Synthesis of Functionalized Acyclic Nitrone Spin Traps

Yongkang Zhang* and Guangzhi Xu

National Laboratory for Structural Chemistry of Unstable and Stable Species, Institute of Chemistry, Academia Sinica, Beijing 100080, China

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Four new spin traps with functionalized acyclic nitrone structures, $EtCH(CH_2CH_2CO_2Et)CH{=}N(O)CMe_3$ (**3**), $EtCH(CH_2CH_2CH_2OH)CH{=}N(O)CMe_3$ (**4**), $EtCH(CH_2CH_2CN)CH{=}N(O)CMe_3$ (**6**), $EtCH(CH_2CH_2CO_2H)CH{=}N(O)CMe_3$ (**10**), were prepared and characterized by infrared spectrometry, mass spectrometry and ^1H NMR.

The spin trapping technique which is the combination of the spin trapping procedure and the electron spin resonance spectrometry [1, 2] is a successful method by which free radicals can be studied. In the spin trapping process, some kinds of compounds such as nitrones and nitroso-derivatives are used as spin traps to convert reactive free radicals into relatively stable nitroxides. Obviously, the physical and chemical properties of spin traps are very important in the spin trapping technique. Much more attention has been payed to the designing and synthesis of spin traps [3, 4]. How to synthesize a suitable spin trap to study free radicals within some special systems is the key point of the spin trapping chemistry. Considering function groups could improve the radical-trapping selectivity of spin traps [4], we introduced hydroxy, cyano, ethoxycarbonyl and carboxy groups into the acyclic nitrones. In this paper, we want to disclose the synthetic method of such functionalized nitrones **3, 4, 6** and **10.**

The aldehyde enamine alkylation with acrylate, especially with acrylonitrile, is relatively difficult than ketone's. Methyl 4-ethyl-5-oxopentanoate was prepared by J. Dolfini according to the Stork method [5], but the ethyl ester analogue **2** has not been reported. Likewise, the alkylation of heptaldehyde enamine with acrylonitrile was reported by Stork [5], but that of butylaldehyde enamine **1** with acrylonitrile has not been reported in their and other papers, the reason of which was probably very low reactivity of this enamine with acrylonitrile. Fortunately, by carefully repeating of Stork method, the enamine **1** was alkylated with ethyl acrylate and acrylonitrile to give the aldehydes **2** and **5** followed by condensation with N-*tert*-butylhydroxylamine **11** to afford the corresponding nitrones **3** and **6.** N-*tert*-butylhydroxylamine **11** was prepared by the oxidation of *tert*-butylamine with $KMnO_4$, followed by the practically uncontaminated reduction with zinc and ammonium chloride which is different from the usual method, *i.e.*, the Al–Hg reduction procedure [6]. The ester nitrone **3** was reduced with lithium aluminium hydride in absolute ether, then decomposed with water to give **12.** The ESR signals, obtained when the hydroxylamine **12** was immediately measured with an ESR spectrometer, indicated that the hydroxylamine can easily be oxidated by air to convert into the corresponding nitroxide radical of which the ESR data were a_N = 15.44, $a_H^\beta(2H)$ = 10.83 Gauss in the benzene solution. By air oxidation of **12** in the presence of Cu(II), the nitrone with hydroxy function **4** was obtained. Direct convertion of ester-aldehyde **2** to acid-aldehyde **9** by base-catalysed hydrolysis was impossible, and the aldehyde function of **2** was first reacted with ethylene glycol to result ester-acetal **7** which was then hydrolyzed in the basic condition. By hydrolysis in HCl/acetone the acid-acetal **8** was readily converted into acid-aldehyde **9** which reacted with **11** to offer the carboxy-functionalized nitrone **10** instead of the salt.

Experimental

IR spectra were recorded on a Carl Zeiss Jena Specord-75 spectrometer. Mass spectra were obtained using an AEI MS-50/DS-30 spectrometer. ^1H NMR spectra were determined on a Varian EM-360 (60 MHz) spectrometer. ESR spectra were recorded on a Bruker ESP-300 ESR spectrometer in benzene solution at room temperature.

