Nitroalkanes as nucleophiles in a self-catalytic Michael reaction

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Received (in Cambridge, UK) 23rd September 2002, Accepted 15th October 2002
First published as an Advance Article on the web 13th November 2002

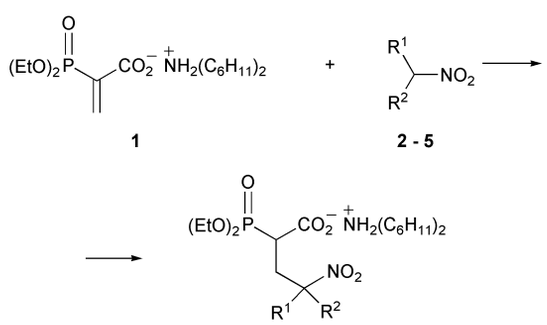
A simple, effective procedure for the preparation of 4-nitroalkanoates **6**–**9** by the Michael reaction of nitroalkanes **2**–**5** with the acrylate **1** is described. The primary nitro adduct **6** undergoes isomerization to hydroxamic acid **10** while heated in boiling nitromethane. Consecutive reactions of the latter compound lead to the formation of *N*-hydroxysuccinimide **11** and its *N*-ethoxy derivative **12**. The spontaneous Nef reaction of the mother 4-nitrobutanoic acid **15** gives *N*-hydroxysuccinimide **14**. The analogous reaction of secondary nitroalkanoic acids **16** and **17** provides 4-oxoalkanoic acids **18** and **19**, respectively. Intramolecular participation by the carboxylic acid group in the Nef reaction is proposed.

Introduction

Aliphatic nitro compounds are of great importance as synthetic intermediates. It has been recognized for many years that highly stabilized anions of nitroalkanes serve as synthetic equivalents of acyl anion, α-carbonyl cation and alkyl anion synthons.[1–4] Michael addition of primary and secondary nitroalkanes to electron-deficient alkenes followed by the functional interconversion of the nitro group in the resulting adducts emerged as an important and practical method for the construction both the carbon–carbon bond and one or more carbon–heteroatom bonds.[3,5] Over the past two decades these additions resulted in development of efficient methodologies for the synthesis of 1,4-diketones, 4-oxoalkanoates and various heterocyclic compounds.[6,7]

Recently we have demonstrated that the Michael additions of various C- and N- nucleophiles to dicyclohexylammonium 2-(diethoxyphosphoryl)acrylate **1** proceed without any external catalyst.[8,9] Furthermore, we have found that this type of self-catalysis is particularly useful for C-alkylation of electron-rich hydroxyarenes[10] and indoles.[11] In continuation of our research program we were interested in exploring the scope of the self-catalytic Michael reactions of nitroalkanes. Nitromethane **2**, nitroethane **3**, 1-nitropropane **4** and 2-nitropropane **5** were selected as model pronucleophiles (Scheme 1).

This approach seemed to be well suited to the generation and further elaboration of functionalized 4-nitroalkanoic acids.[12] It is important to note that a carboxylic acid group appropriately located in a primary or secondary nitroalkane molecule may participate in the Nef reaction.[13,14] The literature contains two examples of such intramolecular catalysis. Interactions of a neighboring carboxylic acid group in the hydrolysis of (*o*-nitromethyl)benzoic acids led to the formation of *N*-hydroxyphtalimides.[15] Moreover, the presence of a neighboring carboxylate group caused an accelerated Nef reaction with 4-nitropentanoic acid to give levulinic acid.[16]



2,6 $R^1=R^2=H$
3,7 $R^1=H$, $R^2=CH_3$
4,8 $R^1=H$, $R^2=CH_2CH_3$
5,9 $R^1=R^2=CH_3$

Scheme 1

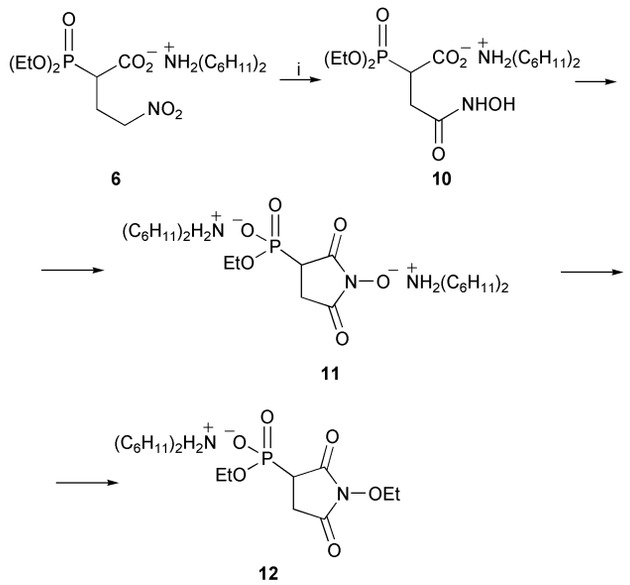
Results and discussion

At the outset of our studies we examined the addition of nitromethane **2** to the acrylate **1** in previously optimized conditions.[8] However, treatment of the acrylate **1** with nitromethane **2** used in an equimolar amount of benzene at room temperature has not led to the desired product **6**. ^{31}P NMR analysis of the crude reaction mixture revealed that within a few hours the unreacted acrylate **1** was accompanied by a complex mixture of unidentified organophosphorus products. After screening a variety of reaction conditions it was found that considerable excess of nitromethane **2** had to be used to perform effectively the expected reaction. Using nitromethane as both the reagent and the solvent in the reaction with **1** resulted in the formation of 4-nitrobutanoate **6** in 65% yield within 3 h.

