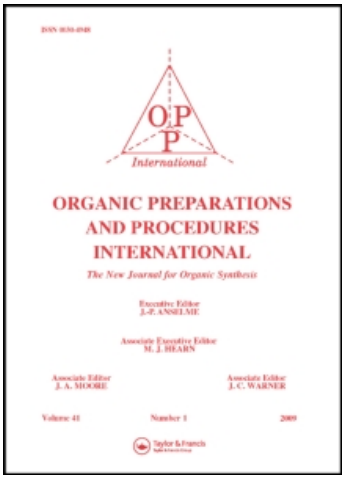

Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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Tamás Kalai[a]; Zoltán Szabó[b]; József Jekö[b]; Kálmán Hideg[a]
[a] Central Research Laboratory Chemistry, University of Pecs, Pecs, HUNGARY [b] Alkaloida Chemical Company, Ltd., Tiszavasvdri, HUNGARY

To cite this Article Kalai, Tamás , Szabó, Zoltán , Jekö, József and Hideg, Kálmán(1996) 'SYNTHESIS OF NEW ALLYLIC MTROXIDES *via* THE WADSWORTH-EMMONS REACTION', Organic Preparations and Procedures International, 28: 4, 443 — 452
To link to this Article: DOI: 10.1080/00304949609356551
URL: http://dx.doi.org/10.1080/00304949609356551

ORGANIC PREPARATIONS AND PROCEDURES INT., 28 (4), 443-452 (1996)

SYNTHESIS OF NEW ALLYLIC NITROXIDES

via THE WADSWORTH-EMMONS REACTION

Tamás Kálai[†], Zoltán Szabó[††], József Jekö[††] and Kálmán Hideg*[†]

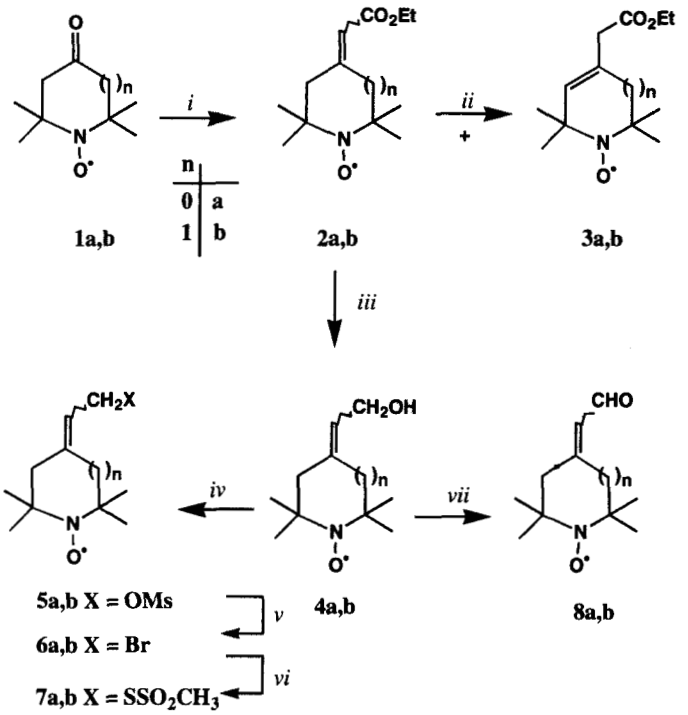
[†]*Central Research Laboratory Chemistry*
University of Pécs, H-7643 Pécs, P. O. Box 99, HUNGARY

[††]*Alkaloida Chemical Company, Ltd.*
H-4440 Tiszavasvári, P. O. Box 1, HUNGARY

Biophysical labels such as stable nitroxide radicals have proven effective tools in solving problems at the molecular level in biological systems.[1] Therefore nitroxide radicals with a chemically active group are often used for the paramagnetic labeling of biomolecules, e. g. proteins, lipids and drugs.[2] Among the spin labels, the ones which have an allylic reactive group proved the most useful due to their increased reactivity and selectivity.[3] The synthesis of allylic spin labels described in this paper is based on the Wadsworth-Emmons modification of the Wittig reaction.[4] The starting materials of the synthesis are the readily available five- and six-membered paramagnetic ketones **1a, b**.[5] Although the synthesis of six-membered ester **2b** was reported earlier,[6-8] we have synthesized the more stable pyrroline **3a** and pyrrolidine **2a** analogs.[9,10]

The reaction of five- and six-membered ketones **1** with the ylide of triethyl phosphonoacetate generated with NaH afforded α,β-unsaturated esters **2**. In the case of ester **2a,** elevated temperature was necessary to complete the reaction. The asymmetry of the five-membered ring results in the formation of *E/Z* isomers about in 1:1 ratio according to ^{1}H NMR measurements. In both cases, excess of NaH or carbanion results in the appearance of β,γ-unsaturated esters **3a, b** as by-products or the double bond could be migrated directly with NaOMe treatment.[11] The reduction of α,β-unsaturated esters **2** with sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) afforded the corresponding allylic alcohols **4** without significant reduction of the nitroxide group.