N-tert-Butylhydroxylamine (**11**)

2-Methyl-2-nitropropane (17.5 g, 0.17 mole), obtained in 61% yield from N-*tert*-butylamine (20 g, 0.278 mole) according to ref. [6], was reduced with zinc and ammonium chloride in ethanol water solution by the literature procedure [7] to give 7.2 g (48%) of the crude N-*tert*-butylhydroxylamine **11,** m.p. 59–61 °C (Lit. [6] m.p. 59–60 °C), which was sufficiently pure for use in following steps.

^1H NMR (CCl_4/TMS): δ = 1.10 (s, 9H, Bu^t), 5.90 ppm (s, 2H, NHOH, exchangable in D_2O).

* Reprint requests to Dr. Yongkang Zhang.

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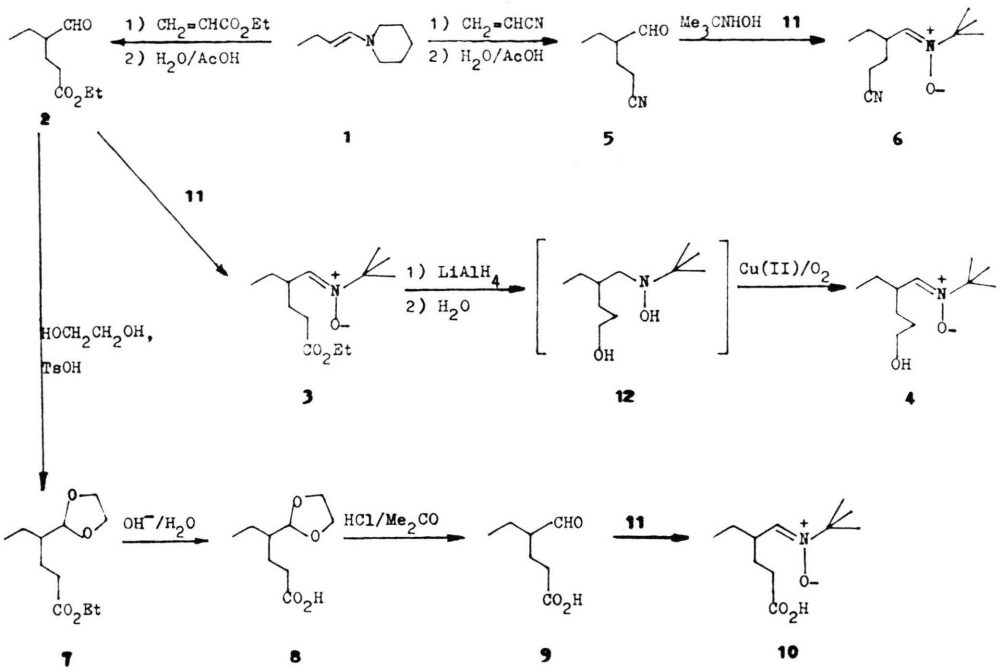

Ethyl-4-ethyl-5-oxopentanoate (**2**)

This compound was prepared from the butylaldehyde piperidine enamine **1** and ethyl acrylate by the literature method [5]; b.p. 98–102 °C/2 mm Hg; yield 90%.

^{1}H NMR ($CDCl_3$/TMS): δ = 0.93 (t, 3H, CH_3), 1.23 (t, 3H, CH_3), 2.00–1.50 (m, 4H, $2CH_2$), 2.40–2.20 (m, 3H, CH_2CO_2, CHCO), 4.06 (q, 2H, OCH_2), 9.55 ppm (d, 1H, CHO).

