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Synthesis of bifunctionalized nitroxyls via intramolecular epoxide ring opening

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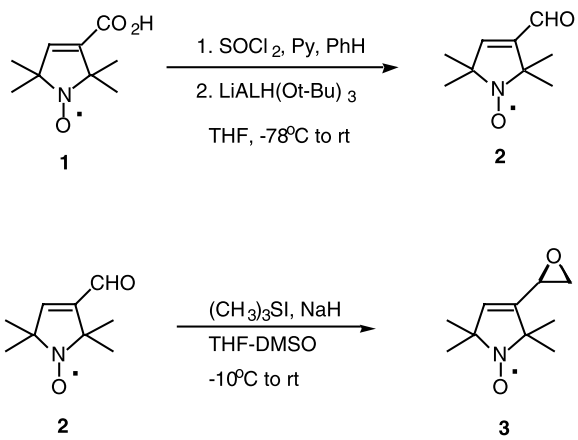
Abstract—The syntheses of nitroxyl oxirane and further functionalized derivatives are described. Ring-cleavage reactions of this epoxide have been carried out with a variety of nucleophiles in order to show the general synthetic utility for preparing nitroxyls bearing two functional groups. The relatively facile synthesis of the nitroxyl amino alcohol should prove to be valuable in various spin labeling applications.

Free nitroxyl radicals have had a long history of noteworthy applications as spin labels. The spin labeling method has become an important tool in studying the structure and dynamics of membranes, proteins and polymers in solution.[1] The synthesis of bifunctionalized nitroxyls is an attractive and powerful challenge in spin label applications.[2] This paper describes a convenient and practical synthesis of bisfunctionalized nitroxyl radicals using an epoxide intermediate.

Epoxides are important synthons in organic chemistry.[3] Indeed, the literature confirms that much effort has been expended on the investigation of epoxide chemistry. They are easily prepared from a variety of starting functional groups and are easily opened under a wide range of conditions. There are a few methods in the literature for the syntheses of epoxy nitroxyls. Rozantsev and co-workers have shown that 3-bromo-4-chloroacetyl-2,2,5,5-tetramethyl-pyrroline-1-oxyl could be reduced to the corresponding chlorohydrin and cyclized to the bromo epoxide.[4] The Corey reaction of carbonyl compounds with sulfur ylides yields an epoxide as the major or sole product.[5] However, Rosen et al.[6] have reported that the ketone, 2,2,6,6-tetramethyl-4-piperidone-*N*-oxyl, did not undergo facile epoxidation by the Corey reaction, and they modified the procedure to form instead the oxaspiro-oct-*N*-oxyl. In the present work, the Corey reaction was applied to the unsaturated aldehyde **2**.[7]

Alkylation of **2** with dimethylsulfonium methylide proceeds efficiently to produce epoxide **3** in 92% yield; this transformation is not complicated by side reactions (Scheme 1).[9] The relative concentration of the sulfonium salt (1.2 equiv. of ylide) and the reaction temperature (−10°C) are critical for an optimal yield without side reactions. Epoxide **3** can be purified by flash chromatography on silica gel without a significant loss of product. However, **3** is rather easily opened and even undergoes decomposition during chromatography on neutral alumina. With the isolated and stable epoxy nitroxyl in hands, ring opening with almost any nucleophile that is known to open epoxides should present little difficulty.

Initial attempts to hydrolyze **3** in aqueous THF in the presence of a Nafion-H perfluorinated resin sulfonic



Scheme 1.

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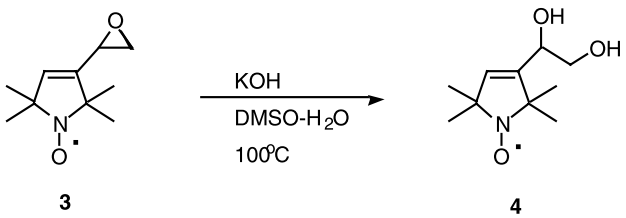
acid catalyst[10] met with little success. This procedure gave extremely low yields of the hydration product and incomplete conversion. The reaction mixture contained large proportions of intractable material. Clearly, in addition to extensive polymerization reactions, one of the major pathways for loss of the diol is deactivation of the catalyst (due to reaction with the nitroxyl radical), which could not be regenerated for further use. To circumvent these difficulties, we advantageously employed the alkaline hydrolysis of **3** in dimethyl sulfoxide. It is known from Berti et al.[11] that Me_2SO is inert to epoxides and it also provides maximum reactivity for the nucleophile. In view of this fact, when epoxide **3** is heated with potassium hydroxide in 85% aqueous dimethyl sulfoxide, the corresponding diol **4** is obtained in fairly good yield (Scheme 2).[12]

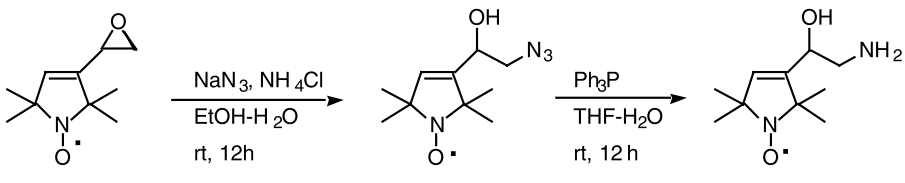
In the Gabriel synthesis,[13] *N*-substituted phthalimides are hydrolyzed to afford primary amines and amino compounds. However, reaction of epoxide **3** with phthalimide and a catalytic amount of its potassium salt did not show uniformity in products obtained. All attempts to find conditions which directly produced the desired Gabriel product failed; this route was consequently abandoned. Alternatively, we synthesized amino alcohol **5** (Scheme 3)[14] by ring cleavage of **3** with sodium azide followed by reduction. The conversion of an epoxide to the corresponding azido alcohol can be accomplished by treatment with NaN_3 and NH_4Cl in 80% ethanol at room temperature.[15] Indeed, NaN_3 proved to be an excellent nucleophile for the ring opening of **3**. Azidotization of **3** provides the azido alcohol **5** in 91% yield.