The allylic alcohols **4a, b** were converted to allylic bromides **6a, b** *via* mesylates **5a, b**, which were not isolated. These allylic bromides could be considered as a paramagnetic derivatives of prenyl bromide which is a useful source of 3,3-dimethyl-allyl group for synthesis of natural products.[12] The allylic bromides **6a, b** were converted to the reversible thiol specific thiosulfonates **7a, b.** Careful oxidation of allylic alcohols **4a, b** affords α,β-unsaturated aldehydes **8a, b** which may be useful substrates for further chain lengthening reactions. Recent publications from our laboratory

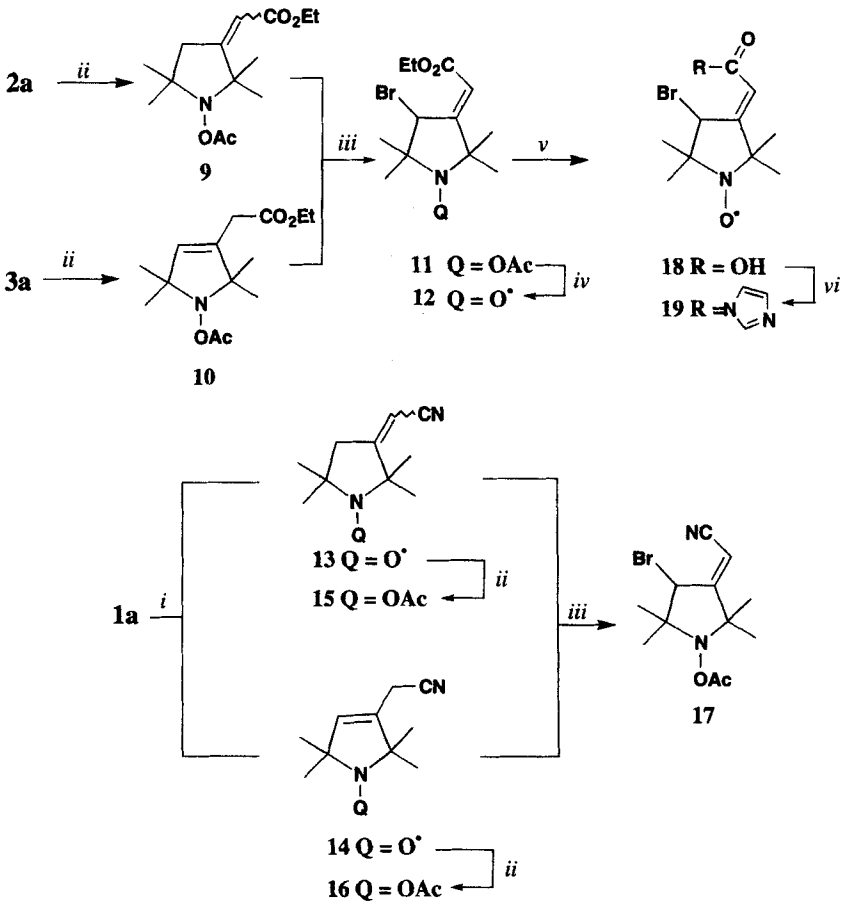


i) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF or toluene, Δ. *ii*) NaOMe, THF, Δ.
iii) $NaAlH_2(OCH_2CH_2OCH_3)_2$, toluene, -78°→ 25°. *iv*) CH_3SO_2Cl, Et_3N, CH_2Cl_2.
v) acetone, LiBr, Δ. *vi*) $NaSSO_2CH_3$, EtOH, H_2O, Δ. *vii*) MnO_2, CH_2Cl_2, 0°.

Figure 1

described methods for the introduction of a second substituent into the ring.[13] This second substituent can be a reactive arm or may be a chemically inert group which has an influence on the lipophilicity or immobility of spin label. Because allylic bromination can not be carried out in the presence of free radical moiety, so it was reduced to diamagnetic *N*-hydroxylamine with ascorbic acid then *O*-acetylated. Since diamagnetic derivative of the six-membered ester **2b** with allylic bromination gave a mixture of isomers due to the two possible allylic-positions, we extended the functionalization only on five-membered diamagnetic compounds **9,10** with one allylic position. Allylic bromination of both *O*-acetates **9,10** in regiospecific and stereospecific way gave the same *Z* isomer of γ-bromo-α,β-unsaturated ester **11,** principally bromination of β,γ-unsaturated compound resulted in the migration of double bond toward conjugation.[14] The steric orientation in compound **11** was proved by ^1H NOE difference spectroscopy. We have synthesized the corresponding α,β-unsaturated nitrile **13** and β,γ-unsaturated nitrile **14** as well. The bromination of their diamagnetic derivatives **15** and **16** in regiospecific and stereospecific way gave the same diamagnetic derivative *Z* isomer of γ-bromo-α,β-unsaturated nitrile **17** as was observed previously in case of esters **9** and **10**. The drastic conditions of hydrolysis of nitrile to carboxylic acid resulted undesirable side-reactions, so the further syntheses