Next we focused on converting nitroethane **3** to the target 4-nitropentanoate **7**. The adduct **7** was obtained in 70% yield as a 3:1 mixture of diastereoisomers by reacting the acrylate **1** with an excess of nitroethane **3** (5 equiv.) in benzene at room temperature for twelve hours. This procedure was also applicable to the synthesis of 4-nitrohexanoate **8** from 1-nitropropane **4**. The adduct **8** was formed as a 3:1 mixture of diastereoisomers in 68% yield. Surprisingly, when we used equimolar amount of 2-nitropropane **5** in the addition to the acrylate **1** we observed a conjugate addition yielding within two days the adduct **9** in 67% yield.

Our efforts to optimize the synthesis of 4-nitrobutanoate **6** led to remarkable observation that this particular compound is thermally unstable and undergoes consecutive transformations

 DOI: 10.1039/b209302m



Scheme 2 *Reagents and conditions:* i, CH_3NO_2, 100 °C, 80 min–30 h.

while heated in boiling nitromethane to form **10**, **11** and **12** (Scheme 2). All the results obtained led us to the conclusion that the above reaction sequence was initiated by an isomerisation of **6** giving the hydroxamic acid **10** as shown in Scheme 2.

Optimum reaction conditions were defined as heating the adduct **6** for 80 min. After that time it was almost fully converted into **10**. Only a small amount (~5%, ^{31}P NMR) of **11** being a further consecutive product has formed. The salt **10** was isolated as a crystalline solid. Heating of the adduct **6** in boiling nitromethane for 10 h gave the 3-(monoethoxyphosphoryl)-succinimide **11** accompanied by its *N*-ethoxy derivative **12**. The salt **11** crystallized out directly from the nitromethane solution. Spectroscopic studies were not useful in determining the structure of **11**. Its complete structure was determined by single crystal X-ray analysis (Fig. 1). The last step of the reaction

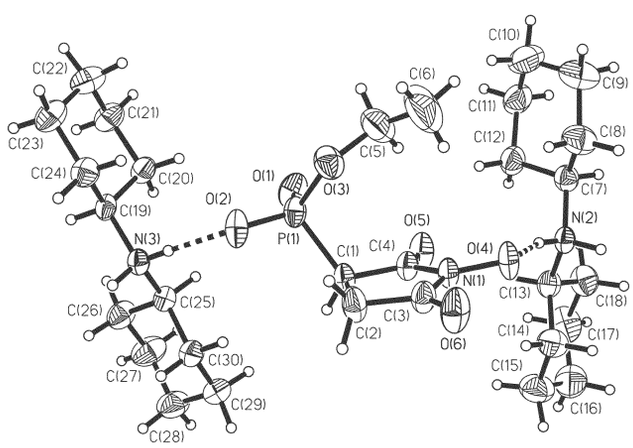
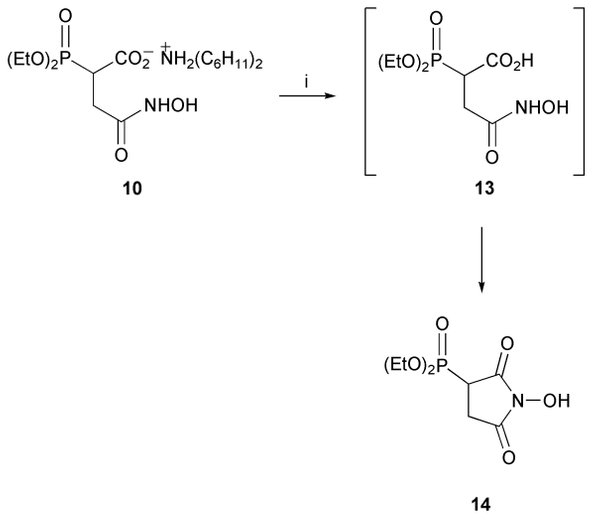


Fig. 1 The molecular structure of the succinimide **11**. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by circles of an arbitrary radius. Hydrogen bonds are shown with dashed lines. The accidentally co-crystallized propan-2-ol molecule which occupies the void in the crystal is omitted for clarity.

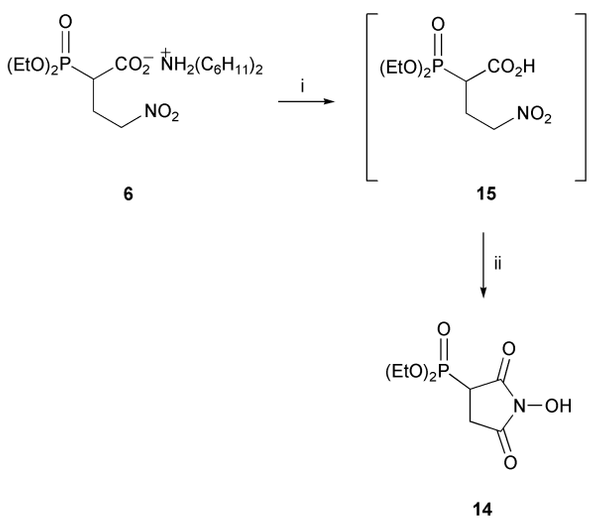
sequence involves *O*-alkylation of the *N*-hydroxysuccinimide **11** leading to the *N*-ethoxysuccinimide **12**. Thus, extended heating of Michael adduct **6** in boiling nitromethane resulted in the formation of mixture containing *N*-hydroxysuccinimide **11** and *N*-ethoxysuccinimide **12** in a ratio of 1:2. Both products were isolated and separated by fractional crystallization.

