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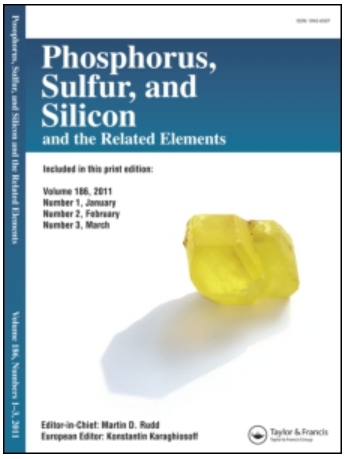

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MICHAEL-TYPE ADDITION OF DIETHYL PHOSPHORAMIDATE TO α,β-UNSATURATED ESTERS

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(Received June 22, 1993)

Michael-type addition of diethyl phosphoramidate to α,β-unsaturated esters occurs when the reactants are refluxed in toluene or xylene with an excess of potassium carbonate in the presence of tetrabutylammonium bromide (TBABr). Dephosphorylation of methyl and ethyl acrylate adducts leads to the respective β-alanine esters.

Key words: Diethyl phosphoramidate; α,β-unsaturated esters; Michael-type addition; β-alanine esters; phase-transfer catalysis.

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INTRODUCTION

Nucleophilic addition of resonance stabilized carbanions to electrophilic alkenes, known as Michael reaction, is an important and versatile process which is particularly successful for C—C bond formation. Addition of amides to electrophilic alkenes has, however, received only scant attention. Neutral amides show only very restricted nucleophilicity but under suitable basic conditions, nitrogen anions derived from them can take part in Michael-type additions to α,β-unsaturated systems. Addition of simple amides of aromatic carboxylic acids to acrylonitrile under catalysis by Triton B has been accomplished[1] and sodium catalyzed addition of formamide to α,β-unsaturated ketones has been claimed.[2] It was also shown that neutral alumina can catalyze the conjugate addition of *p*-toluenesulfonamide to methyl vinyl ketone.[3]

Stirling *et al.* reported the *N*-alkylation of *N*-butylacetamide and some polyamides by means of acrylonitrile or *p*-tolyl vinyl sulfone in the presence of potassium *t*-butoxide in *t*-butyl alcohol as the solvent-base system.[4] Moderate yields and often impure products obtained in all the above mentioned approaches evidently limit their preparative validity.

Hitherto only one report concerning the possibility of cyanoethylation of dialkyl phosphoramidates exists in the chemical literature.[5] Pudovik and Krupnov have found that diethyl and dibutyl phosphoramidate can react with acrylonitrile in the presence of catalytic amounts of sodium ethoxide in ethanol affording mono- and dicyanoethylated adducts depending upon the proportion of reagents. Attempted conjugate addition of these amides to methyl acrylate, methyl methacrylate and dimethyl maleate were, however, totally unsuccessful. In this work we report on Michael-type addition of diethyl phosphoramidate to a number of α,β-unsaturated esters and possible preparative applications of some of the adducts.

RESULTS AND DISCUSSION

Total lack of reactivity of diethyl phosphoramidate towards α,β-unsaturated esters in the presence of catalytic amounts of sodium ethoxide observed by Russian chemists suggested that significant equilibrium concentration of phosphoramidate anion is probably essential for successful conjugate addition. Consequently we decided to study the use of preformed (prepared from diethyl phosphoramidate **1** and sodium hydride in benzene) phosphoramidate anion **2** for the reaction with ethyl acrylate with the hope that conjugate addition should take place preferentially under such conditions (Equation 1).

$$(EtO)_2P(O)NH_2 \xrightarrow[\text{r.t.}]{\text{NaH/benzene}} (EtO)_2P(O)NH^-Na^+$$

$$\xrightarrow[2)NH_4Cl\ \text{aq.}]{1)CH_2{=}CH{-}COOEt/\text{benzene, reflux}} \text{mixture of products} \qquad (1)$$

It turned out, however, that nucleophilic displacement at ester carbonyl prevails leading to a mixture of products containing ca. 50% of unidentified *N*-acylphosphoramidate. This type of structure for the main component of the mixture was deduced from its ^{31}P-NMR spectrum by comparison of the chemical shift (δ = −2.07 ppm) with those typical for various O,O-diethyl-*N*-acylphosphoramidates.[6] The possibility of amidolytic splitting of an ester bond with diethyl phosphoramidate anion was not reported before but it was confirmed by us in an independent experiment. When the sodium derivative of diethyl phosphoramidate **2** was refluxed in toluene with ethyl benzoate **3** in the presence of 10 mol% of tetrabutylammonium bromide (TBABr) O,O-diethyl-*N*-benzoylphosphoramidate **4** was formed in 61% yield as a sole product (Equation 2).