were extended on esters only. The diamagnetic derivative **11** was selectively deprotected by Zemplen's method,[15] the *N*-hydroxy compound was immediately oxidized with MnO_2 to give paramagnetic nitroxide **12**. Hydrolysis of **12** with NaOH gave the mixture of γ-bromo-α,β-unsaturated-carboxylic acid **18** without a lacton formation, presumably because of the low reactivity of bromine atom.[16] The reaction of carboxylic acid **18** with *N,N*-carbonyldiimidazole produced the 3,4-bifunctionalized acylimidazolide **19** capable of labeling amino groups.[17] The advantage of compound **19** presumably is in its increased immobility compared to unsubstituted acylating labels.



i) $(EtO)_2P(O)CH_2CN$, NaH, toluene, Δ. *ii*) ascorbic acid, dioxane, H_2O then AcCl, $CHCl_3$, Et_3N. *iii*) NBS, AIBN, CCl_4, Δ. *iv*) NaOMe, THF, MnO_2. *v*) 5 % NaOH, THF, 5 % H_2SO_4. *vi*) *N,N*-carbonyl-diimidazole, THF.

Figure 2

In conclusion, the synthesis described in this communication provides a convenient route to allylic spin labels with improved reactivity from readily available paramagnetic ketones.

EXPERIMENTAL SECTION

Melting points were determined on a Boetius micro melting point apparatus and are uncorrected. Microanalyses were performed on Heraeus Micro U/E apparatus. Bromine (Br) and sulfur (S) were carried out by Schöniger's method. Infrared spectra were recorded on a Zeiss Specord 75 spectrophotometer. ^{1}H NMR spectra were recorded on Varian-Gemini 200 spectrometer using $CDCl_3$ or DMSO-d_6 as solvent and TMS (δ = 0.00 ppm) as an internal standard. To obtain a high resolution NMR spectra of the radicals they were reduced with an excess codissolved PhNHNHPh additive. In NOE measurements standard Varian NOEDIF sequence was used with a saturation delay of 6 s. Mass spectra were recorded on a VG TRIO-2 instrument in the EI mode (70 eV, direct inlet). The ESR spectra were obtained from 10^{-5} molar solution, using BRUKER 300-E spectrometer. All the monoradicals exhibit three equidistant lines with a_N = 14.7-15.5 G. Flash chromatography was performed on Merck Kieselgel 60 (0.040-0.063 mm).

Ethyl (1-Oxyl-2,2,5,5-tetramethylpyrrolidin-3-ylidene)acetate Radical (2a), Ethyl (1-Oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)acetate Radical (3a).- To a stirred suspension of sodium hydride (720 mg, 30.0 mmol) in dried toluene (20 mL) under N_2 atmosphere was added dropwise triethyl phosphonoacetate (6.72 g, 30.0 mmol) at 0°. Once the gas evolution has stopped and the mixture had become homogeneous, ketone **1a** (4.68 g, 30.0 mmol) in toluene (20 mL) was added dropwise and the mixture was allowed to warm to room temperature. Then the mixture was refluxed for 15 min. After cooling, brine (15 mL) was added, the organic layer was separated and the aqueous phase was washed with ether (20 mL). The organic phase was dried ($MgSO_4$), and evaporated to give a mixture of **2a** and **3a** as an oil 6.60 g (97%). Chromatographic purification (hexane-Et_2O) afforded the pure title compounds and mixture of **2a** and **3a** 3.0 g (44%).

Compound **2a**, 2.50 g (37%), mp. 93-94°; IR: 1710 (C=O), 1650 (C=C) cm^{-1}.

^{1}H NMR: δ 1.14 (s, 6 H), 1.18 (s, 6H), 1.28 (s, 6H), 1.51 (s, 6H), 1.27 (t, 3H), 1.28 (t, 3H), 2.38 (d, 2H), 2.90 (d, 2H), 4.12 (q, 2H), 4.14 (q, 2H), 5.67 (t, 1H), 5.72 (t, 1H). The NMR spectrum of **2a** suggested it to be a ca. 1/1 mixture of *E/Z* isomers.