In an independent experiment we confirmed the crucial role of the *N*-hydroxysuccinamate **10** in the reaction sequence shown in Scheme 2. The *N*-hydroxysuccinamate **10** heated in boiling nitromethane for 8 h underwent conversion into **11**.

We reasoned that 2-diethoxyphosphoryl *N*-hydroxysuccinimide **14** might be readily accessible from both *N*-hydroxysuccinamic acid **13** (Scheme 3) and 4-nitrobutanoic acid **15** (Scheme 4). Indeed, ion-exchange chromatography of the salt



Scheme 3 *Reagents and conditions:* i, Dowex 50 W, water–acetone.

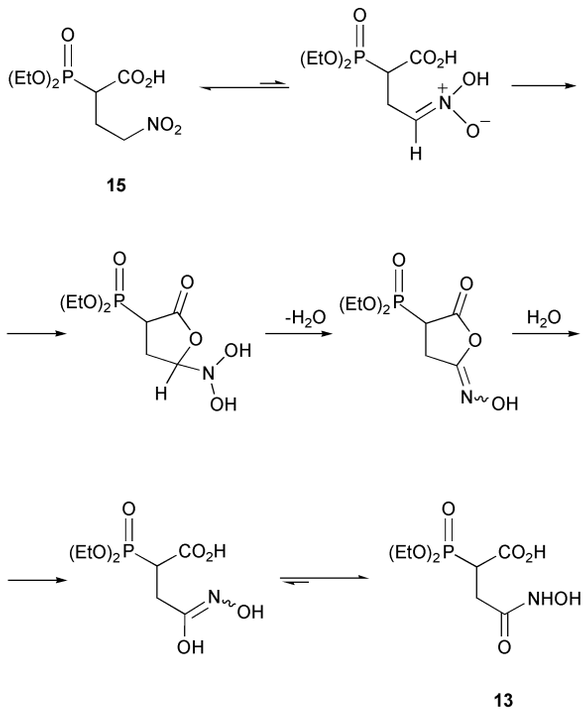


Scheme 4 *Reagents and conditions:* i, Dowex 50 W, water–acetone; ii, H_2O, 100 °C, 2 h; 84%.

10 resulted in the direct formation of *N*-hydroxysuccinimide **14**. It is noteworthy that the diacid **13** being an intermediate in this reaction loses a water molecule to give a five-membered pyrrolidine ring. The structure of **14** was unambiguously confirmed by ^{15}N NMR spectroscopy. On the other hand, the ion-exchange chromatography of the salt **6** gave a 20:1 mixture of 4-nitrobutanoic acid **15** and *N*-hydroxyimide **14** (^{31}P NMR). The 4-nitrobutanoic acid **15** was completely converted into the *N*-hydroxyimide **14** by simple heating of the resulting mixture in boiling water for 2 h.

Careful analysis of the experimental data collected leads to the conclusion that the formation of **10**, **11** and **12** as well as **14** from **6** is directly connected with the ability of the carboxylic acid group to participate in the intramolecular Nef reaction of 2-diethoxyphosphoryl-4-nitrobutanoic acid **15**. The plausible mechanism for isomerisation of 4-nitrobutanoic acid **15** into *N*-hydroxysuccinamic acid **13** is shown in Scheme 5.

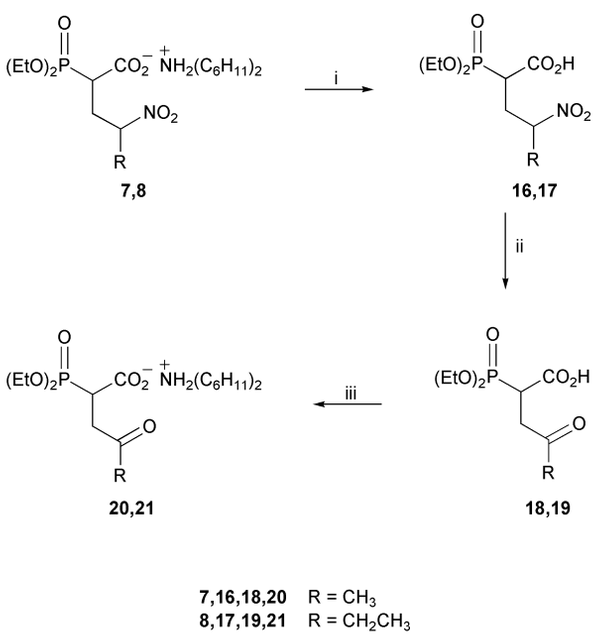
Free diacid **13** loses a water molecule to give the mixed anhydride **14**. Further transformations of the phosphonate **14** are controlled by the reaction conditions. One can assume that



Scheme 5

the diethyl phosphonate **14** and dicyclohexyloamine are participating intermediates in the decomposition of **6** performed in boiling nitromethane. Thermally promoted monodealkylation of dialkyl phosphonates by secondary amines is the known reaction.[17] Dealkylation of the phosphonate **14** with dicyclohexylamine yields the *O*-monoethyl phosphonate **11**. It was interesting to observe that *N*-ethyldicyclohexylamine generated in this step is able to selectively alkylate the product **11** to give the *N*-ethoxysuccinimide **12**.

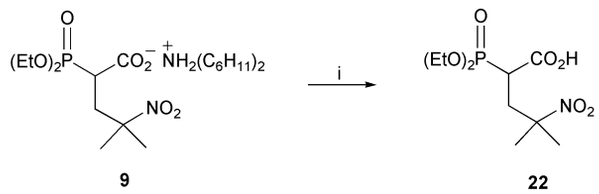
With these results in hand we turned our attention to the Nef reaction of the secondary nitroalkanoic acids **16** and **17** (Scheme 6).