$$\underset{\mathbf{2}}{(EtO)_2P(O)NH^-Na^+} + \underset{\mathbf{3}}{Ph{-}COOEt} \xrightarrow[2.\ 5\%\ HCl\ \text{aq.}]{1.\ \text{toluene/10 mol\% TBABr, reflux, 4 h}}$$

$$\rightarrow \underset{\mathbf{4}}{(EtO)_2P(O)NH.C(O).Ph} \qquad (2)$$

Further attempts to add sodium diethyl phosphoramidate to ethyl acrylate including the change of solvents, reaction temperature, and the use of TBABr as catalyst did not essentially change the final result.

In the light of these findings it became clear that substantial diminishing of the concentration of phosphoramidate anion in the reaction mixture together with possible "softening" it by solvation should minimize the undesired attack at the relatively hard carbonyl center and favor the conjugate addition. Such conditions were found in a solid-liquid phase-transfer catalytic system. Clean Michael-type addition took place when diethyl phosphoramidate and ethyl acrylate were refluxed for 4 h in toluene with an excess of potassium carbonate in the presence of 10 mol% of TBABr (Equation 3).

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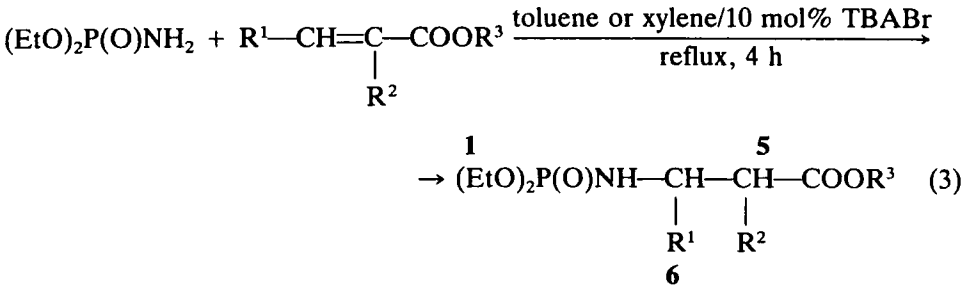

5,6	R^1	R^2	R^3
a	H	H	Et
b	H	H	Me
c	H	Me	Me
d	H	Me	Et
e	Me	H	Et

Pure adduct **6a**, formed in good yield, could be easily separated from the unreacted amide **1** by washing with water in benzene-toluene solution and finally purified by distillation in vacuo. Attempted optimization of the procedure by using different solvents (chloroform, tetrahydrofuran, acetonitrile, chlorobenzene) and different reacting systems (solid-liquid PTC system employing $K_2CO_3/KHCO_3$ as base, liquid-liquid PTC system with toluene and saturated aqueous potassium carbonate) did not improve the yield. The procedure was found to be the general method of

TABLE I

Adducts of diethyl phosphoramidate **1** to α,β-unsaturated esters - **6a–e**[a]

Compound No	Yield[b] (%)	B.p. (°C/torr)	n_D^{20}
6a	76	130-133/0.7	1.4416
6b	57	117-120/0.25	1.4440
6c	20	116-118/0.2	1.4424
6d	19	136-140/0.8	1.4403
6e	20	153-155/3	1.4400

[a] Satisfactory elemental analysis data were obtained (C±0.3%, H±0.2% N±0.2%, P±0.3%;

[b] Yield of pure, distilled material.

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choice also for a number of other α,β-unsaturated esters although the yields of adducts in the case of α- or β-alkyl substituted acrylates were low (see Table I). All adducts **6** are colorless, sirupy oils, sparingly soluble in water. Their yields, physical properties, and elemental analysis data are listed in Table I. Structures of compounds **6** were fully consistent with their IR and NMR (^1H, ^{31}P) spectra (see Table II).