MS, *m/z* (rel. int. %): 226 (M^+, 9), 212 (18), 196 (52), 181 (44), 107 (50), 41 (100).

Anal. Calcd. for $C_{12}H_{20}NO_3$: C, 63.69; H, 8.91; N, 6.19. Found: C, 63.65; H, 9.01; N, 6.11

Compound **3a,** 1.10 g (16%), oil; IR: 1730 (C=O), 1650 (C=C) cm^{-1}.

^{1}H NMR: δ (1.10-1.40 m, 15 H), 2.97 (s, 2H), 4.15 (q, 2H), 5.48 (s, 1H).

MS, *m/z* (rel. int. %): 226 (M^+, 9), 212 (12), 196 (30), 107 (70), 41 (100).

Anal. Calcd. for $C_{12}H_{20}NO_3$: C, 63.69; H, 8.91; N, 6.19. Found: C, 63.65; H, 9.03; N, 6.09

Ethyl (1-Oxyl-2,2,6,6-tetramethylpiperidin-4-ylidene)acetate Radical (2b).- To a stirred suspension of sodium hydride (720 mg, 30.0 mmol) in dried THF (20 mL) under N_2 atmosphere was added dropwise triethyl phosphonoacetate (6.72 g, 30.0 mmol) at 0°. Once the gas evolution has stopped and the mixture had become homogeneous, ketone **1b** (5.10 g, 30.0 mmol) in THF (20 mL) was added dropwise and the mixture was allowed to warm to rt. Then the mixture was refluxed for 5 min. After cooling, brine (15 mL) was added, the organic layer was separated and the aqueous phase was washed with Et_2O (20 mL). The organic phase was dried ($MgSO_4$), filtered, evaporated and flash chro-

matographed to give **2b** as an oil, 6.0 g (83%); IR: 1710 (C=O), 1650 (C=C) cm^{-1}.

^1H NMR: δ 1.12 (s, 6H), 1.16 (s, 6H), 1.18 (t, 3H), 2.18 (d, 2H), 2.86 (broad, 2H), 4.15 (q, 2H) 5.70 (m, 1H).

MS, *m/z* (rel. int. %): 240 (M^+, 10), 226 (13), 210 (39), 195 (94), 41 (100).

Anal. Calcd. for $C_{13}H_{22}NO_3$: C, 64.97; H, 9.23; N, 5.83. Found: C, 64.90; H, 9.12; N, 5.74

Ethyl (1-Oxyl-2,2,6,6-tetramethyl-1,2,5,6-tetrahydropyridine-4-yl)acetate Radical (3b).- The α,β-unsaturated ester **2b** (2.40 g, 10.0 mmol) was dissolved in THF (10 mL) and freshly made 0.1 M NaOEt solution in ethanol (0.5 mL) was added and the mixture was kept at rt. for 15 min. The reaction mixture was evaporated, then brine (10 mL) was added to the residue and extracted with Et_2O (2 x 20 mL). The organic phase was dried ($MgSO_4$), filtered, evaporated and chromatographed (hexane-Et_2O) to give **3b** as an oil 980 mg (41%). IR: 1730 (C=O), 1750 (C=C) cm^{-1}.

^1H NMR: δ 1.18 (s, 6H) 1.22 (s, 6H), 1.26 (t, 3H), 2.10 (m, 2H), 4.13 (q, 2H), 5.33 (m, 1H).

MS, *m/z* (rel. int. %): 240 (M^+, 14), 226 (21), 210 (27), 195 (16), 121 (63), 41 (100).

Anal. Calcd. for $C_{13}H_{22}NO_3$: C, 64.97; H, 9.23; N, 5.83. Found: C, 64.91; H, 9.11; N, 5.68

1-Oxyl-2,2,5,5-tetramethylpyrrolidin-3-ylideneethanol Radical (4a), 1-Oxyl-2,2,6,6-tetramethylpiperidin-4-ylideneethanol Radical (4b).- To stirred solution of α,β-unsaturated ester **2a** (4.52 g, 20.0 mmol), or **2b** (4.80 g, 20.0 mmol) in toluene (20 mL) under N_2 atmosphere was added dropwise SMEAH (70% solution in toluene) (9 mL, 31.0 mmol) diluted with toluene (10 mL) at -30°. The mixture was allowed to warm to rt. and stirred further. The reaction mixture was monitored by TLC (hexane-EtOAc) and after the conversion was complete, the reaction mixture was quenched by pouring into a mixture of 10% NaOH (50 mL) and ice (150 g). THF (50 mL) was added and the mixture was stirred for further 30 min., then organic phase was separated, the aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phase was dried ($MgSO_4$), filtered, evaporated. The residue was dissolved in $CHCl_3$ (40 mL) and PbO_2 (100 mg, 0.4 mmol) was added and the mixture was stirred for 15 min., then filtered, evaporated, chromatographed on silica gel (hexane-EtOAc) to give the corresponding alcohol **4a,** or **4b**. Compound **4a,** 1.50 g (40%), mp. 61-63°; IR: 3360 (OH), 1670 (C=C) cm^{-1}.

