Pergamon

Tetrahedron Letters 43 (2002) 8125–8127

TETRAHEDRON LETTERS

Synthesis of new pyrrolidine nitroxide epoxides as versatile paramagnetic building blocks

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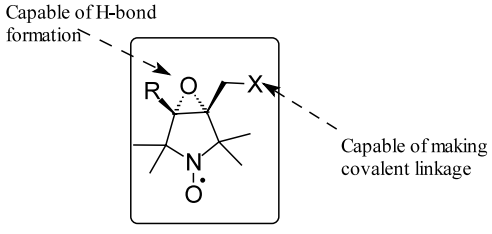
Received 31 July 2002; revised 27 August 2002; accepted 6 September 2002

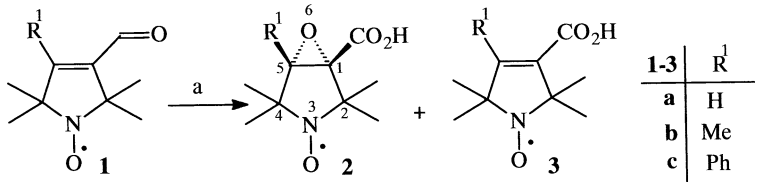
Abstract—Pyrrolidine nitroxide epoxides were synthesized by oxidation of the corresponding alkene, diene and α,β-unsaturated aldehyde with *m*-CPBA or H_2O_2 to provide new spin labels and paramagnetic synthons.

Nitroxides were discovered almost half a century ago[1] and since then they have found diverse uses as spin labels,[2] co-oxidants[3] and spin traps.[4] Their medical applications as SOD mimics,[5] antioxidants[6] and MRI contrast agents[7] have attracted much attention from the scientific community over the last four decades. In our laboratory a series of pyrroline and pyrrolidine anellated five- and six-membered heterocycles were synthesized very recently.[8] However, it is a real challenge to find a simple method for the synthesis of pyrrolidine nitroxide anellated oxiranes that is capable of extra *H*-bond formation (as a *H* acceptor with oxygen), but still affords the possibility of covalent bond formation with a reactive arm via a different reaction site.



Many efficient methods have been developed for the synthesis of epoxides and they have been extensively utilized for the synthesis of 1,2-disubstituted moieties in natural products and drugs.[9] The first paramagnetic epoxides were synthesized by the Darzens-method[1] or as a co-product of the oxidation of the corresponding 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridine.[10]

Cyclization of a chlorohydrin gave an epoxide attached to pyrroline nitroxide[11] and very recently Ozhogina reported[12] the Corey reaction of the paramagnetic aldehyde **1a**[13] with a sulfur ylide to achieve the corresponding epoxide. In our laboratory we have found that H_2O_2 treatment of the aldehyde **1a** in the presence of NaOH in aqueous MeOH gave the 3-oxyl-2,2,4,4-tetramethyl-6-oxa-3-azabicyclo[3.1.0]hexane-1-carboxylic acid radical **2a** and the carboxylic acid **3a**[1] in a 10:1 ratio. This reaction was extendable to other β-substituted-α,β-unsaturated aldehydes **1b** and **1c**,[14] generating the corresponding epoxy acids **2b** and **2c** and carboxylic acids **3b** and **3c** as by-products. This method offers a new reagent type (**2a–c**) in which the 1 and 5 sub-



Scheme 1. Reagents and conditions: (a) 30% aq. H_2O_2, (2.0 equiv.), 10% aq. NaOH (2.0 equiv.), MeOH, rt, 24 h, **2a–c** (80–92%), **3a–c** (8–20%).

Keywords: nitroxides; epoxides; spin labels; ring opening.
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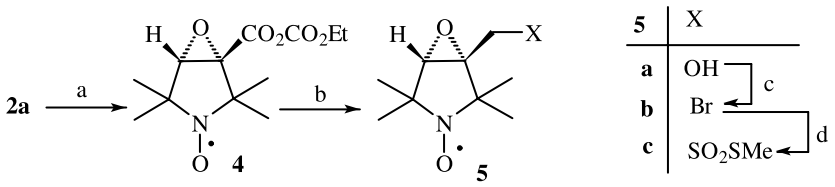
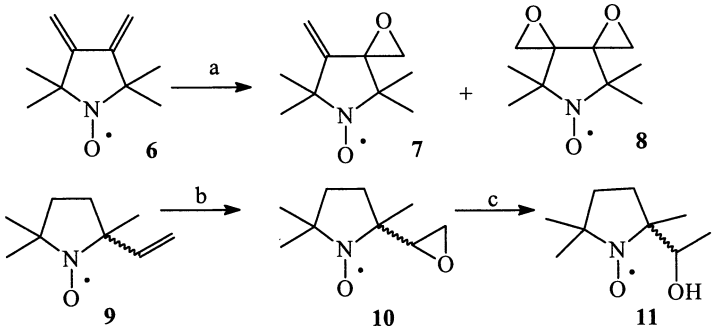


