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Hetero-Cope rearrangement for the synthesis of potassium 5-*tert*-butyl-2-(*tert*-butyl-aminoxy)-benzoate, a highly water-soluble stable free radical

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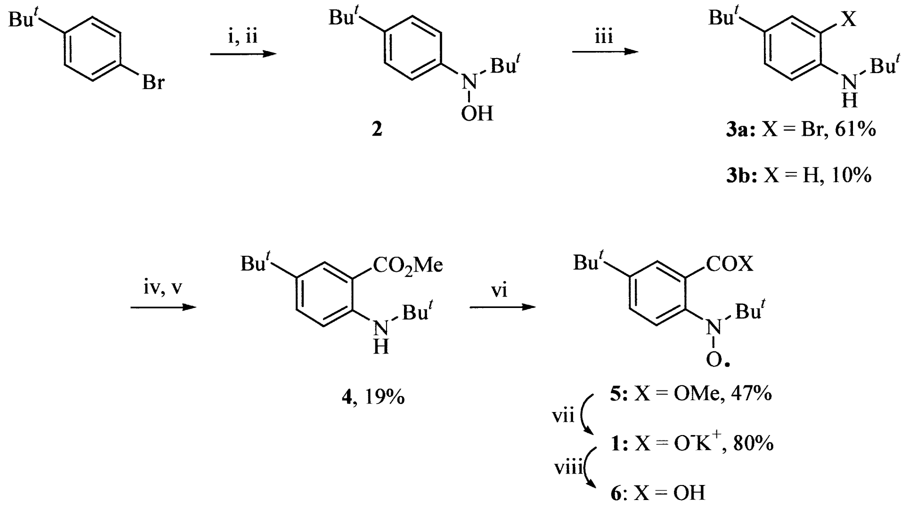
Abstract—The hetero-Cope rearrangement of 4-*tert*-butyl-phenyl-*tert*-butylhydroxylamine provides an easy access to the corresponding *ortho*-bromoaniline, converted to the new highly water-soluble nitroxide, potassium 5-*tert*-butyl-2-(*tert*-butyl-aminoxy)-benzoate. The parent carboxylic acid was found to be very persistent in water at pH 1. © 2002 Elsevier Science Ltd. All rights reserved.

A high solubility in water of nitroxide free radicals is requested in different applications such as electron spin resonance[1] or magnetic resonance imaging,[2] protection from oxidative stress and radiative damage,[3] radical polymerization,[4] and spin labeling.[5] Some carboxylate nitroxides[6] in which the negative charge increases the hydrophilicity have been isolated, but to our knowledge no aromatic one. We present here the synthesis of a water-soluble aromatic carboxylate nitroxide **1**, in which the *tert*-butyl substituent on the aromatic ring provides a convenient protection from the usual bimolecular disproportionation.[7] To our knowledge, such nitroxides have not been tested yet in controlled radical polymerization[4] in water.



Scheme 1. *Reagents and conditions*: (i) *tert*-BuLi, THF, −78°C, then 0°C, 2 h; (ii) *tert*-BuNO, −78°C, 95%; (iii) $SOBr_2$ (1.1 equiv.), Et_3N (1.1 equiv.), CH_2Cl_2, 0°C then rt, 24 h; (iv) *tert*-BuLi (3.3 equiv.), THF, −78°C, then −10°C, 45 min; (v) $(MeO)_2CO$ (5 equiv.), −78°C, then rt 10 h; (vi) *m*-CPBA, CH_2Cl_2, rt; (vii) *t*BuOK, H_2O, THF, 24 h; (viii) HCl (1 mM).

Keywords: nitroxides; hydroxylamines; carboxylate; hetero-Cope rearrangement; decomposition.