N-(2-Ethyl-4-ethoxycarbonylbutylidene)-1,1-dimethylethanamine N-oxide (**3**)

The ester-aldehyde **2** (1.72 g, 10 mmole) and **11** (1.0 g, 11.2 mmole) in ethanol (50 ml) was stirred for 2.5 h at room temperature, then refluxed for 2 h. The liquid after removing of the solvent was dissolved in ether (20 ml), dried over anhydrous sodium sulfate and filtered. The removing of ether was followed by distillation to afford 2.17 g (89%) of the nitrone product **3;** b.p. 88–90 °C/1 mm Hg.

IR (neat): ν = 3067 (HC=), 1727 (ester C=O), 1568 (C=N), 1233 (N–O), 1173 cm^{-1} (C–O).

^{1}H NMR (CCl_4/TMS): δ = 0.90 (t, 3H, CH_3), 1.23 (t, 3H, CH_3), 1.43 (s, 9H, Bu^t), 1.90–1.50 (m, 4H, $2CH_2$), 2.10 (t, 2H, CH_2CO_2), 2.90 (m, 1H, CH), 4.02 (q, 2H, OCH_2), 6.50 ppm (d, 1H, CH=N).

MS: *m/e* (rel. int. %) = 243 (M^+, 16), 170 (35), 142 (21), 141 (33), 124 (47), 100 (24), 57 (100).

N-(2-Ethyl-5-hydroxypentylidene)-1,1-dimethylethanamine N-oxide (**4**)

The ester-nitrone **3** (0.70 g, 2.88 mmole) in absolute ether (25 ml) was added to the solution of lithium aluminium hydride (LAH) (0.25 g, 6.5 mmole) in absolute ether (25 ml). After stirring for 30 minutes, additional LAH (0.25 g, 6.5 mmole) was added, stirred for additional 30 minutes, then water (10 ml) was carefully added. After separation of the ether layer, the aqueous layer was extracted with ether (50 ml) and solvent was removed to give a clear liquid (0.60 g) of **12,** which was mixed with methanol (20 ml), $CuCl_2 \cdot 2H_2O$ (0.04 g) and NH_4OH (30%, 0.2 ml) stirring at room temperature until the dark blue of the solution. After general treatment, the residue was chromatographed on silica gel eluted with ethyl acetate to afford 0.19 g (33%) of **4.**

IR (neat): ν = 3460 (OH), 1580 (C=N), 1230 (N–O), 1070 cm^{-1} (C–O).

^{1}H NMR (CCl_4/TMS): δ = 0.97 (t, 3H, CH_3), 1.47 (s, 9H, Bu^t), 1.55–1.30 (m, 6H, $3CH_2$), 2.73 (m, 1H, CH), 3.53 (t, 2H, CH_2O), 6.60 ppm (d, 1H, CH=N).

MS: *m/e* (rel. int. %) = 201 (M^+, 4), 154 (4), 114 (6), 113 (57), 100 (12), 87 (18), 71 (30), 57 (100).

4-Ethyl-5-oxopentanenitrile (**5**)

Yield 14%; b.p. 81–82 °C/1 mm Hg.

^{1}H NMR (CCl_4/TMS): δ = 1.03 (t, 3H, CH_3), 2.06–1.50 (m, 4H, $2CH_2$), 2.50–2.29 (m, 3H, CHCO, CH_2CN), 9.61 ppm (s, 1H, CHO).

N-(2-Ethyl-4-cyanobutylidene)-1,1-dimethylethanamine N-oxide (**6**)

The nitrile-aldehyde **5** (2.5 g, 20 mmole) and **11** (1.8 g, 20.2 mmole) in benzene (40 ml) was refluxed for 1 h with a Dean-Stark tube to remove water resulted. The solvent was removed on a rotary evaporator under lower pressure and the residue was chromatographed on silica gel with chloroform and ethyl acetate successively to afford 1.92 g (45%) of **6.**

IR (neat): ν = 3068 (HC=), 2240 (C≡N), 1571 (C=N), 1200 cm^{-1} (N–O).