Scheme 2. *Reagents and conditions*: (a) $ClCO_2Et$ (1.1 equiv.), Et_2O, Et_3N (1.1 equiv.), 0°C, 2 h, (72%); (b) for **5a** $NaBH_4$, (3.0 equiv.), EtOH, 0°C, 2 h, (81%); (c) (i) MsCl (1.1 equiv.), Et_3N (1.1 equiv.), CH_2Cl_2, 0°C→rt, 1 h, (ii) LiBr (2.0 equiv.), acetone, 55°C, 1 h, 47%; (d) $NaSSO_2CH_3$ (2.0 equiv.), acetone/H_2O, 30 min, 55°C, 40%.



Scheme 3. *Reagents and conditions*: (a) *m*-CPBA (2.5 equiv.), CH_2Cl_2, rt, 24 h (**7**: 31%, **8**: 52%); (b) *m*-CPBA (1.2 equiv.), benzene, rt, 24 h, (68%); (c) $NaBH_4$ (3.0 equiv.), EtOH, 78°C, 30 min (61%).

stituents are anchored in the *cis* position by the epoxide ring. As far as we know, until now only *trans* 3,4-disubstituted paramagnetic rings were available (Scheme 1).[15]

During studies of the reactions of epoxides **2a–c**, we found the epoxide ring to be rather inert, surviving the reduction of the mixed anhydride ester **4** to the alcohol **5a**. Compound **5a** could be converted to the methanethiosulfonyl compound[16] **5c** via mesylate and bromide **5b** without opening the epoxide ring (Scheme 2).

To amass more reactive epoxides we oxidized *exo*- and isolated double bond containing nitroxides. The symmetric paramagnetic diene **6**[17] can be oxidized with *m*-CPBA in CH_2Cl_2 to monoepoxide **7** and diepoxide **8** in a 3:5 ratio. The latter can be regarded as a potential crosslinking reagent and the biological effect of its diamagnetic analogue, 1,3-butadiene diepoxide, is well studied.[18] We believe the fate of the toxic butadiene diepoxide in a living organism can be easily followed by EPR spectroscopy by monitoring the paramagnetic diepoxide **8**. Oxidation of 2,2,5-trimethyl-5-vinylpyrrolidin-1-yloxy compound **9** [19] with *m*-CPBA in benzene gave 2,2,5-trimethyl-5-oxiran-2-yl-pyrrolidin-1-yloxy radical **10** as mixture of two diastereomers in 1:5 ratio, R_f 0.43 and 0.35, respectively (TLC, silicagel, hexane/Et_2O, 2:1).

The epoxide ring of compound **10** can be opened by $NaBH_4$ reduction in EtOH to give alcohol **11**. The significance of the epoxide ring opening of compound **10** is that it is a simple method to introduce a functionizable group into the vicinity of the nitroxide moiety, which was achievable until now only by multistep sequences (Scheme 3).[20]

In conclusion, new paramagnetic epoxides[21] have been synthesized by oxidation of the corresponding pyrrolines or unsaturated pyrrolidine derivatives. These paramagnetic epoxides open new opportunities in synthesis of multiply functionalized spin labels. Their use and further ring opening reactions including stereochemical outcome are under investigation in our laboratory.

Acknowledgements

This work was supported by grant from Hungarian National Research Foundations (OTKA T34307, T030013 and M 028226). Bolyai fellowships for T. K. and C. S. from Hungarian Academy of Sciences is gratefully acknowledged. The authors thank to Dr. O. H. Hankovszky for helpful discussions. The authors thank to Z. Berente for NMR measurement (University of Pécs, Department of Biochemistry and Medical Chemistry), M. Balog for technical assistance, V. Csokona for elemental analysis and M. Szabó for mass spectral measurements (ICN, Hungary).