The adducts of diethyl phosphoramidate **1** to ethyl and methyl acrylate **6a** and **6b**, which are formed in relatively good yield, can be considered as a convenient source of the respective β-alanine esters. These adducts treated with hydrogen chloride in benzene at room temperature undergo conventional P—N bond cleavage affording β-alanine ester hydrochlorides **7**. From these salts, which are unstable and difficult to purify, free β-alanine esters can be obtained under anhydrous conditions using an excess of $K_2CO_3/KHCO_3$ in dichloromethane in the presence of 5 mol% of TBABr as catalyst[7] (Equation 4).

$$(EtO)_2P(O)NH—CH_2—CH_2—COOR \xrightarrow[\text{r.t.}]{\text{HCl/benzene}} H_3^+N—CH_2—CH_2—COOR$$

6 Cl^- **7**

$$\xrightarrow[5\text{mol}-\%\ \text{TBABr, r.t.}]{K_2CO_3/KHCO_3/CH_2Cl_2} H_2N—CH_2—CH_2COOR \quad (4)$$

6–8a:R=Et
6–8b:R=Me

TABLE II

Spectroscopic characteristic of the adducts **6a–e**

Compound No	IR (cm^{-1})	^1H-NMR δ,ppm;J,Hz	^{31}P-NMR δ,ppm
6a	3130,2980,1735, 1250,1180,1030, 965,790	1.17-1.42(m,9H);2.21-2.26 (m,2H);3.12-3.50(m,2H); 3.88-4.20(m,4H)	9.38
6b	3200,2980,2935, 1735,1450,1435, 1235,1175,1050, 960,793	1.31(t,3H,J=7.0);2.48-2.67 (m,2H);3.17-3.49(m,2H);3.68 (s,3H);3.93-4.11(m,4H)	9.20
6c	3240,2980,2940, 2880,1735,1455, 1440,1230,1180, 1110,1095,1055, 1030,965	1.32,1.33(dt,6H,J=7.1); 1.74,1.76(2d,3H,J=7.2); 2.50-2.75(m,1H);2.90-3.33 (m,2H);3.70(s,3H);4.06,4.14 (2qt,4H,$J_{HH}=^3J_{PH}=7.1$)	9.75
6d	3235,2980,2940, 2880,1730,1455, 1440,1390,1240, 1180,1112,1060, 1030,965	1.17(d,3H,J=7.2);1.27(t,3H, J=7.1);1.32,1.33(2t,6H,J=7.1); 2.50-2.72(m,1H);2.90-3.17 (m,2H);4.06(qt,4H,$J_{HH}\approx{}^3J_{PH}\approx7.1$) 4.15(q,2H,J=7.1)	9.81
6e	3225,2985,2940, 1735,1440,1290, 1235,1180,1060, 1030,965	1.23(d,3H,J=7.1);1.27(t,3H, J=7.1);1.32,1.33(2t,6H,J=7.1); 2.49(d,2H,J=5.6);3.07(s,1H); 3.52-3.71(m,2H);4.05,4.06(2qt, 4H,$J_{HH}\approx{}^3J_{HH}\approx7.1$);4.15(q,2H, J=7.1)	8.35

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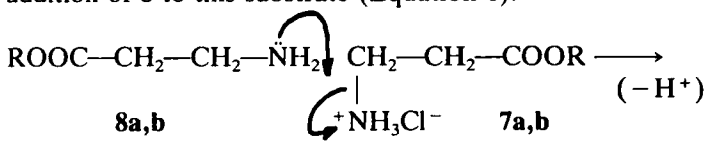
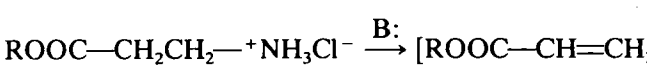
β-Alanine esters **8** thus formed are always contaminated with considerable amounts of 2,2′-dicarboalkoxydiethylamines **9**. The latter compounds may result from the reaction of **8** with the unreacted hydrochloride **7** (Equation 5) or may be formed by base-catalyzed elimination leading to acrylic ester followed by Michael-type addition of **8** to this substrate (Equation 6).



$$\rightarrow \text{ROOC—CH}_2\text{—CH}_2\text{—NH—CH}_2\text{—CH}_2\text{—COOR} \quad (5)$$



(6)

EXPERIMENTAL

Solvents and commercially available substrates were purified and dried by standard methods. Sodium hydride (Fluka, 55–60% dispersion in oil) was used after removing the oil and washing several times with hexane. NMR spectra were recorded on a Bruker AC 200 MHz spectrometer for solutions in $CDCl_3$, and the chemical shifts values are given relative to $SiMe_4$ (^1H) and 85% phosphoric acid (^{31}P). Mass spectra were obtained in the chemical ionization mode using Finnigan MAT 95 spectrometer. IR spectra were measured for liquid films using a Specord M 80 (C.Zeiss) instrument.