MS, *m/z* (rel. int. %): 184 (M^+, 9), 170 (10), 154 (26), 121 (42), 41 (100).

Anal. Calcd. for $C_{10}H_{18}NO_2$: C, 65.19; H, 9.85; N, 7.60; Found: C, 65.14; H, 9.80; N, 7.48

Compound **4b**, 2.95 g (74%), oil; IR: 3400 (OH), 1670 (C=C) cm^{-1}.

MS *m/z* (rel. int. %): 198 (M^+, 4), 184 (11), 135 (17), 74 (78), 41 (100).

Anal. Calcd. for $C_{11}H_{20}NO_2$: C, 66.63; H, 10.17; N, 7.06. Found: C, 66.72; H, 10.11; N, 7.01

2-(1-Oxyl-2,2,5,5-tetramethylpyrrolidin-3-ylidene)bromoethane Radical (6a), 2-(1-Oxyl-2,2,6,6-tetramethylpiperidin-4-ylidene)bromoethane Radical (6b).- To stirred solution of alcohol **4a** (1.84 g, 10.0 mmol), or **4b** (1.98 g, 10.0 mmol) and Et_3N (1.11 g, 11.0 mmol) in dried CH_2Cl_2 (20 mL) was added dropwise CH_3SO_2Cl (1.26 g, 11.0 mmol) at -78°. The cooling bath was removed, the mixture was allowed to warm to rt., then immediately brine (10 mL) was added, the organic phase was separated, dried ($MgSO_4$), filtered and evaporated. The crude mesylate **5a, 5b** was dissolved in dried

acetone (30 mL) and LiBr (1.30 g, 15 mmol) was added and the mixture was stirred and refluxed for 30 min. The acetone was evaporated off, the residue was taken up in brine (10 mL) and extracted with Et_2O (30 mL). The organic phase was dried ($MgSO_4$), evaporated and purified by flash chromatography (hexane-Et_2O) to give allylic bromide **6a, 6b**. Compound **6a**, 1.60 g (66%), oil; IR: 1670 (C=C) cm^{-1}.

MS, *m/z* (rel. int. %): 246 (M^+, 6), 232 (5), 167 (11), 152 (22), 41 (100).

Anal. Calcd. for $C_{10}H_{17}BrNO$: C, 48.60; H, 6.93; N, 5.67; Br, 32.33
Found: C, 48.67; H, 6.71; N, 5.72; Br, 32.46

Compound **6b**, 1.20 g (46%), oil; IR: 1660 (C=C) cm^{-1}.

MS, *m/z* (rel. int. %): 260 (M^+, 2), 181 (5), 166 (11), 74 (100), 41 (92).

Anal. Calcd. for $C_{11}H_{19}BrNO$: C, 50.59; H, 7.33 N, 5.36; Br, 30.59
Found: C, 50.71; H, 7.18; N, 5.45; Br, 30.48

2-(1-Oxyl-2,2,5,5-tetramethylpyrrolidin-3-ylidene)methanethiosulfonatoethane Radical (7a), 2-(1-Oxyl-2,2,6,6-tetramethylpiperidin-4-ylidene)methanethiosulfonatoethane Radical (7b).- To a solution of allylic bromide **6a** (1.23 g, 5.0 mmol), or **6b** (1.30 g, 5.0 mmol) in EtOH (10.0 mL) and water (3 mL) was added $NaSSO_2CH_3$ (1.34 g, 10.0 mmol). The mixture was refluxed for 15 min., EtOH was evaporated, the residue was extracted with $CHCl_3$ (2 x 10 mL), the organic layer was separated, dried ($MgSO_4$), evaporated and purified by chromatography (Et_2O-$CHCl_3$). Methanethiosulfonates **7a**, or **7b** were crystallized from Et_2O.

Compound **7a**, 667 mg (48%), mp. 81-83°; IR: 1660 (C=C) cm^{-1}.

MS, *m/z* (rel. int. %): 278 (M^+,6), 264 (13), 184 (15), 153 (32), 121 (58), 41 (100).

Anal. Calcd. for $C_{11}H_{20}NO_3S_2$: C, 47.46; H, 7.24; N, 5.03; S, 23.03
Found: C, 47.35; H, 7.28; N, 5.15; S, 22.82

Compound **7b**, 481 mg (33%), mp. 59-61°; IR: 1640 (C=C) cm^{-1}.

