20 °C, 3 h, 90%; ix, NH_3, MeOH, reflux, 85%.

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corresponding to **5–10** may easily yield other aminoxyls of different polarity.

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Notes and references

† *Selected data* for **1a**, **1b**, **2a**, **2b** and **11**: **1a**: yellow oil; EIMS: *m/z* (%) 250 ([M]$^+$, 41); Anal. Calc. for $C_{10}H_{20}NSO_4$: C, 48.00; H, 8.25; N, 5.60. Found: C, 47.85; H, 8.00; N, 5.23%. EPR: cyclohexane, a_N = 13.69 G; EtOH, a_N = 14.5 G.

1b: yellow solid; mp 190°C; MS (FAB): *m/z* (%) 221 ([M-(NH_4^+)]$^-$, 100); Anal. Calc. for $C_8H_{19}N_2SO_4$: C, 40.16; H, 7.95; N, 11.71. Found: C, 40.09; H, 8.06; N, 11.65%; EPR, H_2O, a_N = 16.12 G; EtOH, a_N = 15 G.

2a: red oil; MS (CI, NH_3): *m/z* (%) 344 ([M + 2H]$^+$, 5.4) 328 (100); Anal. Calc. for $C_{17}H_{28}NSO_4$: C, 59.64; H, 8.18; N, 4.09. Found: C, 59.67; H, 8.35; N, 3.89%; EPR: toluene, a_N = 12.45 G, a_{Hortho} = 1.82 G, a_{Hmeta} = 0.80 G; EtOH, a_N = 13.37 G, a_{Hortho} = 1.77 G, a_{Hmeta} = 0.89 G.

2b: red solid; mp 168 °C; MS (FAB): *m/z* (%) 314 ([M-(NH_4^+)]$^-$, 100), 298 (74); EPR, H_2O, a_N = 14.51 G, (unresolved a_H); EtOH, a_N = 13.35 G, a_{Hortho} = 0.96 G, a_{Hmeta} = 0.53 G.

11: white solid; mp 63 °C; δ_H(250 MHz, $CDCl_3$) 7.12 (d, *J* = 8.64Hz, 2H), 6.595 (d, *J* = 8.64 Hz, 2H), 3.411 (q, *J* = 7.03 Hz, 2H), 3.142 (d, 2H), 2.130 (m, 2H), 1.264 (t, *J* = 7.03 Hz, 3H), 1.232 (s, 6H), 1.200 (s, 9H); δ_C(50 MHz, $CDCl_3$) 143.03, 141.94, 125.84, 117.04, 65.98, 52.73, 46.13, 34.14, 33.76, 31.31, 28.45, 14.92; EIMS: *m/z* (%) = 327 ([M]$^+$, 16.53), 312 (13.38), 190 (100); Anal. Calc. for $C_{17}H_{29}NSO_3$: C, 62.38; H, 8.86; N, 4.28. Found: C, 62.20; H, 9.04; N, 4.31%.

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