Although nitroxyls are extraordinary stable free radicals, they may be destroyed (with loss of paramagnetism), under reducing conditions.[1a] One of the routes to converting azides to amines involves reaction of the former with triphenylphosphine to form the corresponding iminophosphorane followed by subsequent hydrolysis.[16] Accordingly, there was concern that the azide moiety would not compete well with the nitroxyl group. Fortunately, Ph_3P reduces **5** cleanly to the corresponding amino alcohol **6**.[17] In a typical procedure, a solution of **5** in THF in the presence of water (1:2 equiv.) at room temperature was treated with triphenylphosphine until its complete consumption was observed by TLC. A standard extractive workup afforded crude amino alcohol **6**, which could be isolated chromatographically in 78% yield. In addition, there is flexibility in the choice of the amine nucleophile to be used, since opening has also been observed with allylamine as the nucleophile. In summary, the ease of the epoxide-opening strategy employed herein is expected to lead to more efficient syntheses of other spin labels of biological importance.



3 **4**

Scheme 2.



3 **5** **6**

Scheme 3.

Acknowledgements

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7. **3-Formyl-2,2,5,5-tetramethyl-pyrroline-1-oxyl 2**. 3-Carboxy-2,2,5,5-tetramethyl-3-pyrroline-1-oxyl (**1**) was pre-

pared as described by Rozantsev (Ref. 1) and was converted to the acid chloride by treatment with thionyl chloride and pyridine in benzene solution. Reduction with $LiAlH(O\text{-}t\text{-}Bu)_3$ was carried out as described previously,[8] with a modification in the purification scheme. The crude aldehyde was purified by column chromatography (silica gel, 8:2 pentane/ethylacetate), yielding 65% of **2**. Mass spectrum (70 eV), m/z 168 (M^+).

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9. **3-Epoxyethyl-2,2,5,5-tetramethyl-pyrroline-1-oxyl 3**. A mixture of 0.15 g (6.29 mmol) of powdered sodium hydride in 4 mL of dry Me_2SO was heated at 65°C for 1 h under argon. The mixture was cooled to room temperature and diluted with 5 mL of dry THF and cooled in a NaCl ice bath. A solution of 1.28 g (6.29 mmol) of trimethylsulfonium iodide in 5 mL of dry Me_2SO was added, in portions, at −10°C under argon. The mixture was stirred for 5 min, and 0.88 g (5.24 mmol) of 3-formyl-2,2,5,5-tetramethyl-pyrroline-1-oxyl was added. The reaction was stirred at −10°C for 30 min and at room temperature for 2 h. It was then poured into 90 mL of water and extracted with ether (5×50 mL). The combined organics were dried over $MgSO_4$ and concentrated. The crude epoxide was chromatographed on silica gel eluted with 5:1 pentane/ethylacetate to yield 92% of the desired epoxide as a red oil. Mass spectrum (70 eV), m/z 182.1190 (M^+ 182.1181 calcd for $C_{10}H_{16}NO_2$).
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12. **3-[Ethyl-1-hydroxy-2-azido]-2,2,5,5-tetramethyl-pyrroline-1-oxyl 4**. A solution containing 0.2 g (1.1 mmol) of epoxide **2**, NH_4Cl (0.12 g, 2.2 mmol), and NaN_3 (0.14 g, 2.2 mmol) in 5 mL of 80% EtOH was stirred at room temperature for 12 h. Water (5 mL) was added to this mixture, which was then extracted with ether and dried over $MgSO_4$. The solvent was removed to give a crude product which was purified by column chromatography (silica gel, 2:1 pentane/ethylacetate) to give the azido alcohol (0.225 g, 91%). Mass spectrum (70 eV), m/z 225 (M^+).
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14. **3-[Ethyl-1-hydroxy-2-amino]-2,2,5,5-tetramethyl-pyrroline-1-oxyl 5**. The azido alcohol (0.2 g, 0.8 mmol) obtained from the above reaction in THF (1 mL) was reduced with triphenylphosphine (0.233 g, 0.8 mmol) to the corresponding amine in the presence of water (0.025 mL). The reaction mixture was stirred at room temperature for 12 h, the solvent was evaporated, and a mixture of ether and petroleum ether (1:1) was added. Triphenylphosphine oxide which formed was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue obtained was purified by column chromatography (silica gel, 1:1 ethyl acetate/methanol) to afford the pure amino alcohol in 78% yield (138 mg). Mass spectrum (70 eV), m/z 199.1848 (M^+ 199.1446 calcd for $C_{10}H_{19}N_2O_2$).
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17. **3-[Ethyl-1,2-diol]-2,2,5,5-tetramethyl-pyrroline-1-oxyl 6**. Epoxide **2** (0.2 g, 1.1 mmol) was dissolved in DMSO (8.5 mL), and a solution of potassium hydroxide (0.168 g, 3 mmol) in water (1.5 mL) was added. The mixture was stirred at 100°C for 12 h. When the starting oxirane could no longer be detected by TLC, the reaction mixture was cooled to room temperature, neutralized with HCl, and the solvent was evaporated. The crude product was chromatographed on silica gel eluted with ethylacetate to yield 60% of the desired diol. Mass spectrum (70 eV), m/z 200.1704 (M^+ 200.1286 calcd for $C_{10}H_{18}NO_3$).