^{1}H NMR (CCl_4/TMS): δ = 0.95 (t, 3H, CH_3), 1.47 (s, 9H, Bu^t), 2.10–1.60 (m, 4H, $2CH_2$), 2.37 (t, 2H, CH_2CN), 3.06 (m, 1H, CH), 6.58 ppm (d, 1H, CH=N).

MS: *m/e* (rel. int. %) = 196 (M^+, 21), 156 (15), 145 (46), 110 (34), 100 (37), 96 (16), 87 (12), 57 (100).

$C_{11}H_{20}N_2O$ (196.28)

Calcd C 67.31 H 10.27 N 14.26,
Found C 66.73 H 9.84 N 14.46.

Ethylene glycol acetal of ethyl 4-ethyl-5-oxopentanoate (**7**)

The mixture of the ester-aldehyde **2** (15.5 g, 90.5 mmole), ethylene glycol (5.85 g, 90.5 mmole) and *p*-toluenesulfonic acid (0.35 g, 1.8 mmole) was stirred for 1 h and toluene or benzene (200 ml) was added, refluxing for 2.5 h with a Dean-Stark tube to remove water (1.8 ml). General treatment was followed by the distillation to afford 17.7 g (91%) of **7;** b.p. 122–124 °C/2 mm Hg.

^{1}H NMR ($CDCl_3$/TMS): δ = 0.97 (t, 3H, CH_3), 1.23 (t, 3H, CH_3), 2.00–1.40 (m, 5H, CH_2CHCH_2), 2.40 (t, 2H, CH_2CO_2), 3.90 (m, 4H, OCH_2CH_2O), 4.07 (q, 2H, $COOCH_2$), 4.74 ppm (d, 1H, OCHO).

Ethylene glycol acetal of 4-ethyl-5-oxopentanoic acid (**8**)

Hydrolysis of **7** (4.32 g, 20 mmole) in a solution of sodium hydroxide (1.6 g, 40 mmole), 1,4-dioxane (20 ml) and water (40 ml) was carried out at 80 °C for 10 h. After the general treatment, 3.6 g (96%) of a clear liquid **8** was obtained.

^{1}H NMR (CCl_4/TMS): δ = 0.93 (t, 3H, CH_3), 1.87–1.27 (m, 5H, CH_2CHCH_2), 2.33 (t, 2H, CH_2CO_2), 3.75 (m, 4H, OCH_2CH_2O), 4.60 (br. s, 1H, OCHO), 10.87 ppm (s, 1H, COOH).

4-Ethyl-5-oxopentanoic acid (**9**)

The mixture of crude **8** (3.6 g, 19.1 mmole), 5% HCl (20 ml), and acetone (40 ml) was stirred at 40 °C for 24 h. Usual treatment was followed by distillation to give 2.33 g (85%) of the colorless liquid **9;** b.p. 132–134 °C/1.5 mm Hg.

^{1}H NMR (CCl_4/TMS): δ = 0.97 (t, 3H, CH_3), 2.00–1.45 (m, 4H, $2CH_2$), 2.60–2.23 (m, 3H, CHCO, CH_2CO_2), 9.45 (d, 1H, CHO), 11.13 ppm (s, 1H, COOH).

N-(2-Ethyl-4-carboxybutylidene)-1,1-dimethylethanamine N-oxide (**10**)

This compound was prepared by the same procedure as that used for the preparation of **3;** yield 95%.

IR (neat): ν = 3400–2500 (br., OH), 1700 (C=O), 1580 (C=N), 1225 cm^{-1} (C–O, N–O).

^{1}H NMR (CCl_4/TMS): δ = 0.90 (t, 3H, CH_3), 1.90–1.30 (m, 4H, $2CH_2$), 1.40 (s, 9H, Bu^t), 2.20 (t, 2H, CH_2CO_2), 2.90 (m, 1H, CH), 6.74 (d, 1H, CH=N), 11.20 ppm (s, 1H, COOH).

MS: *m/e* (rel. int. %) = 215 (M^+, 20), 141 (22), 113 (20), 100 (17), 87 (11), 86 (15), 74 (36), 73 (35), 57 (100).

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