Scheme 6 *Reagents and conditions:* i, Dowex 50 W, water–acetone; ii, H_2O, rt; iii, $(C_6H_{11})_2$ NH (1 equiv.); 73% (**20**), 72% (**21**).

First, dicyclohexylamonium alkanoates **7** and **8** were converted into free 4-nitroalkanoic acids **16** and **17**. Interestingly, it was observed that ion-exchange chromatography of the salts **7** and **8** did not afford the corresponding carboxylic acids alone. In both cases mixtures of diastereoisomeric nitroalkanoic acids **16** and **17** were accompanied by 4-oxoalkanoic acids **18** and **19**, respectively. Both reactions were allowed to continue at ambient temperature. Under these conditions oxoacids **18** and **19** were effectively obtained as the sole products. The Nef reaction of 4-nitrohexanoic acid **17** was completed within two days. In the case of 4-nitropentanoic acid **16** the reaction proceeded much slower and the formation of 4-oxopentanoic acid **18** was terminated within two weeks. The oxoacids **18** and **19** were then isolated as dicyclohexylammonium salts **20** and **21**, respectively in good overall yields.

According to the expectations the ion-exchange chromatography of the tertiary nitropentanoate **9** provided the corresponding nitropentanoic acid **22** in nearly quantitative yield (Scheme 7).



Scheme 7 *Reagents and conditions:* i, Dowex 50 W, water–acetone.

In summary, we have succeeded in performing self-catalyzed Michael reactions of selected nitroalkanes with dicyclohexylammonium 2-(diethoxyphosphoryl)acrylate **1**. We have also demonstrated the occurrence of intramolecular catalysis by the carboxylic acid group in the Nef reaction of the resulting primary and secondary 4-nitroalkanoates.

Experimental

NMR spectra were recorded on a Bruker DPX 250 instrument at 250.13 MHz for ^{1}H and 62.9 MHz for ^{13}C and 101.3 MHz for ^{31}P NMR, respectively using tetramethylsilane as internal and 85% H_3PO_4 as external standard. The multiplicity of carbons were determined by DEPT experiments. IR spectra were measured on a Specord M80 (Zeiss) instrument. FAB/MS were recorded on a PO Electron Modell MI 1201 E mass spectrometer equipped with FAB ion source (thioglycerol matrix). Elemental analyses were performed on a Perkin–Elmer PE 2400 analyzer. Melting points were determined in open capillaries and are uncorrected. Dicyclohexylammonium 2-(diethoxyphosphoryl)acrylate (**1**) was prepared according to the literature procedure.[8]

Dicyclohexylammonium 2-diethoxyphosphoryl-4-nitrobutanoate 6

A solution of acrylate **1** (3.89 g, 10 mmol) in nitromethane (25 ml) was left for 3 hours at room temperature. The solvent was evaporated off. The solid residue was suspended in diethyl ether and the crystals were collected by filtration to afford the crude product. Recrystallization of the solid from methylene chloride–acetone afforded the butanoate **6** as a white powder (2.95 g, 65%), mp 127–128 °C; δ_P ($CDCl_3$) 26.69; δ_H ($CDCl_3$) 1.14–1.35 (m, 6H), 1.31 (t, 3H, *J* 7.0, CH_3CH_2O), 1.32 (t, 3H, *J* 7.0, CH_3CH_2O), 1.48 (m, 4H), 1.66 (m, 2H), 1.80 (m, 4H), 2.02 (m, 4H), 2.52 (m, 2H), 2.85 (ddd, *J* 5.0, *J* 9.5, $^2J_{HP}$ 23.5, CHP), 3.02 (m, 2H, 2 × CHN), 4.15 (m, 4H, 2 × CH_2O), 4.55 (t, 2H, *J* 7.0, CH_2NO_2); δ_C ($CDCl_3$) 16.43 (d, $^3J_{CP}$ 6.0, 2 × CH_3), 24.81 (s, 4 × CH_2), 25.19 (s, 2 × CH_2), 26.03 (d, $^2J_{CP}$ 3.7, CH_2), 29.06 (s, 4 × CH_2), 44.94 (d, $^1J_{CP}$ 129.3, CH), 52.65 (s, 2 × CHN), 62.07 (d, $^2J_{CP}$ 6.0, CH_2O), 62.17 (d, $^2J_{CP}$ 6.0, CH_2O), 75.97 (d, $^3J_{CP}$ 16.3, CH_2NO_2), 170.35 (d, $^2J_{CP}$ 4.4, COO^-); ν_{max}(KBr)/cm^{-1} 1630 (COO^-), 1230 (P=O); FAB/MS MH^+ 451

(Found: C, 53.17; H, 8.59. $C_{20}H_{39}N_2O_7P$ requires C, 53.32; H, 8.72%).

