^{31}P-Labeled Pyrroline *N*-Oxides: Synthesis of 5-Diethylphosphono-5-methyl-1-pyrroline *N*-Oxide (DEPMPO) by Oxidation of Diethyl (2-Methylpyrrolidin-2-yl)phosphonate

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Abstract: The synthesis of DEPMPO from diethyl (2-methylpyrrolidin-2-yl)phosphonate **(3)**, prepared by the addition of diethyl phosphite to 2-methylpyrroline, was carried out using different oxidation reagents: H_2O_2, *m*-CPBA, Oxone, 2-phenylsulfonyl-3-phenyloxaziridine (PSPO), dimethyldioxirane (DMD) and *N*-methylmorpholine *N*-oxide with catalytic amounts of tetrapropylammonium perruthenate (NMO/TPAP). The highest yield of DEPMPO (>80%) was obtained using two equivalents of PSPO or DMD. Different compounds involved in the oxidation of **3** have been isolated and characterized.

Key words: aminophosphorylation, secondary amines, oxidations, nitrones, heterocycles, spin label, phosphorus, additions

Introduction

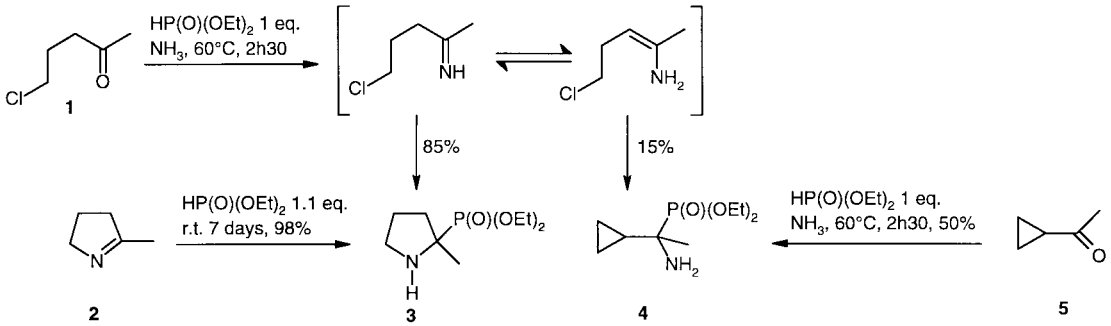
Most β-phosphorylated five-membered ring nitroxides possess a large ESR phosphorus coupling which is strongly dependent on the ring conformation and constitute a very sensitive structural probe.[1, 2] In order to facilitate the identification of spin adducts produced in spin trapping experiments it was thus tempting to design new pyrroline *N*-oxide spin traps to generate spin adducts bearing a β-phosphorus substituent. We recently prepared the 5-diethylphosphono-5-methyl-1-pyrroline *N*-oxide (DEPMPO), and clearly established[3] that it was a very promising trap, particularly to investigate oxygen free radical processes in biology. Since many researchers[4] are now using DEPMPO to trap free radicals in biological milieu and that significant amounts of very pure traps could be needed to perform spin trapping or ESR imaging experiments on cell cultures, perfused organs or whole animals, we worked out a satisfactory synthesis of DEPMPO.

Results and Discussion

Synthesis of Diethyl (2-Methylpyrrolidin-2-yl)phosphonate (3)

The synthesis of **3** was performed from 5-chloropentan-2-one **1** (Scheme 1). However, **3** was always accompanied by a significant amount of diethyl 1-cyclopropyl-1-aminoethylphosphonate **(4)**. Compound **4** was identified by comparison with an authentic sample obtained by bubbling ammonia into an ethanolic solution of acetylcyclopropane **(5)** and diethyl phosphite. Formation of **4** during the aminophosphorylation of **1** could be explained by the addition of diethyl phosphite to an intermediate enamine (Scheme 1).

