New Synthesis of Five-Membered Cyclic Nitrones from Tartaric Acid

Stefano Cicchi, Ingeborg Höld, and Alberto Brandi*

Dipartimento di Chimica organica "U. Schiff", Università di Firenze, Via G. Capponi 9, I-50121 Firenze, Italy

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During our ongoing research[1] on the synthesis of indolizidine alkaloids we needed to synthesize five-membered cyclic nitrones with oxygen functionality (as **1**). In the course of our work an efficient synthesis of nitrone **1a** (R = methoxymethyl) by Petrini and colleagues[2] appeared in the literature, in which nitrone **1a** was obtained in five steps from L-tartaric acid via hydroxy group protection of pyrrolidine **3** followed by hydrogenolysis and oxidation with H_2O_2 catalyzed by selenium dioxide (Scheme I).[2] This publication prompted us to report our results on the same subject.

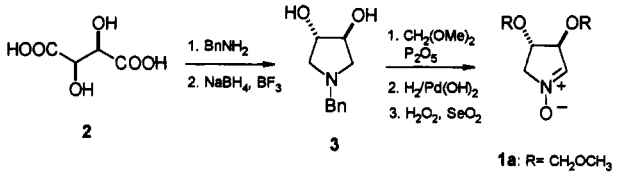
In this paper we report on our alternative strategy for the synthesis of compound **1**, which differs from the previous one in the choice of substrates for the hydroxy group protection and pyrrolidine ring formation.

Our starting material, (*R,R*)-tartaric acid ethyl (or methyl) ester, was first protected to give the *O,O'*-dimethyl (**4b**),[3] *O,O'*-dibenzyl (**4c**),[4] and *O,O'*-di-*tert*-butyl (**4d**)[5] ethyl tartrates according to literature procedures. Lithium aluminum hydride reduction followed by tosylation[3,6] gave the protected threitols **5** in high yields. Threitols **5** were cyclized by reaction with hydroxylamine in refluxing ethanol and afforded the *N*-hydroxypyrrolidines **6b–d** in very good yields. Pyrrolidines **6** were then oxidized by HgO (yellow) in dichloromethane to give nitrones **1b–d** in quantitiative yields. The nitrones were isolated in high purity by filtration of mercury salts and concentration of the dichloromethane solution (Scheme II).

In every case, formation of the *N*-hydroxypyrrolidine **6** was accompanied by direct oxidation to the nitrone **1** when the samples were exposed to atmospheric oxygen. The *tert*-butyl analog **6d** was particularly prone to oxidation, perceptible even in an NMR tube after a few days. Analogous oxidation of secondary hydroxylamines in air has been previously reported.[7]

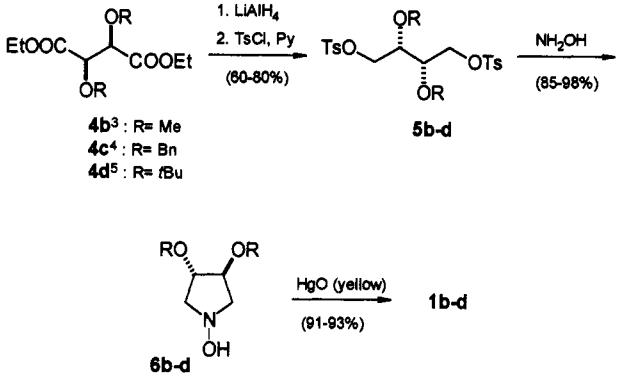
The ^{1}H NMR spectra of nitrones **1** are highly diagnostic for the structure assignment. Although not all of them give well-resolved spectra, the downfield resonance (δ 6.97, 6.88, and 6.79 ppm for **1b**, **1c**, and **1d**, respectively) is distinctive for the deshielded proton on C2. Besides the expected coupling with the H3 proton (1.5–1.7 Hz), the signal also shows long-range couplings with the methylene protons on C5 (1.7–1.8 Hz).[8]