Dicyclohexylammonium 2-diethoxyphosphoryl-4-nitropentanoate 7

To a solution of acrylate **1** (3.89 g, 10 mmol) in benzene (20 ml) was added nitroethane (4 ml) and the reaction mixture was left for 12 hours at room temperature. The solvent was evaporated off. The solid residue was suspended in diethyl ether and the crystals were collected by filtration to afford the crude product. Recrystallization of the solid from methylene chloride–acetone afforded the pentanoate **7** as a white powder (3.25 g, 70%), $\delta_P(CDCl_3)$ 26.70, 27.10 (3:1), $\delta_H(CDCl_3)$ 1.15–1.66 (m, 12H), 1.31 (m, 6H, *J* 7.0, 2 × *CH*$_3$CH$_2$O), 1.55 (d, 3H, *J* 6.8, CH_3 minor), 1.58 (d, 3H, *J* 6.8, CH_3 major), 1.81 (m, 4H), 2.04 (m, 4H), 2.36 (m, 2H), 2.71 (m, 1H), 3.04 (m, 2H, 2 × CHN), 4.12 (m, 4H, 2 × CH_2O), 4.81 (m, 1H, $CHNO_2$); ν_{max}(KBr)/cm^{-1} 1624 (COO^-), 1235 (P=O); FAB/MS MH^+ 465 (Found: C, 54.13; H, 8.78. $C_{21}H_{41}N_2O_7P$ requires C, 54.29; H, 8.89%).

Dicyclohexylammonium 2-diethoxyphosphoryl-4-nitrohexanoate 8

Compound **8** was prepared in the same manner to that described above. White solid (3.25 g, 68%); $\delta_P(CDCl_3)$ 26.38, 26.89 (3:1); FAB/MS MH^+ 479 (Found: C, 55.06; H, 8.90. $C_{22}H_{43}N_2O_7P$ requires C, 55.21; H, 9.05%).

Dicyclohexylammonium 2-diethoxyphosphoryl-4-methyl-4-nitropentanoate 9

To a solution of acrylate **1** (3.89 g, 10 mmol) in benzene (15 ml) was added 2-nitropropane (0.94 g, 10.5 mmol) and the reaction mixture was left for 2 days at room temperature. The solvent was evaporated off. The solid residue was suspended in diethyl ether and the crystals were collected by filtration to afford the crude product. Recrystallization of the solid from methylene chloride–acetone afforded the pentanoate **9** as a white solid (3.2 g, 67%), mp 159–160 °C; $\delta_P(CDCl_3)$ 27.33; $\delta_H(CDCl_3)$ 1.15–1.65 (m, 12H), 1.30 (t, 3H, *J* 7.0, *CH*$_3$CH$_2$O), 1.31 (t, 3H, *J* 7.0, *CH*$_3$CH$_2$O), 1.61 (s, 6H, 2 × CH_3), 1.80 (m, 4H), 2.02 (m, 4H), 2.45 (m, 1H), 2.73 (m, 2H), 3.04 (m, 2H, 2 × CHN), 4.10 (m, 4H, 2 × CH_2O); δ_C ($CDCl_3$) 16.42 (d, $^3J_{CP}$ 6.0, CH_3), 16.47 (d, $^3J_{CP}$ 6.0, CH_3), 24.56 (s, CH_3), 24.89 (s, 4 × CH_2), 25.24 (s, CH_3), 26.71 (s, 2 × CH_2), 28.95 (s, 4 × CH_2), 38.47 (d, $^2J_{CP}$ 3.0, CH_2), 44.83 (d,$^1J_{CP}$ 125.1, CH), 52.43 (s, 2 × CHN), 62.04 (d, $^2J_{CP}$ 6.8, CH_2O), 62.15 (d, $^2J_{CP}$ 6.8, CH_2O), 88.52 (d, $^3J_{CP}$ 16.8, C), 171.22 (d, $^2J_{CP}$ 5.0, COO); (ν_{max}(KBr)/cm^{-1} 1640 (COO^-) 1248 (P=O); FAB/MS MH^+ 479 (Found: C, 55.11; H, 8.94. $C_{22}H_{43}N_2O_7P$ requires C, 55.21; H, 9.05%).

Dicyclohexylammonium 2-diethoxyphosphoryl-*N*-hydroxysuccinamate 10

A solution of nitrobutanoate **6** (2.25 g, 5 mmol) in nitromethane (20 ml) was heated at reflux for 80 minutes. The solvent was evaporated off. The solid residue was suspended in diethyl ether–acetone (10:1) and the crystals were collected by filtration to give the crude product. Recrystallization of the solid from methylene chloride–acetone afforded the salt **10** as a white powder (1.35 g, 60%), mp 149–150 °C; $\delta_P(CDCl_3)$ 22.63; $\delta_H(CDCl_3)$ 1.15–1.65 (m, 12H), 1.33 (t, 3H, *J* 7.0, *CH*$_3$CH$_2$O), 1.34, (t, 3H, *J* 7.0, *CH*$_3$CH$_2$O), 1.75 (m, 4H), 2.01 (m, 2H), 2.79 (m, 2H), 3.01 (m, 3H), 4.16 (m, 4H, 2 × CH_2O); δ_C ($CDCl_3$) 16.41 (d, $^3J_{CP}$ 5.3, CH_3), 16.50 (d, $^3J_{PC}$ 5.3, CH_3), 25.02 (s, 4 × CH_2), 25.30 (s, 2 × CH_2), 27.68 (d, $^2J_{CP}$ 3.5, CH_2), 29.55 (s, 4 × CH_2), 36.35 (d,$^1J_{CP}$ 144.6, CHP), 52.56 (s, 2 × CHN), 62.72 (d, $^2J_{CP}$ 6.5, CH_2), 63.14 (d, $^2J_{CP}$ 6.5, CH_2), 170.20 (d, J_{CP} 6.0), 173.54 (d, J_{CP} 5.0); ν_{max}(KBr)/cm^{-1} 1735 (C=O), 1248 (P=O); FAB/MS MH^+ 451 (Found: C, 53.19; H, 8.59. $C_{20}H_{39}N_2O_7P$ requires C, 53.32; H, 8.72%).