Addition of phosphite to the double bond of an imine is a usual procedure to generate open-chain aminophosphonates,[5] and we have now showed that this approach was appropriate to prepare large amounts of pure **3**. Stirring 2-methylpyrroline **(2)** for 7 days with a slight excess of diethyl phosphite led to **3** in 98% yield (Scheme 1). ^{31}P, ^{13}C and ^{1}H NMR data showed that the purity of **3** obtained in



Scheme 1

this way was very good and the compound was used without further purification in the subsequent oxidation step.

Oxidation of Diethyl (2-Methylpyrrolidin-2-yl)phosphonate (3)

m-Chloroperbenzoic Acid (*m*-CPBA)

The oxidation of **3** with *m*-CPBA yielded DEPMPO in approximately 50% yield and has been described elsewhere.[3] This reagent promoted the formation of side products **10** and **11** resulting from the overoxidation of DEPMPO (Table). During the course of the oxidation, a sample removed from the reaction mixture exhibited an intense ESR signal (a_N, 1.419 mT; a_P, 4.950 mT; $a_{H\beta1}$, 1.907 mT; $a_{H\beta2}$, 1.839 mT; $a_{H\gamma}$, 0.047 mT (3H); $a_{H\gamma1}$, 0.037 mT; $a_{H\gamma2}$, 0.040 mT; $a_{H\gamma3}$, 0.027 mT; $a_{H\gamma4}$, 0.011 mT) which was also observed with other oxidation reagents (DMD, PSPO and Oxone). This ESR signal was assigned to the nitroxide **6•** (Scheme 2) and the same spectrum was observed for an authentic sample of **6•** prepared by reducing DEPMPO with $NaBH_4$ in the presence of molecular oxygen.

Davis' Reagent or 2-Phenylsulfonyl-3-phenyloxaziridine (PSPO)

The Davis' reagent[6] has been used by Zajac et al. to oxidize amines.[7] They found that primary and tertiary amines led essentially to nitroso and *N*-oxide compounds respectively, while with secondary amines, mixtures of hydroxylamines and nitrones were obtained. The precursor of 2-phenylsulfonyl-3-phenyloxaziridine (PSPO), *N*-benzylidenebenzenesulfonamide, was obtained as described by Jennings and Lovely[8] and was oxidized to PSPO with Oxone according to the procedure of Davis et al.[9] The oxidation of **3** was carried out in chloroform at 0 °C by the dropwise addition of 2 equivalents of PSPO. The reaction led to the exclusive formation of DEPMPO (83% isolated yield) even in the presence of an excess of PSPO (Table).

Dimethyldioxirane (DMD)

Dimethyldioxirane (DMD) is a good oxidizing agent which has been used to oxidize various organic compounds.[10] Murray[10c] reported that DMD can be used for a smooth one-step synthesis of *C*-arylnitrones. Acetone solutions of DMD were prepared and titrated (0.07 M–0.12 M) according to Adam's procedure.[11] The oxidation of an acetone solution of **3** during 20 min at 0 °C with 1 or 2 equivalents of DMD led respectively to the hydroxylamine **6** (75% isolated yield)[12] and to the DEPMPO (80% isolated yield). With an excess of DMD the formation of the hydroxamic acid **9** was observed (Scheme 2). Very good yields of DEPMPO were obtained by oxidizing **6** with molecular oxygen in the presence of a catalytic amount of copper acetate (81% yield in aqueous ammonia and 90% in acetonitrile) (Table). Different attempts were made to oxidize **3** with DMD generated in situ from oxidation of acetone by Oxone as described by Murray.[14c,14f,14 g] However, a blue color characteristic of nitroso compounds rapidly developed in the reaction mixture. Oxone acted as a competitive oxidant favoring the overoxidation of DEPMPO into **10** and **11** (Scheme 2).

