Synthesis of Stable α,α'-Bis(carboxymethyl) Substituted Nitroxides *via* an Original Dianion-based Strategy

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New stable nitroxides, analogous to TEMPO (tetramethylpiperidine-*N*-oxyl) where two α,α' methyl groups are formally replaced by ester functions, are prepared *via* dienolate chemistry followed by a deprotection–oxidation sequence.

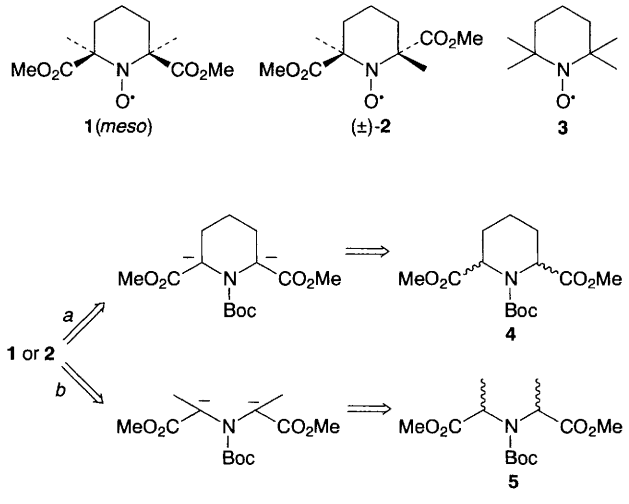
Among various purely organic stable free radicals, nitroxides continue to play a central role. They are used not only as stable spin labels[1] and in spin trapping experiments,[2] but also for the elaboration of organic magnetic materials[3] and, in recent years, as precursors of organic oxidants.[4] A number of commercial nitroxides derive from the readily available 2,2,6,6-tetramethyl-4-piperidone,[5] the ketone function being transformed into various functional groups which allow covalent attachment to other molecules or macromolecules. We were interested in the preparation of nitroxides capable of being integrated into more complex structures (*e.g.* macrocyclic compounds) by two covalent linkages.[6] Such molecules could be of value for the preparation of new spin labels, for the design of new magnetic materials or for the preparation of more selective (*e.g.* enantioselective) organic oxidants. Interesting targets among such nitroxides are the two diastereoisomeric compounds **1** and **2**, where two methyl groups of the well-known TEMPO **3** have been formally replaced by two ester functions. Although it is known that nitroxides bearing free carboxylic acid functions in the α position of the nitrogen atom are not stable,[7] some examples found in the literature indicate that esters can be tolerated.[7,8]

We describe here the preparation of the new stable diastereoisomeric nitroxides **1** and **2**. The key feature of the synthesis involves symmetrical dinucleophilic species of the dienolate type which are able to react with electrophiles, the nitrogen being temporarily Boc-protected. Following this idea, we considered two retrosynthetic approaches to **1** and/or **2** (Scheme 1).