Bis(dicyclohexylammonium) *O*-ethyl 3-(1-hydroxysuccinimidyl) phosphonate 11

A solution of nitrobutanoate **6** (2.25 g, 5 mmol) in nitromethane (20 ml) was heated at reflux for 10 h. The resulting mixture was left for crystallization at room temperature. The crystals were collected by filtration, washed with diethyl ether to afford the crude product. Recrystallization of the solid from nitromethane afforded the phosphonate **11** as a white powder (0.63 g, 43% mp 181–182 °C); $\delta_P(CDCl_3)$ 10.76 or $\delta_P(CD_3OD)$ 15.01; $\delta_H(CDCl_3)$ 1.12–1.45 (m, 20H), 1.28 (t, 3H, *J* 7.0, *CH*$_3$CH$_2$O), 1.65 (m, 4H), 1.79 (m, 8H), 2.01 (m, 8H), 2.72–3.18 (m, 7H, CH_2, CH, 4 × CHN), 4.06 (dq, 2H, $^3J = {}^3J_{HP}$ 7.0, CH_2O; $\delta_C(CD_3OD)$ 17.13 (d, $^3J_{CP}$ 6.5, CH_3), 25.56 (s, 8 × CH_2), 26.14 (s, 4 × CH_2), 29.76 (d, $^2J_{CP}$ 3.5, CH_2), 30.52 (s, 8 × CH_2), 38.50 (d, $^1J_{CP}$ 130.2, CH), 54.16 (s, 4 × CHN), 61.85 (d, $^2J_{CP}$ 6.0, CH_2), 174.62 (d, J_{CP} 5.5, CO), 176.28 (d, J_{CP} 4.5, CO); ν_{max}(KBr)/cm^{-1} 1724 (C=O), 1216 (P=O); FAB/MS MH^+ 586 (Found: C, 61.32; H, 9.37. $C_{30}H_{56}N_3O_6P$ requires C, 61.51; H, 9.63%).

Dicyclohexylammonium *O*-ethyl 3-(1-ethoxysuccinimidyl) phosphonate 12

A solution of nitrobutanoate **6** (2.25 g, 5 mmol) in nitromethane (20 ml) was heated at reflux for 30 h. The solvent was evaporated off. The solid residue was suspended in acetone–diethyl ether (1:10) and collected by filtration. Recrystallization of the solid (1.47 g) from methanol–acetone gave the phosphonate **11** (0.22 g). The mother liquor was partially evaporated to give a further crop of the phosphonate **11** (0.1 g). The filtrate was concentrated and the oily residue was crystallized from acetone to give the phosphonate **12** as a white solid (0.92 g). ^{31}P NMR analysis revealed that the phosphonate **12** is contaminated with 4% of the phosphonate **11**. $\delta_P(CDCl_3)$ 10.75 or $\delta_P(CD_3OD)$ 13.62; $\delta_H(CDCl_3)$ 1.25 (t, 3H, *J* 7.0, *CH*$_3$CH$_2$O), 1.34 (t, 3H, *J* 7.0, *CH*$_3$CH$_2$O), 1.15–1.67 (m, 12H), 1.80 (m, 4H), 2.01 (m, 4H), 2.71–3.18 (m, 5H, CH_2, CH, 2 × CHN), 3.99 (dq, 2H, ^3J=$^3J_{HP}$ 7.0, CH_2O), 4.14 (q, 2H, *J* 7.0, CH_2O); $\delta_C(CD_3OD)$ 13.69 (s, CH_3), 17.00 (d, $^3J_{CP}$ 6.5, CH_3), 25.41 (s, 4 × CH_2), 26.02 (s, 2 × CH_2), 30.04 (d, $^2J_{CP}$ 3.5, CH_2), 30.41 (s, 4 × CH_2), 38.92 (d, $^1J_{CP}$ 125.9, CH), 54.32 (s, 2 × CHN), 62.01 (d, $^2J_{CP}$ 6.0, CH_2), 73.56 (s, CH_2), 171.66 (d, J_{CP} 6.9, CO), 173.19 (d, J_{CP} 3.0, CO), ν_{max}(KBr)/cm^{-1} 1724 (C=O), 1224 (P=O); FAB/MS MH^+ 433.

3-Diethoxyphosphoryl-1-hydroxysuccinimide 14

Method A:

Ion-exchange chromatography of the phosphonate **10** (2.25 g, 5 mmol) was performed on a glass column packed with Dowex 50 W using water–acetone (1:1) as eluent. The eluent was evaporated to give an oily residue. The residue was dissolved in acetone and after evaporation of the solvent left for crystallization. The solid was suspended in diethyl ether, collected by filtration and air dried to give the succinimide **14** as a white solid (1.16 g, 92%), mp 101–102 °C; $\delta_P(CDCl_3)$ 20.50; $\delta^{15}{}_N$ (CH_3NO_2) −166.28 (s); $\delta_H(CDCl_3)$ 1.35 (t, 3H, *J* 7.0, *CH*$_3$CH$_2$O), 1.37 (t, 3H, *J* 7.0, *CH*$_3$CH$_2$O), 2.93 (m, 2H), 3.35 (dt, *J* 7.0, $^2J_{HP}$ 24.5, CHP), 4.25 (m, 4H, 2 × CH_2O); $\delta_C(CDCl_3)$ 16.35 (d, $^3J_{CP}$ 4.6, CH_3), 16.43 (d, $^3J_{CP}$ 4.6, CH_3), 25.78 (d, $^2J_{CP}$ 3.8, CH_2), 34.48 (d, $^1J_{CP}$ 145.0, CH), 64.18 (d, $^2J_{CP}$ 6.8, CH_2), 64.78 (d, $^2J_{CP}$ 6.8, CH_2), 165.77 (d, J_{CP} 5.0, CO), 168.67 (d, J_{CP} 5.8, CO), ν_{max}(KBr)/cm^{-1} 1720 (C=O), 1216 (P=O); FAB/MS MH^+ 252 (Found: C, 38.11; H, 5.49. $C_8H_{14}NO_6P$ requires C, 38.25; H, 5.61%).