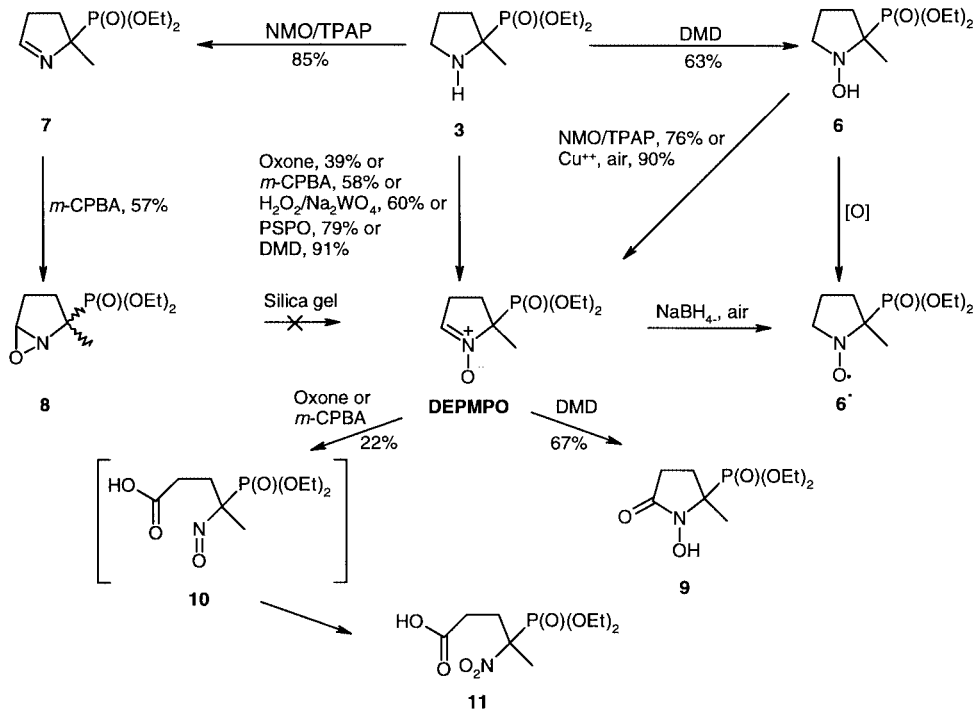
N-Methylmorpholine *N*-Oxide/Tetrapropylammonium Perruthenate (NMO/TPAP)

Recently Goti et al. have used this reagent to oxidize either secondary amines to imines[13] or hydroxylamines to nitrones.[14] The experimental procedure used by Goti et al. was applied to the oxidation of pyrrolidine **3** and hydroxylamine **6** and yielded the corresponding imine **7** (85% yield) and DEPMPO (76% yield), respectively (Scheme 2). The conversion of imines to the corresponding nitrones has been reported using permanganate ions,[15] dioxiranes,[16] oxaziridinium tetrafluoroborates[17] as oxidizing reagents. In some instances the formation of the nitrone

Table Products Observed During the Oxidation of **3**, **8** and DEPMPO with Different Oxidants

Substrates	Oxidizing Agents	Equiv	Solvents	Products (%)[a]							
				3	**6**	**7**	DEPMPO	**8**	**9**	**10**	**11**
3	*m*-CPBA	2.0	H_2O/Et_2O	10	–	–	88(60)	–	–	–	–
	PSPO	2.0	$CHCl_3$	–	–	–	100(83)	–	–	–	–
	DMD	1.0	acetone	14	75(63)	–	11	–	–	–	–
		2.0	acetone	–	4	–	91(81)	–	5	–	–
	TPAP/NMO	3.0	MeCN	8	–	92(85)	–	–	–	–	–
	Oxone	1.0	Buffer	–	43	–	23(39)[b]	–	–	25(22)[b]	9
6	Cu^{2+}, air	1.0	MeCN	–	–	–	(90)	–	–	–	–
DEPMPO	*m*-CPBA	2.0	$CHCl_3$	–	–	–	–	–	78	14	8
		3.0	$CHCl_3$	–	–	–	–	–	65	4	31(22)
	DMD	1.0	$CHCl_3$	–	–	–	–	–	95(67)	5	–
7	*m*-CPBA	1.0	$CHCl_3$	5	–	–	–	95(57)	–	–	–

[a] Estimated yields by ^{31}P NMR. Yields of isolated products are given in parenthesis.
[b] Yields of isolated products after having completed the oxidation in aerated MeCN solution of $Cu(OAc)_2$.