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The hydroxylamine **2**, easily prepared in high yield (95%)[8] by a modification (lithiation of 4-*tert*-butyl-bromobenzene) of the published procedure[9] (Scheme 1) is a convenient starting material. Functionalization at the nitrogen *ortho* position of **2** was achieved by a hetero-Cope rearrangement, analogous to the one reported by Nikrad.[10]

Thus, reaction of **2** with thionyl bromide gave the brominated aromatic amine **3a**[11] (61%)[9] and the amine **3b**[12] (10%).[9] The lithio-derivative of **3a** was reacted with dimethylcarbonate[13] to afford **4**[14] (19%)[9] and **3b** (57%).[9] Compound **4** was oxidized by *m*-CPBA to the nitroxide **5**[15] (47%)[9] which was then hydrolyzed with freshly prepared KOH.[16] Evaporation to dryness and trituration of the residue with ether led to carboxylate **1**,[17] an orange solid, indefinitely stable in the solid state. Compound **1** was found to be soluble in water at a concentration of 40 mM, one of the highest reported solubility for a nitroxide.[6c]

A solution of carboxylic acid **6** was obtained by dissolving **1** (5×10^{-3} M) in molar hydrochloric acid. When **6** was kept under these very acidic conditions during 24 h at room temperature, the intensity of its ESR signal only lost half of its initial value. Contrary to other nitroxides, **6** is thus extremely persistent at pH 1: under the same conditions, a typical nitroxide, TEMPOL has a half-life of 5.5 h while another carboxylic acid nitroxide decomposes even much more rapidly.[6b]

In conclusion we have developed a short synthesis of a highly water-soluble aromatic nitroxide in five steps. The bromoaniline **3a**, easily available on a gram-scale, is a potentially useful derivative for the synthesis of highly substituted aromatic nitroxides, since it may allow the introduction of a variety of substituents, as illustrated here by the preparation of **5**.

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11. (2-Bromo-4-*tert*-butyl-phenyl)-*tert*-butyl-amine **3a**: δ_H ($CDCl_3$, 250 MHz): 7.366 (d, $J=2.29$ Hz, 1H); 7.084 (dd, $J=2.29$, 8.63 Hz, 1H); 6.846 (d, $J=8.63$ Hz, 1H); 4.09 (s, 1H); 1.31 (s, 9H); 1.193 (s, 9H); δ_{13C} ($CDCl_3$, 50 MHz): 141.4, 141.2, 129.4, 124.7, 115, 112.3, 51.5, 33.7, 31.3, 29.8; EIMS: *m*/*z* (%) 284, 286 (M, 85.8, 82.8), 214 (31.3), 206 (20.2), 150 (21.7), 106 (100). Anal. calcd for $C_{14}H_{22}BrN$: C, 59.15; H, 7.74; N, 4.92. Found: C, 59.28; H, 7.72; N, 4.9%.
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14. 5-*tert*-Butyl-2-*tert*-butylamino-benzoic acid methyl ester **4**: δ_H ($CDCl_3$, 250 MHz): 7.837 (d, $J=2.56$ Hz, 1H); 7.296 (dd, $J=2.56$, 9 Hz, 1H); 6.827 (d, $J=9$ Hz, 1H); 1.364 (s, 9H); 1.207 (s, 9H); 3.773 (s, 3H); δ_{13C}($CDCl_3$, 50 MHz): 169.22, 148.22, 136.02, 131.17, 127.74, 113.56, 109.60, 51.16, 50.26, 33.42, 31.12, 29.60; EIMS: *m*/*z* (%) 263 (M–15, 42.6), 248 (100), 216 (92.2), 192 (75.2). Anal. calcd for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57; N, 5.32. Found: C, 72.82; H, 9.67; N, 5.22%
15. 5-*tert*-Butyl-2-(*tert*-butyl-aminoxy)-benzoic acid methyl ester **5**: red oil; EIMS: *m*/*z* (%) 263 (M–15, 10) 207 (26.3) 192 (100). Anal. calcd for $C_{16}H_{24}NO_3$: C, 69.04; H, 8.69; N, 5.03%. Found: C, 68.87; H, 8.89; N, 4.94%. EPR, toluene, $a_N=13.63$ G, (unresolved a_H); EtOH, $a_N=14.2$ G, (unresolved a_H).
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17. Potassium 5-*tert*-Butyl-2-(*tert*-butyl-aminoxy)-benzoate: orange solid, mp≥250°C; MS (FAB): *m*/*z* (%)=264.27 ($[M-(K^+)]^-$, 59), 248.26 (100). EPR, EtOH, $a_N=15.64$ G, (unresolved a_H); H_2O, $a_N=16.29$ G, (unresolved a_H).