Method B:

Ion-exchange chromatography of nitrobutanoate **6** (2.25 g, 5 mmol) was performed in the same manner to that described above. The eluent was evaporated to afford an oily residue. ^{31}P NMR revealed the formation of **15** and **14** in a ratio 20:1,

δ_P(acetone-d_6), 22.8 and 21.5, respectively. The nitrobutanoic acid **15** was identified on the basis of ^{1}H NMR: δ_H(acetone-d_6) 1.31 (t, 3H *J* 7.0 CH_3CH_2O), 1.32 (t, 3H *J* 7.0 CH_3CH_2O), 2.53 (m, 2H), 3.21 (ddd, 1H, *J* 7.5, *J* 8.5, $^2J_{HP}$ 24.5, CHP), 4.21 (m, 4H, 2 × CH_2O), 4.68 (m, 2H, CH_2NO_2). A solution of the product in water was heated at reflux for 2 h to give the succinimide **14**.

Dicyclohexylammonium 2-diethoxyphosphoryl-4-oxopentanoate 20

Ion-exchange chromatography of nitropentanoate **7** (2.32 g, 5 mmol) was performed according to the standard procedure. ^{31}P NMR analysis of the crude product revealed that the 4-nitropentanoic acid **16**: $\delta_P(D_2O)$ 24.40 and 24.61 (2:1) was accompanied by 6% of the 4-oxopentanoic acid **18**: $\delta_p(D_2O)$ 25.23. The nitropentanoic acid **16** was identified on the basis of ^{1}H NMR analysis: $\delta_H(D_2O)$ 1.32 (t, 3H, *J* 7.0 CH_3CH_2O), 1.33 (t, 3H, *J* 7.0 CH_3CH_2O), 1.56 (d, 3H, *J* 6.5, CH_3 minor) 1.58 (d, 3H, *J* 6.5, CH_3 major), 2.40 (m, 2H), 3.16 (ddd, 1H, *J* 4.5, *J* 10.0, $^2J_{HP}$ 25.0, CHP major), 3.25 (ddd, 1H, *J* 4.5, *J* 9.5, $^2J_{HP}$ 27.0, CHP minor), 4.20 (m, 4H, 2 × CH_2O), 4.72 (m, 1H, $CHNO_2$). The solution of the product in water was kept for two weeks at room temperature. After reaction was complete the solvent was evaporated off . The oily residue was dissolved in acetone and dicyclohexylamine (0.9 g, 5 mmol) was added. The solvent was evaporated off. The solid residue was suspended in diethyl ether and the crystals were collected by filtration to afford the crude product **20**. Recrystallization of the solid from methylene chloride–acetone afforded the pentanoate **20** as a white solid (1.58 g, 73%), mp 105–106 °C. $\delta_P(CDCl_3)$ 28.71; $\delta_H(CDCl_3)$ 1.17–1.35 (m, 6H), 1.29 (t, 3H, *J* 7.0, CH_3CH_2O), 1.30 (t, 3H, *J* 7.0, CH_3CH_2O), 1.48 (m, 4H), 1.63 (m, 2H), 1.78 (m, 4H), 2.03 (m, 4H), 2.16 (s, 3H, CH_3), 2.69 (ddd, 1H, *J* 3.0, J_{AB} 17.0, $^3J_{HP}$ 13.7, CH_A), 2.97 (m, 2H, 2 × CHN), 3.24 (ddd, 1H, *J* 10.5, J_{AB} 17.0, $^3J_{HP}$ 7.5, CH_B), 3.37 (ddd, 1H, *J* 3.0, *J* 10.5, $^2J_{HP}$ 24.0, CHP), 4.15 (m, 4H, 2 × CH_2O); $\delta_C(CDCl_3)$ 16.06 (d, $^3J_{CP}$ 6.0, 2 × CH_3), 24.53 (s, 4 × CH_2), 24.78 (s, 2 × CH_2), 28.45 (s, 4 × CH_2), 29.63 (d, $^4J_{CP}$ 0.8, CH_3), 41.21 (d, $^2J_{CP}$ 2.5, CH_2), 42.51 (d, $^1J_{CP}$ 129.0, CH), 52.14 (s, 2 × CHN), 61.39 (d, $^2J_{CP}$ 6.5, CH_2), 61.90 (d, $^2J_{CP}$ 6.5, CH_2), 170.30 (d, $^2J_{CP}$ 4.0, COO^-), 205.75 (d, $^3J_{CP}$ 16.3, CO); ν_{max}(KBr)/cm^{-1} 1720 (C=O), 1610 (COO^-), 1222 (P=O); FAB/MS MH^+ 434 (Found: C, 58.07; H, 9.23. $C_{21}H_{40}NO_6P$ requires C, 58.18; H, 9.30%).

2-Diethoxyphosphoryl-4-oxopentanoic acid 18

Ion exchange chromatography of oxopentanoate **20** afforded the oxopentanoic acid **18**.