Scheme I



2 **3** **1a**: R= CH_2OCH_3

Scheme II



4b[3] : R= Me
4c[4] : R= Bn
4d[5] : R= *t*Bu

5b-d

6b-d **1b-d**

The present methodology for compounds **1** presents several advantages over the earlier method described.[2] The critical step of Petrini's synthesis[2] is the hydroxyl group protection of pyrrolidine **3** that is complicated by the presence of a nucleophilic nitrogen. This is likely to give salts in acidic conditions or quaternization with electrophiles, lowering the reaction yields. The difficulty of introducing protecting groups has been already experienced by the same authors.[2] The introduction of the protecting group on the starting tartrate allows the choice of the most convenient reaction conditions for the introduction of the protecting group, and, moreover, allows the most critical reaction to be run using commercially available starting materials. Moreover, the present methodology permits the protection of hydroxyls as benzyl ethers (as in **1c**), which is not possible with the other procedure. The use of hydroxylamine as a nucleophile for the synthesis of cyclic hydroxylamines on the route to cyclic nitrones is, to our knowledge, unprecedented in the literature. The only reported example[9] referred to the use of *O*-benzylhydroxylamine, but the procedure for nitrone formation requires, in this case, more severe reaction conditions. Our methodology, which requires inexpensive hydroxylamine as a reagent and milder reaction conditions and gives higher yields, should, in general, be preferred for the synthesis of this class of compounds.

Experimental Section

All the reactions were run under nitrogen. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution. Chemical shift values are reported in ppm from tetramethylsilane: s, d, t, q, m, and br designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. The coupling constants *J* are given in Hz. IR spectra were recorded in CCl_4 solution, unless otherwise stated. Mass

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(8) In ref 2 the same proton in **1a** was reported as a singlet. In our hands, **1a** shows a ^{1}H NMR analogous to **1b–d**: δ 6.93 (dt, *J* = 2.1, 1.8, 1H), 4.79–4.64 (m, 5H), 4.41–4.27 (m, 2H), 3.91–3.75 (m, 1H), 3.39 (s, 3H), 3.38 (s, 3H).

(9) Kreher, R.; Morgenstern, H. *Chem. Ber.* **1982**, *115*, 2679–2681.

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spectra were recorded at 70 eV by GC inlet. *O,O'*-Dialkylsubstituted tartrates were synthesized according to refs 3 (**4b**), 4 (**4c**), and 5 (**4d**). The 1,4-butanediols and the bis-*p*-toluenesulfonates were synthesized according to refs 3 (**5b**) and 6 (**5c**). In the same way were synthesized (2*S*,3*S*)-2,3-di-*tert*-butoxy-1,4-butanediol: [99% waxy solid; $[\alpha]^{25}_D = -27.8$ ($c = 0.98$ CCl_4); ^1H NMR δ 3.85–3.60 (m, 6H), 3.05–2.95 (m, 2H), 1.23 (s, 18H); ^{13}C NMR δ 74.8 (s), 71.9 (d), 62.4 (t), 28.2 (q); IR (CCl_4) 3510, 2976, 1463, 1366, 1186, 1061 cm^{-1}. Anal. Calcd for $C_{12}H_{26}O_4$: C, 61.51; H, 11.18. Found: C, 61.42; H, 11.34] and (2*S*,3*S*)-2,3-di-*tert*-butoxy-1,4-[[bis(4-methylphenyl)sulfonyl]oxy]butane (**5d**) [86% viscous oil; $[\alpha]^{25}_D = -47.2$ ($c = 1.41$ CCl_4); ^1H NMR δ 7.80–7.70 (m, 4H), 7.40–7.30 (m, 4H), 4.23 (dd, J = 10.0, 2.0 Hz, 2H), 3.88–3.65 (m, 4H), 2.46 (s, 6H), 1.09 (s, 18H); ^{13}C NMR δ 144.7 (s), 132.9 (s), 129.8 (d), 127.9 (d), 74.6 (s), 70.9 (d), 70.2 (t), 28.3 (q), 21.6 (q); IR (CCl_4) 2978, 1598, 1370, 1187, 1177, 1089 cm^{-1}. Anal. Calcd for $C_{26}H_{38}O_8S_2$: C, 57.54; H, 7.06. Found: C, 57.10; H, 7.05].

Synthesis of *N*-Hydroxypyrrolidines 6b–d. General Procedure. A solution of tosylates **5** (10 mmol), NH_2OH·HCl (40 mmol), and NEt_3 (80 mmol) in 20 mL of absolute ethanol was refluxed for 8 h and then left at rt for a further 12 h. The solution was diluted with CH_2Cl_2 (50 mL), washed with H_2O (3 × 20 mL), and dried. Concentration of the solution gave the *N*-hydroxypyrrolidines almost pure. A purification on a short pad of silica gel (eluent CH_2Cl_2–MeOH (15:1)) is necessary to have a sample pure for elemental analysis.

6b: 85% yield (pale yellow oil); $[\alpha]^{25}_D = 16.9$ ($c = 1$ $CHCl_3$); ^1H NMR δ 5.70–4.60 (s, 1H), 3.82 (m, 2H), 3.40 (m, 2H), 3.37 (s, 6H), 3.10 (m, 2H); ^{13}C NMR δ 84.2 (d), 62.2 (t), 57.2 (q); IR ($CHCl_3$) 3585, 2868, 1454, 1230, 1090 cm^{-1}. Anal. Calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; N, 9.52. Found: C, 48.82; H, 8.90; N, 9.26.