MS, *m/z* (rel. int. %): 292 (M^+, 2), 278 (4), 182 (10), 166 (15), 74 (100), 41 (96).

Anal. Calcd. for $C_{12}H_{22}NO_3S_2$: C, 49.29; H, 7.58; N, 4.79; S, 21.93
Found: C, 49.33; H, 7.69; N, 4.96; S, 21.77

1-Oxyl-2,2,5,5-tetramethylpyrrolidin-3-ylideneacetaldehyde Radical (8a), 1-Oxyl-2,2,6,6-tetramethylpiperidin-4-ylideneacetaldehyde Radical (8b).- To a stirred solution of alcohol **4a** (921 mg, 5.0 mmol), or **4b** (990 mg, 5.0 mmol) in dried CH_2Cl_2 (40 mL) was added active MnO_2 (15.0 g, 172 mmol) and the mixture was stirred for 30 min. at 0°. Then MnO_2 was filtered off, the solution was evaporated at 30°, reaction mixture was purified by chromatography to give α,β-unsaturated aldehydes **8a, 8b.**

Compound **8a**, 738 mg, (81%), mp. 68-70°; IR: 1660 (C=O), 1640 (C=C) cm^{-1}.

MS, *m/z* (rel. int. %): 182 (M^+, 5), 168 (29), 152 (21), 137 (16), 109 (40), 41 (100).

Anal. Calcd. for $C_{10}H_{16}NO_2$: C, 65.91; H, 8.85; N, 7.69; Found: C, 65.83; H, 8.75; N, 7.73

Compound **8b**, 676 mg, (69%), mp. 65-67°; IR: 1670 (C=O), 1650 (C=C) cm^{-1}.

MS, *m/z* (rel. int. %): 196 (M^+, 4), 187 (7), 170 (9), 154 (23), 121 (35), 41 (100).

Anal. Calcd. for $C_{11}H_{18}NO_2$: C, 67.32; H, 9.24; N, 7.14. Found: C, 67.22; H, 9.18; N, 7.08

1-Oxyl-2,2,5,5-tetramethylpyrrolidin-3-ylideneacetonitrile Radical (13), 1-Oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-ylacetonitrile Radical (14).- To a stirred suspension of sodium hydride (600 mg, 25.0 mmol) in dried toluene (20 mL) under N_2 atmosphere was added dropwise diethyl cyanomethylphosphonate (4.42 g, 25.0 mmol) at 0°. Once the gas evolution has stopped and the mixture had become homogeneous, ketone **1a** (3.90 g, 25.0 mmol) in toluene (20 mL) was added dropwise and the mixture was allowed to warm to room temperature. Then the mixture was refluxed for 60 minutes. After cooling, brine (15 mL) was added, the organic layer was separated and aqueous phase was washed with ether (20 mL). The organic phase were dried ($MgSO_4$), evaporated to give mixture of **13** and **14** as an oil 4.30 g, (96%). Chromatographic purification (hexane-Et_2O) afforded pure nitriles **13** and **14** and mixture of **13** and **14** 1.92 g (43%).

Compound **13**, 1.39 g, (31%), mp. 80-83°; IR: 2210 (CN), 1640 (C=C) cm^{-1}.

MS *m/z* (rel. int. %): 179 (M^+, 32), 165 (18), 149 (36), 134 (66), 107 (100).

Anal. Calcd. for $C_{10}H_{15}N_2O$: C, 67.01; H, 8.44; N, 15.63. Found: C, 66.98; H, 8.34; N, 15.70

Compound **14**, 984 mg (22%), oil; IR: 2240 (CN), 1620 (C=C) cm^{-1}.

MS *m/z* (rel. int. %): 179 (M^+,34), 164 (19), 149 (97), 134 (100), 109 (87).

Anal. Calcd. for $C_{10}H_{15}N_2O$: C, 67.01; H, 8.44; N, 15.63. Found: C, 67.10; H, 8.50; N, 15.55

Protecting of *N*-oxyl moiety (9, 10, 15, 16). Typical Procedure.- To a solution of radical **2a,** or **3a,** or **13,** or **14** (10.0 mmol) in dioxane (10 mL) was added ascorbic acid (8.80 g, 50.0 mmol) in water (10.0 mL) under N_2 and the mixture was stirred for 15 min. at 40°. The colorless solution was extracted with $CHCl_3$ (50 mL) and dried ($MgSO_4$) under N_2. First Et_3N (1.21 g, 12.0 mmol) and then AcCl (0.942 g, 12.0 mmol) were added at 0°. The stirring was continued for 1 hr at rt., the mixture was filtered and evaporated to dryness. The residue was dissolved in brine and extracted with EtOAc (40 mL). The organic layer was dried ($MgSO_4$), filtered, evaporated and the residue was purified by chromatography (hexane-Et_2O) to give diamagnetic compounds **9,** or **10,** or **15,** or **16**.