Addition of diethyl phosphoramidate **1** *to α,β-unsaturated esters. General procedure.* A mixture of diethyl phosphoramidate (1, 15.32 g. 0.1 mol), α,β-unsaturated ester (5, 0.12 mol), finely powdered anhydrous potassium carbonate (27.6 g, 0.2 mol), tetrabutylammonium bromide (3.22 g, 0.01 mol), and toluene (75 ml) was refluxed with efficient stirring for 4 h. After cooling to room temperature the product was diluted with benzene (100 ml) and water (10 ml) was added dropwise with stirring. The solution was then decanted and potassium carbonate was washed with benzene (3 × 25 ml). The combined solution and washings were washed with cold water (2 × 25 ml) to remove the unreacted diethyl phosphoroamidate 1. The water layer was reextracted with benzene (2 × 25 ml). After drying the combined organic solutions with anhydrous magnesium sulfate the solvent was removed under reduced pressure, yielding crude adduct **6** as yellow oil, which was finally purified by distillation in vacuo affording analytically pure sample (see Table I).

The adducts **6c–e** were prepared as described immediately above using boiling xylene instead of toluene as solvent. According to ^{31}P-NMR crude adducts **6c** and **6d** contained ca 10% of unreacted **1** which could not be removed by distillation. Purification could be, however, accomplished by additional extraction with water from benzene solution: crude adduct **6c** or **6d** (2.0 g) was dissolved in benzene (25 ml) and the solution was washed with cold water (2 × 4 ml). The water phase was reextracted with benzene (2 × 4 ml). After drying ($MgSO_4$) the combined benzene solutions the solvent was evaporated under reduced pressure to give the adducts **6c** and **6d** which did not contain (^{31}P-NMR) the unreacted amide **1**. They were then finally purified by distillation in vacuo to give analytically pure samples.

Amidolysis of ethyl benzoate. Preparation of O,O-diethyl-N-benzoylphosphoramidate **4**. A solution of diethyl phosphoramidate (1, 7.66 g, 0.05 mol) in toluene (30 ml) was added dropwise with stirring to a suspension of sodium hydride (1.2 g, 0.05 mol) in toluene (40 ml) during 30 min. at 15–20°. After evolution of hydrogen has ceased and a grey, jelly sodium derivative **2** has been obtained, the ethyl benzoate (3, 7.5 g, 0.05 mol) and tetrabutylammonium bromide (1.61 g, 0.005 mol) were added and the mixture was refluxed with stirring for 4 h. The resultant solution was cooled to 5–10°, diluted with toluene (50 ml), and treated dropwise with 5% hydrochloric acid (40 ml) until slightly acidic. The organic phase was separated and washed with saturated sodium bicarbonate solution (25 ml) and water (10 ml). After evaporation of solvent the residue was kept at 50°/0.2 torr for 4 h to remove traces of volatile material. The residual oil (7.8 g, 61%) crystallized on cooling. Analytically pure sample was obtained by crystallization from cyclohexane, m.p. 73–75° (Reference 6: m.p. 72.6–75.6°). ^1H- and ^{31}P-NMR spectra of this specimen were fully consistent with those of the authentic sample obtained by an independent method.[6]

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Degradation of the adduct **6a**. *Preparation of β-alanine ester* **8a**. The distilled adduct **6a** (12.7 g, 0.05 mol) was dissolved in benzene (50 ml) the solution was saturated with hydrogen chloride and left at room temperature for ca 48 h until the signal of the substrate in ^{31}P-NMR spectrum at δ = 9.38 ppm disappeared. After removal of an excess of HCl under reduced pressure the resultant oil, insoluble in benzene, was separated by decantation and thoroughly washed with benzene to remove diethyl phosphorochloridate formed on degradation. The oily β-alanine ethyl ester hydrochloride **7a** was dissolved in dichloromethane (100 ml), potassium carbonate (13.8 g, 0.01 mol), potassium bicarbonate (10.0 g, 0.1 mol), and tetrabutylammonium bromide (0.8 g, 0.0025 mol) were added to this solution, and the mixture was stirred for 12 h at room temperature. Inorganic salts were then filtered off with suction and the precipitate was washed with dichloromethane (2 × 25 ml). The organic solution was dried ($MgSO_4$), evaporated, and distilled in vacuo to give two fractions.