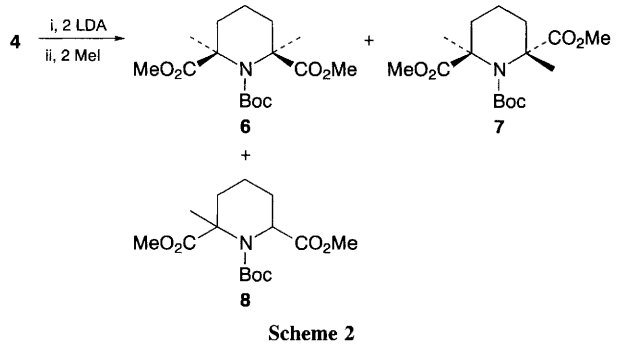
Both approaches *a* and *b* proved to be successful, but there were some differences in yields, diastereoisomeric distribution and ease of product purification. Treatment of **4**† with 2 equiv. LDA‡ at −78 °C for 1 h, followed by the addition of excess iodomethane gives, after workup, a 66 : 34 ratio of dimethylated diastereoisomers **6** and **7** in a 67% overall yield (Scheme 2).§ The presence of about 12% monomethylated product **8** and of some starting material in the crude product makes the purification of **6** and **7** difficult. Several variations of the metallation step using other strong bases, solvents or temperature conditions did not give better results. Larger excesses of LDA or longer metallation periods are rather detrimental to the reaction. Consequently, we treated the crude product a second time with LDA–iodomethane in order to transform the remaining starting material and **8**. A final yield of 75% of **6** and **7** (2 : 1 ratio) can thus be obtained. In approach *b*, **5** is reacted in the same way with 2 equiv. LDA followed by 1,3-diiodopropane (Scheme 3). As before, a second LDA–electrophile treatment ensures a nearly complete transformation, and **6** and **7** are obtained in a 54% isolated yield (1 : 1). They are easily separated by column chromatography over silica-gel.¶ The configuration of each diastereoisomer has been determined by ^{1}H NMR at 80 MHz by adding increasing amounts of tris-[3-(heptafluropropylhydroxymethylene)-(+)-camphorato]europium, [Eu(hfc)$_3$] to a solution of **6** or **7** in $CDCl_3$ and observing the evolution of the Boc singlet. For the same amount of added [Eu(hfc)$_3$], splitting of the signal is observed for **7** whereas the corresponding signal for **6** remains a sharp singlet.[9]

The rest of the synthesis is straightforward: the Boc protecting group is cleaved under acidic conditions [acetic acid containing 10% (*v*/*v*) commercial aq. hydrobromic acid, 1 h at room temp.]. The ester functions remain unaffected under these conditions and the free amines are obtained after basic (Na_2CO_3) workup with excellent isolated yields (95% from **6**, 94% from **7**). The nitroxides **1** and **2** are then obtained from the corresponding amines under standard oxidation conditions,[10] with high isolated yields (**1** 71%, **2** 100%).‖ Both are stable free radicals (**1** is a red crystalline solid, **2** an orange oil) which exhibit characteristic triplet ESR signals. The signals of solutions freshly prepared from the pure products which have been stored in the dark at room temperature remain unchanged in intensity even after several months.

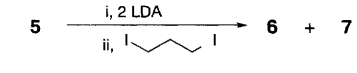
We are currently studying chemical transformations of the ester groups of **1** or **2** that do not affect the radical centre. We are also investigating the scope of the new dienolate formation–dialkylation sequence that could potentially give access to various new highly hindered amino-diacid derivatives and



Scheme 1



Scheme 2



Scheme 3

thence to the corresponding nitroxides. Moreover, the resolution of the (±)-diastereoisomers would lead to valuable C_2-symmetric chiral amines and nitroxides.[4d,11]

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Footnotes

† The starting materials **4** or **5** can be prepared by a conventional method: Boc protection of 2,6-piperidine dicarboxylic acid dimethyl ester[12] or 2,2′-iminodipropionic acid dimethyl ester[13] with di-*tert*-butyldicarbonate without any solvent or in dry acetonitrile, these reactions being rather sluggish (see ref. 14 for similar observations). They can also be prepared by our recently described method starting from *N*-Boc-protected iminodiacetic acid dimethyl ester *via* dialkylation of the corresponding dienolate.[15] Both **4** and **5** can be used as mixtures of their diastereoisomers as both give the same dianionic species.

‡ We have routinely used LDA solutions prepared from diisopropylamine, isoprene and metallic lithium in THF under ultrasonic irradiation (see ref. 16), standardized immediately before use.

§ Determined by GC on a OV17 capillary column with an internal standard.

¶ All new compounds gave C, H and N combustion analysis and spectroscopic data in agreement with the given structures. *Selected data* for **6**: colourless crystals, mp 70 °C (from hexane), ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.73 (s, 6 H), 1.90–1.70 (m, 6 H), 1.53 (s, 6 H), 1.39 (s, 9 H); FTIR ν/cm^{-1} 1738, 1687; CIMS *m/z* 330 (MH^+), 230, 170 (100%). For **7**: light yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.69 (s, 6 H), 2.10–1.60 (m, 6 H), 1.67 (s, 6 H), 1.39 (s, 9 H); FTIR ν/cm^{-1} 1744, 1694; CIMS *m/z* 330 (MH^+), 230 (100%), 170.