Compound **9**, 1.72 g (64%), oil; IR: 1760 (OAc), 1710 (C=O), 1650 (C=C) cm^{-1}.

^1H NMR: δ 1.12-1.35 (m, 9H), 1.52 and 1.55 (s, 6H), 2.12 (s, 3H), 2.50 and 3.00 (broad, 2H), 4.12 and 4.18 (q, 2H), 5.71 and 5.73 (t, 3H). The NMR spectrum of **9** suggested it to be a ca. 1/1 mixture of *E/Z* isomers.

MS, *m/z* (rel. int. %): 269 (M^+, 1), 254 (5), 227 (15), 212 (100), 196 (27)

Anal. Calcd. for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.38; H, 8.45; N, 5.18

Compound **10**, 1.23 g (45%), oil; IR: 1760 (OAc), 1730 (C=O), 1650 (C=C) cm^{-1}.

^1H NMR: δ 1.22 (s, 6H), 1.24 (s, 6H), 1.28 (t, 3H), 2.13 (s, 3H), 2.96 (d, 2H), 4.16 (q, 2H), 5.52 (t, 1H).

MS, *m/z* (rel. int. %): 269 (M^+, 2), 254 (13), 228 (11), 212 (100), 196 (58).

Anal. Calcd. for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.36; H, 8.47; N, 5.27

Compound **15**, 1.33 g (60%), mp. 55-65°; IR: 2205 (CN), 1760 (OAc), 1640 (C=C) cm^{-1}.

^1H NMR: δ 1.18, 1.22 and 1.31 (s, 9H), 1.52 and 1.62 (s, 3H), 2.12 and 2.14 (s, 3H), 2.60 and 2.78 (d, 2H), 5.22 and 5.28 (t, 1H). The NMR spectrum of **15** suggested it to be a ca. 1.7 / 1 mixture of *E/Z* isomers.

MS, *m/z* (rel. int. %): 222 (M^+, 2), 207 (2), 180 (16), 165 (100), 149 (10).

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.80; H, 8.26; N, 12.54

Compound **16,** 920 mg (41%), oil; IR: 2245 (CN), 1760 (OAc), 1640 (C=C) cm^{-1}.

^1H NMR: δ 1.25 (s, 12 H), 2.14 (s, 3H) 3.05 (d , 2H), 5.72 (t, 1H).

MS, *m/z* (rel. int. %): 222 (M^+, 2), 207 (6), 180 (11), 165 (100), 149 (11).

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.86; H, 8.22; N, 12.68

Ethyl (1-Acetoxy-4-bromo-2,2,5,5-tetramethylpyrrolidin-3-(*Z*)-ylidene)acetate Radical (11), 1-Acetoxy-4-bromo-2,2,5,5-tetramethylpyrrolidin-3-(*Z*)-ylideneacetonitrile Radical (17).- To a solution of *O*-acetate **9, 10** (1.34 g, 5.0 mmol), **15, 16** (1.11 g, 5.0 mmol) in CCl_4 (30 mL) was added brominating reagent NBS (1.0 g, 5.6 mmol) or DDH (750 mg, 2.6 mmol) and mixture was refluxed for 48 hrs. The reaction mixture was monitored by TLC (hexane-Et_2O). The succinimide or 5,5-dimethylhydantoin was filtered and washed with CCl_4 (10 mL). The filtrate was evaporated, the residue was taken up in EtOAc (30 mL), washed with brine (10 mL), the organic phase was dried ($MgSO_4$), filtered, evaporated and purified by chromatography (hexane-Et_2O). Compound **11**, 700 mg (40%), mp. 75-77°; IR: 1760 (OAc), 1720 (C=O), 1650 (C=C) cm^{-1};

^1H NMR: δ 1.21 (s, 3H), 1.32 (s, 3H), 1.33 (t, 3H), 1.40 (s, 3H), 1.56 (s, 3H), 2.18 (s, 3H), 4.23 (q, 2H), 5.62 (d, 1H), 5.79 (d, 1H).

MS *m/z* (rel. int. %): 347 (M^+,1), 332 (1), 305 (2), 290 (8), 227 (13), 212 (100)

Anal. Calcd. for $C_{14}H_{22}BrNO_4$: C, 48.29; H, 6.37; N, 4.02; Br, 22.95

Found: C, 48.37; H, 6.52; N, 3.95; Br, 22.62

Compound **17**, 1.05 g (67%), mp. 65-66°; IR: 2215 (CN), 1760 (OAc), 1630 (C=C) cm^{-1}.