Scheme 2

occurs through the isomerization of the corresponding oxaziridine.[18] The oxidation of **7** with *m*-CPBA led to oxaziridine **8** (Scheme 2). However, all attemps to isomerize **8** to DEPMPO, following procedures reported in the literature [18d,19]failed.[18f]

Hydrogen Peroxide/Sodium Tungstate (H_2O_2/Na_2WO_4)

Among the different oxidizing reagents used to oxidize secondary amines to nitrones, hydrogen peroxide[20] is one of the most commonly used and appeared as the most appropriate to develop a large scale preparation of DEPMPO. Na_2WO_4-catalyzed oxidation of **3** with hydrogen peroxide in water led smoothly to DEPMPO in quantitative yield, which was then purified by column chromatography on silica gel and molecular distillation. This two-step purification is essential for obtaining highly purified DEPMPO.

Conclusion

We have shown that the addition of diethyl phosphite to pyrroline **2** was very efficient and led to almost quantitative yields of the β−phosphorylated pyrrolidine **3**. In a laboratory scale, five different oxidizing reagents (*m*-CPBA, PSPO, DMD, Oxone and NMO/TPAP) were used to oxidize **3**. The nitrone DEPMPO was formed with *m*-CPBA, PSPO, DMD and Oxone, the best yields (>80%) and the highest purity being obtained with DMD and PSPO. The formation of DEPMPO was accompanied by the formation of overoxidation products except when PSPO was used. The use of 1 equivalent of DMD yielded the hydroxylamine **6** which can be isolated and easily oxidized to DEPMPO. On industrial scale, Na_2WO_4-catalyzed oxidation with H_2O_2 has been the most efficient method for obtaining DEPMPO.

^{31}P NMR spectra were recorded at 40.53 MHz (Bruker AC 100 spectrometer) with 85% H_3PO_4 as external reference. ^1H and ^{13}C NMR spectra were recorded on Bruker AC 200 and AM 400X instruments respectively, at 200 or 400 MHz and 50.32 or 100.61 MHz. ESR spectra were recorded using an ESP-300 Bruker spectrometer operating at 9.5 GHz microwave frequency with 100 KHz modulation frequency. The purity of DEPMPO was checked by HPLC. HPLC was performed by using a Waters model 600E multisolvent delivery system with a Pye Unicam PU 4021 photodiode array detector, a Spectra Physic SP4600 integrator and a Shandon Ultrabase C18 column (25 cm length 4.6 i.d.). HPLC column conditions were as follows: flow rate, 1.0 mL/min; injection volume 20 μL (solution 10% in eluent solvent); gradient elution programmed from 4 to 15% A in 15 min, with 10% in B (solvent A: MeOH; solvent B: 2% Et_3N, 80% MeOH, 18% H_2O; solvent C: H_2O). The UV detector was set between 210 and 320 nm. DEPMPO retention time: 6.60 min.

Molecular distillation: KDL1 apparatus (UIC Society, Germany). T_{vap} = 100 °C; Condenser: 5–10 °C; Pressure: 0.001 mbar; flow: 100 droplets/h; stirrer: 400 rpm.

Diethyl (2-Methylpyrrolidin-2-yl)phosphonate (3)

A mixture of 2-methylpyrroline (**2**; 10.9 g, 0.13 mol) and diethyl phosphite (21.7 g, 0.16 mol) was stirred for 7 days at r.t. The product was poured into a 1 N HCl solution (100 mL) and the solution washed with CH_2Cl_2 (2 × 80 mL). The aqueous layer was then basified with aq sat. Na_2CO_3 and the product extracted with $CHCl_3$

(3 × 100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure (0.001 mbar). Pure **3** was obtained as a colorless oil (28.4 g, 98%) and characterized by ^{1}H, ^{13}C and ^{31}P NMR spectra as previously described.[3]

5-Diethylphosphono-5-methyl-1-pyrroline *N*-Oxide (DEPMPO)

*Oxidation of **3** with Dimethyldioxirane (DMD)*: An acetone solution of DMD[11] (0.075 M, 200 mL, 2 equiv) was added to a solution of **3** (1.66 g, 7.50 mmol) in acetone (20 mL). The addition was carried out dropwise at 0 °C under inert atmosphere over 15 min. After stirring the mixture for 5 min was dried ($MgSO_4$), concentrated and chromatographed (silica gel, EtOH/CH_2Cl_2,1:9). DEPMPO was obtained as a pale yellow oil (1.43 g, 81% yield).