Fractions 1: b.p. 60°/13 torr. n_D^{20} – 1.4294, 3.4 g (58%) was identified as β-alanine ethyl ester 8a (Reference 8: b.p. 56–58°/12 torr, n_D^{20} – 1.4250). IR (film): 3300 (NH_2), 2980, 2880, 2810, 1740 (C=O), 1470, 1370, 1260, 1180, 1045, 980, 835, 800 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ, ppm: 1.26 (t, J_{HH} = 7.0 Hz, 3H) $C\underline{H}_3$-CH_2-O; 1.62 (s, 2H) $N\underline{H}_2$; 2.39–2.49 (m, 2H) $C\underline{H}_2$-NH_2; 2.56–2.92 (m, 2H) $C\underline{H}_2$-COOEt; 4.15 (q, J_{HH} = 7.0 Hz, 2H) CH_3-$C\underline{H}_2$-O.

Fraction 2: b.p. 115°/13 torr, n_D^{20} – 1.4369, 1.8 g, was identified as 2,2′-dicarboethoxydiethylamine **9a**. IR (film): 2990, 2850, 1745 (C=O), 1470, 1370, 1250, 1180, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ, ppm: 1.26 (t, J_{HH} = 7.1 Hz, 6H) $C\underline{H}_3$-CH_2-O; 1.64 (s, 1H) $N\underline{H}$; 2.39–2.49 (m, 4H) $C\underline{H}_2$-NH; 2.56–2.99 (m, 4H) $C\underline{H}_2$-COOEt; 4.14 (q, J_{HH} = 7.1 Hz, 4H) CH_3-$C\underline{H}_2$-O. MS(Cl) Calc. for $C_{10}H_{19}NO_4$ + H^+ – 218; found – 218. Anal. calc. for $C_{10}H_{19}NO_4$: C 55.28, H 8.81; found: C 55.4, H 8.9.

Degradation of the adduct **6b**. Preparation of β-alanine methyl ester **8b**. Degradation was carried out as described immediately above starting from 12.0 g (0.05 mol) of the adduct **6b**. Crude β-alanine methyl ester hydrochloride **7b**, which crystallized out from benzene, was filtered off, washed with benzene, and transformed into free β-alanine methyl ester **8b** as described for the ethyl ester **8a**. Distillation in vacuo of crude **8b** gave two fractions.

Fraction 1: b.p. 55–56°/13 torr, n_D^{20} – 1.4315, 2.2 g (44%) was identified as β-alanine methyl ester 8b (Reference 9: b.p. 54–55°/13 torr. IR (film): 3300 (NH), 2960, 1735 (C=O), 1640, 1550, 1440, 1185, 1030 cm^{-1}.^{1}H-NMR ($CDCl_3$) δ, ppm: 1.64 (s, 2H) $N\underline{H}_2$; 2.39–2.58 (m, 2H) $C\underline{H}_2$-NH_2; 2.89–2.99 (m, 2H) $C\underline{H}_2$-COOMe; 3.69 (s, 3H) $OC\underline{H}_3$.

Fraction 2: b.p. 110–112°/13 torr, n_D^{20} – 1.4420, 2.6 g, was identified as 2,2′-dicarbomethoxydiethylamine **9b**. IR (film): 2960, 2850, 1740 (C=O), 1360, 1200, 1170, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ, ppm: 1.53 (s, 1H) $N\underline{H}$; 2.41–2.59 (m, 4H) NH—$C\underline{H}_2$; 2.82–3.00 (m, 4H) $C\underline{H}_2$; 2.82–3.00 (m, 4H) $C\underline{H}_2$-COOMe; 3.69 (s, 6H) $OC\underline{H}_3$. MS (Cl) Calc.for $C_8H_{15}NO_4$ + H^+ – 190; found – 190. Anal.calc. for $C_8H_{15}NO_4$: C 50.78, H 7.99; found: C 50.6, H 8.1.

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