6c: 87% yield (white solid); mp = 64–65 °C; $[\alpha]^{25}_D = 26.3$ ($c = 1.04$ CCl_4); ^1H NMR δ 7.33 (m, 10H), 4.52 (s, 4H), 4.12 (t, J = 4.6 Hz, 2H), 3.57–3.32 (m, 2H), 3.15–3.05 (m, 2H); ^{13}C NMR δ 128.4 (d), 127.8 (d), 82.4 (d), 71.6 (t), 62.8 (t); IR (CCl_4) 3592, 3031, 1452, 1358, 1205, 1096 cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.20; H, 7.26; N, 5.00.

6d: 98% (contaminated with nitrone **1d**); mp = 65–66 °C; $[\alpha]^{25}_D = 78.2$ ($c = 1.25$ $CHCl_3$); ^1H NMR δ 3.98 (m, 2H), 3.29 (m, 2H), 2.88 (m, 2H), 1.17 (s, 18H); ^{13}C NMR δ 76.8 (d), 73.6 (s), 64.4 (t), 28.3 (q); IR (CCl_4) 3575, 2973, 1364, 1188, 1082 cm^{-1}.

Synthesis of Nitrones 1b–d. General Procedure. To a solution of the *N*-hydroxypyrrolidine (5 mmol) in 20 mL of CH_2Cl_2 at 0 °C was added HgO (yellow) (10 mmol). The mixture was allowed to stir vigorously at rt for 2 h and then was filtered on Celite. Concentration of the solution gave the nitrones pure by NMR. A sample for elemental analysis was obtained by chromatography on a short pad of silica gel (eluent CH_2Cl_2–MeOH (15:1)).

1b: 91% (colorless oil); $[\alpha]^{25}_D = 106.7$ ($c = 5.0$ $CHCl_3$); ^1H NMR δ 6.97 (dt, J = 1.8, 1.5 Hz, 1H), 4.40 (m, 1H); 4.29 (ddt, J = 14.6, 6.0, 1.6 Hz, 1H), 4.00 (ddd, J = 6.3, 2.5, 1.6 Hz, 1H), 3.86 (br d, J = 14.6 Hz, 1H), 3.42 (s, 3H), 3.40 (s, 3H); ^{13}C NMR δ 132.0 (d), 85.1 (d), 79.9 (d), 66.7 (t), 57.1 (q), 57.0 (q); IR ($CHCl_3$) 3101, 2997, 1585, 1356, 1281, 1096 cm^{-1}. Anal. Calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.68; H, 7.92; N, 9.32.

1c: 93% yield (colorless oil); $[\alpha]^{25}_D = 76.7$ ($c = 0.88$ $CHCl_3$); ^1H NMR δ 7.45–7.22 (m, 10H), 6.88 (q, J = 1.7 Hz, 1H), 4.67 (d, J = 1.5 Hz, 1H), 4.57 (s, 2H), 4.54 (s, 2H), 4.30 (tt, J = 6.6, 1.5 Hz, 1H), 4.25 (m, 1H), 3.92–3.80 (m, 1H); ^{13}C NMR δ 136.8 (s), 136.7 (s), 132.2 (d), 128.6 (d, 2C), 128.5 (d, 2C), 128.3 (d), 128.2 (d), 128.0 (d, 2C), 127.9 (d, 2C), 83.7 (d), 78.4 (d), 72.0 (t), 71.9 (t), 66.9 (t); IR ($CDCl_3$) 3032, 2866, 1584, 1452, 1283, 1203, 1073 cm^{-1}. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.42; H, 6.62; N, 4.52.

1d: 92% (waxy solid); $[\alpha]^{25}_D = 153.7$ ($c = 0.68$ CCl_4); ^1H NMR δ 6.79 (q, J = 1.7 Hz, 1H), 4.58 (m, 1H), 4.22–4.05 (m, 2H), 3.78–3.62 (m, 1H), 1.23 (s, 9H), 1.20 (s, 9H); ^{13}C NMR δ 135.1 (d), 78.9 (d), 74.8 (s), 74.6 (s), 74.1 (d), 68.1 (t), 28.1 (q); MS (rel abundance) m/z 173 ($M^+ - 56$), 117, 100, 88, 70, 57; IR (CCl_4) 3041, 2873, 1583, 1366, 1184, 1082 cm^{-1}. Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.52; H, 10.19; N, 5.87.

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