*Large Scale Preparation : Oxidation of **3** with H_2O_2/Na_2WO_4*: Aq solution of Na_2WO_4 (25 g in 1 L, 0.075 M) was mixed with **3** (400 g, 1.81 mol) in a 5-L reactor at 0 °C. A 35% solution of H_2O_2 (350 mL) was added at 0 °C over 1.5 h. The mixture was kept at 0 °C for 48 h. After filtration of a very fine solid, the filtrate was extracted with *tert*-butyl methyl ether (300 mL) and with $CHCl_3$ (4 × 250 mL). The aq phase was saturated with brine (350 g) and then extracted with $CHCl_3$ (8 × 300 mL). The combined organic phases were dried (Na_2SO_4, 300 g) for 12 h. The solvent was removed under reduced pressure below 40 °C. The crude compound was first purified by column chromatography by small fractions at laboratory scale (silica gel, CH_2Cl_2, 1:19). Pure DEPMPO was obtained after molecular distillation (300 g, 60%).

*Oxidation of **6** with Copper Acetate*: A solution of hydroxylamine **6** (765 mg, 3.2 mmol) and $Cu(OAc)_2$ (6.4 mg, 32 μmol) in MeCN (20 mL) was aerated for 30 min. The solution was filtered over Celite and washed with MeOH/CH_2Cl_2 (1:4). The organic phase was evaporated and the residue chromatographed (silica gel, EtOH/CH_2Cl_2, 1:9). DEPMPO was obtained as a pale yellow oil (680 mg, 90%).

Diethyl (1-Hydroxy-2-methylpyrrolidin-2-yl)phosphonate (6)

An acetone solution of dimethyldioxirane[11] (0.098 M, 83 mL, 1 equiv) was added dropwise at 0 °C under inert atmosphere over 15 min to a solution of **3** (1.79 g, 8.10 mmol) in acetone (50 mL). After stirring for 5 min, the mixture was evaporated and stored at –18 °C overnight. The obtained pale yellow crystals were crystallized from pentane and stored at 6 °C to afford 1.21 g (63%) of colorless crystals of hydroxylamine **6**; mp 39–40 °C.

IR (KBr): ν = 3287 (m, br), 2977 (m), 1202 (m), 1056 (s), 1026 cm^{-1} (s).

^{31}P NMR ($CDCl_3$): δ = 27.71.

^{1}H NMR (200 MHz, C_6D_6): δ = 1.09 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 1.16 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 1.56 (d, $^3J_{H,P}$ = 15.9 Hz, 3 H), 1.40–1.80 (m, 3 H), 2.20–2.60 (m, 1 H), 3.00–3.20 (m, 1 H), 3.40–3.60 (m, 1 H), 3.90–4.40 (m, 4 H).

^{13}C NMR (200 MHz, C_6D_6): δ = 16.58 (d, $^3J_{C,P}$ = 5.2 Hz), 16.77 (d, $^3J_{C,P}$ = 5.7 Hz), 17.78 (d, $^2J_{C,P}$ = 4.9 Hz), 20.30 (d, $^3J_{C,P}$ = 5.6 Hz), 33.76, 56.14 (d, $^3J_{C,P}$ = 13.4 Hz), 61.45 (d, $^2J_{C,P}$ = 7.20 Hz), 63.06 (d, $^2J_{C,P}$ = 6.82 Hz), 65.93 (d, $^1J_{C,P}$ = 169.5 Hz).

Anal. calcd for $C_9H_{20}NO_4P$ (237.2): C 45.54, H 8.50, N 5.90; found C 45.57, H 8.45, N 5.89.