^1H NMR: δ 1.17 (s, 3H), 1.26 (s, 3H), 1.28 (s, 3H), 1.42 (s, 3h) 2.12 (s, 3H), 5.22(d, 1H), 6.18 (d, 1H).

MS, *m/z* (rel. int. %): 300 (M^+, 1), 285 (1), 258 (7), 243 (19), 180 (15), 165 (100).

Anal. Calcd. for $C_{12}H_{17}BrN_2O_2$: C, 47.86; H, 5.69; N, 9.30; Br, 26.53

Found: C, 47.77; H, 5.60; N, 9.45; Br, 26.16

Ethyl (1-Oxyl-4-bromo-2,2,5,5-tetramethylpyrrolidin-3-(*Z*)-ylidene)acetate Radical (12).- The acetate **11** (600 mg, 1.72 mmol) was dissolved in THF (15 mL) then freshly made 0.1 M NaOMe solution (0.5 mL) was added and reaction mixture was kept at rt. for 20 min. Then solvents were evaporated, the residue was taken up in $CHCl_3$ (30 mL), washed with brine (5 mL), dried ($MgSO_4$), filtered. To the filtrate active MnO_2 (87 mg, 1.0 mmol) was added and allowed to stand at rt. overnight. The MnO_2 was filtered off, evaporated, the residue was chromatographed (hexane-Et_2O) to give **12,** 220 mg (42%), mp. 88-90°; IR: 1710 (C=O), 1660 (C=C) cm^{-1}.

^1H NMR: δ 1.13 (s, 3H), 1.31 (t, 3H), 1.32 (s, 3H), 1.42 (s, 3H), 1.50 (s, 3H), 4.22 (q, 2H), 5.58 (d, 1H), 5.78 (d, 1H).

MS, *m/z* (rel. int. %): 304 (M^+,6), 290 (11), 274 (22), 195 (77), 121 (85), 41 (100).

Anal. Calcd. for $C_{12}H_{19}BrNO_3$: C, 47.23; H, 6.28; N, 4.59; Br, 26.18

Found: C, 47.26; H, 6.30; N, 4.68; Br, 26.79

1-Oxyl-4-bromo-2,2,5,5-tetramethylpyrrolidin-3-(*Z*)-ylideneacetic Acid Radical (18).-Ester **12**

(200 mg, 0.65 mmol) was dissolved in THF (5 mL), 5% NaOH solution (5 mL) was added and the mixture was vigorously stirred at rt. for 30 min. THF was evaporated, the aqueous phase was washed with Et_2O, acidified with 5% H_2SO_4 to pH 2, extracted with $CHCl_3$ (20 mL), dried ($MgSO_4$), evaporated. The residue was crystallized (hexane-Et_2O) to give **18**, 103 mg (57%), mp. 177-179°; IR: 3400 (OH), 1700 (C=O), 1640 (C=C) cm^{-1}.

^1H NMR: δ 1.09 (s, 3H), 1.24 (s, 3H), 1.35 (s, 3H), 1.43 (s, 3H), 5.80 (d, 1H), 5.88 (d, 1H).

MS *m/z* (rel. int. %): 276 (M^+, 13), 261 (8), 182 (26), 167 (32), 121 (82), 41 (100).

Anal. Calcd. for $C_{10}H_{15}BrNO_3$: C, 43.34; H, 5.46; N, 5.05; Br, 28.83

Found: C, 43.27; H, 5.37; N, 5.10; Br, 28.06

***N*-(1-Oxyl-4-bromo-2,2,5,5-tetramethylpyrrolidin-3-(*Z*)-ylideneacetic Acyl)imidazole Radical (19)**.- To a stirred solution of acid **18** (100 mg, 0.36 mmol) in dried THF (5 mL) was added *N,N'*-carbonyldiimidazole (130 mg, 0.8 mmol) at 0. Then cooling bath was removed and the mixture was stirred for 30 min. at rt., the mixture was diluted with Et_2O (20 mL), the organic layer was washed with water (10 mL), and satd. $NaHCO_3$ solution (5 mL). After drying ($MgSO_4$) and evaporation the residue was crystallized from hexane to give **19,** 70 mg (60%), mp. 134-136°; IR: 1695 (C=O), 1640 (C=C) cm^{-1}.

MS *m/z* (rel. int. %): 326 (M^+, 2), 276 (23), 246 (22), 167 (66),121 (100).

Anal. Calcd. for $C_{13}H_{17}BrN_3O_2$: C, 47.72; H, 5.24; N, 12.84; Br, 24.42

Found: C, 47.67; H, 5.15; N, 12.75; Br, 24.82

Acknowledgement.- The support of this work by the Hungarian National Research Foundation (T017842) is gratefully acknowledged.

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(Received November 6, 1995; in revised form February 7, 1996)