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21. Compounds were characterized by ESR, MS, NMR and elemental analysis. Spectra were in each case consistent with the assigned structures. All the monoradicals exhibited free equidistant lines $a_N = 14.7$–15.5 G. To obtain high resolution NMR spectra of the NO radicals were reduced to diamagnetic *N*-hydroxy compounds by codissolving PhNHNHPh reducing agent in NMR tube. Physical and spectroscopic data for selected compounds: **2a**: mp 179–182°C, calcd for $C_9H_{14}NO_4$: C, 53.99; H, 7.05; N, 7.00; found: C, 53.83; H, 7.01; N, 6.99%. ^{1}H NMR ($CDCl_3$) (400 MHz) 3.87 (s, 1H), 1.60 (s, 3H), 1.52 (s, 3H), 1.45 (s, 3H), 1.39 (s, 3H). MS (EI) *m*/*z* (rel. int.%) 200 (M^+, 4), 199 (23), 126 (27), 113 (100). **2b**: mp 142–144°C, calcd for $C_{10}H_{16}NO_4$: C, 56.06; H, 7.53; N, 6.54; found: C, 56.20; H, 7.41; N, 6.40%. MS (EI) *m*/*z* (rel. int.%) 214 (M^+, 5), 200 (2), 116 (4), 41 (100). **2c**: mp 153–155°C calcd for $C_{15}H_{18}NO_4$: C, 65.20; H, 6.57; N, 5.07; found: C, 65.32; H, 6.50; N, 4.93%. MS (EI) *m*/*z* (rel. int.%): 276 (M^+, 6), 246 (3), 132 (100), 91 (69). **5a**: mp 100–102°C, calcd for $C_9H_{16}NO_3$: C, 58.05; H, 8.66; N, 7.52; found: C, 58.01; H, 8.64; N, 7.48%. MS (EI) *m*/*z* (rel. int.%) 186 (M^+, 9), 156 (19), 97 (35), 41 (100). **5b**: mp 103–105°C, calcd for $C_9H_{15}BrNO_2$: C, 43.39; H, 6.07; N, 5.62; found: C, 43.42; H, 6.11; N, 5.55%. MS (EI) *m*/*z* (rel. int.%) 248/250 (M^+, 7/7), 218/220 (11/11), 139 (17), 43 (100). **5c**: mp 127–129°C, calcd for $C_{10}H_{18}NO_4S_2$: C, 42.84; H, 6.47; N, 5.00; S, 22.87; found: C, 42.90; H, 6.45: N, 4.94; S, 22.75%. MS (EI) *m*/*z* (rel. int.%) 280 (M^+, 7), 250 (3), 171 (48), 44 (100). **7**: mp 44–46°C, calcd for $C_{10}H_{16}NO_2$: C, 65.91; H, 8.85; N, 7.69; found: C, 65.95; H, 8.86; N, 7.72%. MS (EI) *m*/*z* (rel. int.%) 182 (M^+, 47), 137 (55), 107 (74), 43 (100). **8**: mp 78–80 °C, calcd for $C_{10}H_{16}NO_3$: C, 60.59; H, 8.14; N, 7.07; found: C, 60.60; H, 8.20; N, 7.02%. ^{1}H NMR ($CDCl_3$) (400 MHz) 2.79 (d, $J = 4.7$ Hz, 2H), 2.58 (d, $J = 4.7$ Hz, 2H), 1.18 (s, 6H), 1.15 (s, 6H). MS (EI) *m*/*z* (rel. int.%) 198 (M^+, 100), 184 (23), 153 (40), 123 (49). **10**: orange oil, calcd for $C_9H_{16}NO_2$: C, 63.50; H, 9.47; N, 8.23; found: C, 63.33; H, 9.40; N, 8.06%. MS (EI) *m*/*z* (rel. int.%) 170 (M^+, 3), 128 (6), 113 (9), 43 (100). **11**: yellow oil, calcd for $C_9H_{18}NO_2$: C, 62.76; H, 10.53; N, 8.13; found: C, 62.60; H, 10.41; N, 7.95%. MS (EI) *m*/*z* (rel. int.%) 172 (M^+, 1), 128 (52), 112 (24), 41 (100).