Diethyl (2-Methylpyrrolin-2-yl)phosphonate (7)

A solution of *N*-methylmorpholine *N*-oxide (NMO, 1.6 g, 13.60 mmol) in anhyd MeCN (12 mL) was added under inert atmosphere at r.t. to a solution of **3** (1.0 g, 4.51 mmol), powdered 4 Å molecular sieves (2.1 g) and tetrapropylammonium perruthenate (TPAP, 31.8 mg, 0.090 mmol) in anhyd MeCN (13 mL). The mixture was stirred for 4 h at r.t. The mixture was filtered over Celite and MeCN was removed under reduced pressure. After chromatography (silica gel, EtOH/CH_2Cl_2, 1:9) **7** was obtained as a pale yellow oil (870 mg, 85%). After distillation (57°C, p 0.02 mbar) a colorless oil was obtained (420 mg, 42%).

IR (KBr): ν = 2976 (m), 1664 (s), 1246 (m), 1052 (s), 1024 cm^{-1} (s).

^{31}P NMR ($CDCl_3$): δ = 26.72.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.33 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.34 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.50 (d, $^3J_{H,P}$ = 13.34 Hz, 3 H), 1.40–1.70 (m, 1 H), 2.30–2.60 (m, 1 H), 2.60–2.80 (m, 2 H), 4.10–4.30 (m, 4 H), 7.65 (d, $^4J_{H,P}$ = 4.0 Hz, 1 H).

^{13}C NMR (200 MHz, C_6D_6): δ = 16.52 (d, $^3J_{C,P}$ = 5.8 Hz), 16.58 (d, $^3J_{C,P}$ = 5.7 Hz), 23.60, 30.40 (d, $^3J_{C,P}$ = 4.4 Hz), 37.68, 62.37 (d, $^2J_{C,P}$ = 7.24 Hz), 62.69 (d, $^2J_{C,P}$ = 7.3 Hz), 75.97 (d, $^1J_{C,P}$ = 159.2 Hz), 168.56 (d, $^3J_{C,P}$ = 14.3 Hz).

Anal. calcd for $C_9H_{18}NO_3P$•5% H_2O (230.7): C 49.11, H 8.29, N 6.36; found C 48.98, H 8.89, N 6.18.

Diethyl (2-Methyl-6-oxa-1-azabicyclo[3.1.0]hex-2-yl)phosphonate (8)

A solution of *m*-CPBA (Jansen 72%, 387 mg, 2.31 mmol) in Et_2O (10 mL) was added dropwise over 15 min to a solution of pyrroline **7** (530 mg, 2.3 mmol) in Et_2O (10 mL) at 0 °C. The mixture was stirred for 30 min and then an aq solution of K_2CO_3 (15 mL) was added to the mixture and stirred for 10 min. The organic layer was washed with a brine (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a yellow oil. After chromatography (silica gel, EtOH/CH_2Cl_2, 1:9) **8** was obtained as a pale yellow oil (324 mg, 57%) (diastereoisomers were not identified).

IR (KBr): ν = 2983 (s), 1456 (m), 1246 (s), 1052 (s), 1024 (s) cm^{-1}.

^{31}P NMR ($CDCl_3$): δ = 24.17.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.36 (t, $^3J_{H,H}$ = 7.4 Hz, 6 H), 1.30–1.50 (m, 1 H), 1.54 (d, $^3J_{H,P}$ = 15.1 Hz, 3 H), 2.00–2.50 (m, 3 H), 4.10-4.30 (m, 4 H), 4.64 (s, 1 H).

^{13}C NMR (200 MHz, C_6D_6): δ = 16.40 (d, $^3J_{C,P}$ = 5.9 Hz), 19.81, 28.04, 28.46, 62.64 (d, $^2J_{C,P}$ = 7.9 Hz), 62.97 (d, $^2J_{C,P}$ = 7.3 Hz), 69.25 (d, $^1J_{C,P}$ = 150.6 Hz), 82.79.

Anal. calcd for $C_9H_{18}NO_4P$ (235.2): C 45.96, H 7.71, N 5.95; found C 45.43, H 7.78, N 5.68.

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