Colorless oil (95%); δ_P(acetone-d_6) 23.41; δ_H(acetone-d_6) 1.28 (dt, 3H, *J* 7.0, $^4J_{HP}$ 0.6, CH_3CH_2O), 1.30 (dt, 3H, *J* 7.0, $^4J_{HP}$ 0.6, CH_3CH_2O), 2.17 (s, 3H, CH_3), 2.88 (ddd, 1H, *J* 3.0, J_{AB} 18.1, $^3J_{HP}$, 9.3, CH_A), 3.17 (ddd, 1H, *J* 11.0, J_{AB} 18.1, $^3J_{HP}$ 6.2, CH_B), 3.40 (ddd, 1H, *J* 3.0, *J* 11.0, $^2J_{HP}$ 24.0, CHP), 4.13 (m, 4H, 2 × CH_2O); $\delta_C(D_2O)$ 15.98 (d, $^3J_{CP}$ 2.6, CH_3), 16.08 (d, $^3J_{CP}$ 2.6, CH_3), 29.37 (s, CH_3), 39.59 (d, $^1J_{CP}$ 132.5, CH), 39.84 (d, $^2J_{CP}$ 2.5, CH_2), 63.29 (d, $^2J_{CP}$ 6.0, CH_2), 63.39 (d, $^2J_{CP}$ 6.0, CH_2), 169.93 (d, $^2J_{CP}$ 6.0, COOH), 204.90 (d, $^3J_{CP}$ 15.0, CO), ν_{max}(film)/cm^{-1} 1720 (C=O), 1212(P=O).

2-Diethoxyphosphoryl-4-oxohexanoic acid 19

Compound **19** was obtained in the same manner to that described above.

Colorless oil (78%) δ_P(acetone-d_6) 23.57; δ_H(acetone-d_6) 0.98 (t, 3H, *J* 7.2, CH_3), 1.28 (t, 3H, *J* 7.0, CH_3CH_2O), 1.30 (t, 3H, *J* 7.0, CH_3CH_2O), 2.52 (m, 2H, CH_2), 2.84 (ddd, 1H, *J* 3.0, J_{AB} 18.0, $^3J_{HP}$, 9.5, CH_A), 3.14 (ddd, 1H, *J* 11.0, J_{AB} 18.0, $^3J_{HP}$, 7.0, CH_B), 3.45 (ddd, 1H, *J* 3.0, *J* 11.0, $^2J_{HP}$, 24.0, CHP), 4.15 (m, 4H, 2 × CH_2O); δ_C 7.82 (s, CH_3), 16.44 (d, $^3J_{CP}$ 6.0, 2 × CH_3), 35.62 (s, CH_2), 39.22 (d, $^2J_{CP}$ 2.0, CH_2), 40.35 (d, $^1J_{CP}$ 132.0, CH), 63.70 (d, $^2J_{CP}$ 7.0, CH_2), 63.81 (d, $^2J_{CP}$ 7.0, CH_2), 169.50 (d, $^2J_{CP}$ 4.5, COOH), 207.75 (d, $^3J_{CP}$ 15.0, CO); ν_{max}(film)/cm^{-1} 1720 (C=O), 1216 (P=O).

2-Diethoxyphosphoryl-4-methyl-4-nitropentanoic acid 22

Colorless oil (96%); δ_P(acetone-d_6) 22.33; δ_H(acetone-d_6) 1.30 (t, 3H, *J* 7.0, CH_3CH_2O), 1.31 (t, 3H, *J* 7.0, CH_3CH_2O), 1.59 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 2.49 (ddd, 1H, *J* 1.7, J_{AB} 15.0, $^3J_{HP}$, 15.0, CH_A), 2.67 (ddd, 1H, *J* 10.0, J_{AB} 15.0, $^3J_{HP}$ 3.5, CH_B), 3.00 (ddd, 1H, *J* 1.7, *J* 10.0, $^2J_{HP}$ 25.7, CHP), 4.15(m, 4H, 2 × CH_2O); δ_C(acetone-d_6) 16.48 (d, $^3J_{CP}$ 6.0, 2 × CH_3), 24.65 (s, CH_3), 26.54 (s, CH_3), 37.65 (d, $^2J_{CP}$ 4.0, CH_2), 42.37 (d, $^1J_{CP}$ 127.8, CH), 63.79 (d, $^2J_{CP}$ 7.0, CH_2O), 63.90 (d, $^2J_{CP}$ 7.0, CH_2O), 88.62 (d, $^3J_{CP}$ 14.6, C–NO_2), 170.63 (d, $^2J_{CP}$ 5.4, COOH); ν_{max}(film)/cm^{-1} 1732 (C=O), 1215(P=O).

Crystal structure determination of 11

The crystal used for structure determination was obtained by slow evaporation from the 1:1 mixture of chloroform and propan-2-ol. X-Ray data were collected on the KUMA Diffraction KM4 diffractometer. The structure was solved with direct methods (SHELXS-97[18]) and refined on F^2 by full-matrix least squares technique (SHELXL-97[19]).

Crystal data. $C_{30}H_{56}N_3O_6P{\cdot}C_3H_8O$, *M* = 645.84, monoclinic, *a* = 17.464(2), *b* = 9.908(1), *c* = 22.979(2) Å, *β* = 110.74(1) °, *U* = 3718.5 Å^3, space group $P2_1/c$, *Z* = 4, *T* = 291(2) K, *λ*(Cu–K_α) = 1.54178 Å, *μ* = 1.026 mm^{-1}, *F*(000) = 1412, 7937 reflections measured, all 6562 unique reflections (R_{int} = 0.022) were used in the structure refinement, final *R* = 0.065 for 5141 observed reflections [$F_o > 4\sigma(F_o)$], wR_2 = 0.204, *S* = 1.026. CCDC 194257. See http://www.rsc.org/suppdata/p1/b2/b209302m/ for crystallographic files in .cif or other electronic format.

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