‖ Nitroxides **1** and **2** have been purified by column chromatography on silica gel with *n*-hexane–ethyl acetate mixture (80:20) elution. *Selected data* for **1**: ESR (water, 10^{-3} mol dm^{-3}) 3 lines, a_N = 15.2 G; FTIR ν/cm^{-1} 1732, 1349. For **2**: ESR (water, 10^{-3} mol dm^{-3}) 3 lines, a_N = 15.2 G; FTIR ν/cm^{-1} 1747, 1374.

References

1 J. F. Keana, *Chem. Rev.*, 1978, **78**, 37; G. I. Likhtenstein, *Pure Appl. Chem.*, 1990, **62**, 281; D. Marsch, *Pure Appl. Chem.*, 1990, **62**, 265; C. Degrand, B. Limoges and R. L. Blankespoor, *J. Org. Chem.*, 1993, **58**, 2573.

2 H. G. Aurich, *Nitrones, Nitronates and Nitroxides*, ed. S. Patai and Z. Rappoport, Wiley, New York, 1989, pp. 313, 371.

3 A. Rassat, *Pure Appl. Chem.*, 1990, **62**, 223; R. Chiarelli, M. A. Novak, A. Rassat and J. L. Tholence, *Nature*, 1993, **363**, 147; H. Oshio, T. Watanabe, A. Ohto, T. Ito and U. Nagashima, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 670; K. Inoue and H. Iwamura, *J. Chem. Soc., Chem. Commun.*, 1994, 2273.

4 (*a*) M. Yamaguchi, T. Miyazawa, T. Takata and T. Endo, *Pure Appl. Chem.*, 1990, **62**, 217; (*b*) Z. Ma and J. M. Bobbitt, *J. Org. Chem.*, 1991, **56**, 6110; (*c*) M. R. Leanna, T. J. Sowin and H. E. Morton, *Tetrahedron Lett.*, 1992, **33**, 5029; (*d*) Z. Ma, Q. Huang and J. M. Bobbitt, *J. Org. Chem.*, 1993, **58**, 4837; (*e*) M. Banwell, V. Bridges, J. Dupuche, S. L. Richards and J. Walter, *J. Org. Chem.*, 1994, **59**, 6338.

5 M. Dagonneau, E. S. Kagan, V. I. Mikhailov, E. G. Rozantsev and V. D. Sholle, *Synthesis*, 1984, 895.

6 For examples of α,α′-difunctionalized nitroxides prepared *via* nitrone nucleophilic attack–oxidation sequences, see: J. F. Keana, S. E. Seyedrezai and G. Gaughan, *J. Org. Chem.*, 1983, **48**, 2644; J. F. Keana, J. Cuomo, L. Lex and S. E. Seyedrezai, *J. Org. Chem.*, 1983, **48**, 2647.

7 J. F. Keana, S. Pou and G. M. Rosen, *J. Org. Chem.*, 1989, **54**, 2417.

8 E. Flesia and J. M. Surzur, *Tetrahedron Lett.*, 1975, **33**, 2893.

9 D. Parker, *Chem. Rev.*, 1991, **91**, 1441.

10 E. Rauckman, G. Rosen and M. Abou-Donia, *Synth. Commun.*, 1975, **5**, 409.

11 J. K. Whitesell, *Chem. Rev.*, 1989, **89**, 1581.

12 R. A. Barnes and H. M. Fales, *J. Am. Chem. Soc.*, 1953, **75**, 975.

13 B. Garrigues, *Tetrahedron*, 1984, **40**, 1151.

14 D. Kemp and T. Curran, *J. Org. Chem.*, 1988, **53**, 5729.

15 J. Einhorn, C. Einhorn and J. L. Pierre, *Synlett*, 1994, 1023.

16 A. De Nicola, J. Einhorn and J. L. Luche, *J. Chem. Res. (S)*, 1991, 278.