Preparation of Amino(diethoxyphosphoryl)acetic Esters. Catalytic Hydrogenation of Diazo Compounds to Amines

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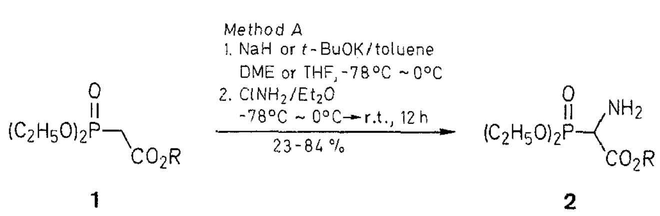
tert-Butyl amino(diethoxyphosphoryl)acetate (**2a**) is prepared on a multigram scale from *tert*-butyl diethoxyphosphorylacetate (**1a**) in a facile two-step synthesis. The method involves the formation of diazo derivative **4** and subsequent catalytic hydrogenation. Compound **2a** is also synthesized by reduction of the oxime derivative **3**. Direct amination of diethoxyphosphorylacetic esters with chloramine gives other types of esters **2b–e** in addition to the *tert*-butyl ester **2a**.

Amino(diethoxyphosphoryl)acetic esters are key building blocks in the total synthesis of various fused β-lactams. Many methods are known for the preparation of these compounds.[1-5]

We have recently reported the total synthesis of carbacephems and their interesting antimicrobial activities.[6] In the course of our research for a practical large scale process for the preparation of these carbacephems, a simple and efficient preparation of **2**, especially **2a**, was required. None of the reported procedures are suitable for a large scale synthesis; because these are not only poor in their yield, but also include the use of hazardous reagents, chromatographic purification or very low reaction temperature.

We describe here a practical multigram synthesis of these compounds, especially one with *tert*-butyl ester group, which is readily deesterified under mild conditions in the presence of labile β-lactam moiety.

Firstly, direct amination of diethoxyphosphorylacetic ester **1** was attempted (Method A). Amination with chloramine, which is a known aminating agent,[7,8] was carried out for several esters. To the solution of the sodium salts of diethoxyphosphorylacetates **1a–e** was added one equivalent of an ether solution of chloramine, and the amines were obtained in 24–84 % yield. The high yield of 84 % resulted when *tert*-butyl ester was reacted at – 78 °C. And the reaction even at 0 °C gave the amine in 46 % yield using potassium *tert*-butoxide instead of sodium hydride as the base. The results of this amination are shown in Table 1. Although the method can be applicable for various esters and the yields are fairly good, this is not a suitable process for large scale preparations, because of the difficulty in the generation of hazardous chloramine in large quantity.

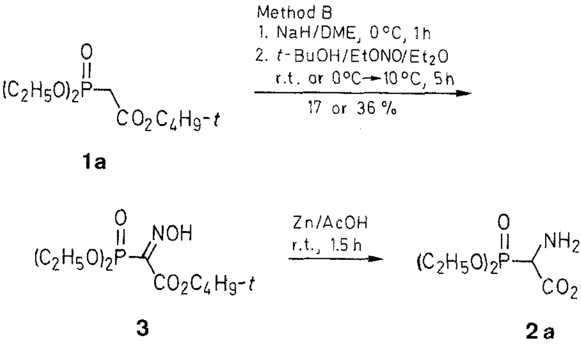


1 **2**

1, 2	R	1, 2	R
a	t-C_4H_9	**d**	$CH_2C_6H_5$
b	C_2H_5	**e**	$CH_2C_6H_3NO_2$-4
c	CH_2CCl_3		

A two step method via the oxime (Method B) was attempted next. The oxime **3** of *tert*-butyl diethoxyphosphorylacetates was obtained by the reaction of the anion of **1a** with ethyl nitrite. But the formation of the oxime was realized only under restricted conditions and the yield was not satisfactory. An alcohol like *tert*-butyl alcohol was required in the reaction media (Table 2). Ethyl esters, as a result of transesterification, were formed as by-product. The use of *tert*-butyl nitrite gave poorer results. Reaction under acidic contitions such as sodium nitrite/acetic acid/water and ethyl nitrite/hydrochloric acid gave no oxime derivatives. Subsequent reduction with zinc/acetic acid proceeded quantitatively.

Several 2-diethoxyphosphorylacetates are known to be diazotized effectively.[9] We found that a *tert*-butyl ester was easily converted into a diazo derivative using p-toluenesulfonyl (tosyl)azide in the presence of a base such as sodium hydride. Diazo compounds usually lose nitrogen on catalytic reduction,[10] producing a variety of products, including amines and hydrazines, depending on the substrate and the reaction condition employed. Therefore, the reduction of diazo compounds has been rather limited in preparing amines. We found, however, that *tert*-butyl diazo(diethoxyphosphoryl)acetate could be effectively converted to the corresponding amine in high yield by catalytic hydrogenation in the presence of acid.



Reaction of a sodium salt of *tert*-butyl diethoxyphosphorylacetate (**1a**)[11,12] with one equivalent of tosyl azide[13] in 1,2-dimethoxyethane (DME) at 0 °C led to the *tert*-butyl diazo(diethoxyphosphoryl)acetate (**4**) in excellent yield. This diazo compound **4** was very stable on purification by silica gel chromatography. And simple heating experiment revealed that no explosion occured up to 100 °C. This proved to be safe enough for large scale handling. Subsequent catalytic hydrogenation using 10 % palladium on carbon in ethanol gave a mixture including desired amine **2a** with the denitrogenated compound, starting material **1a**, as the major product. To improve the yield of the amine, several reaction conditions were applied. Addition of an acid to the reaction media was found to raise the yield of amine remarkably and suppress the elimination of nitrogen. The

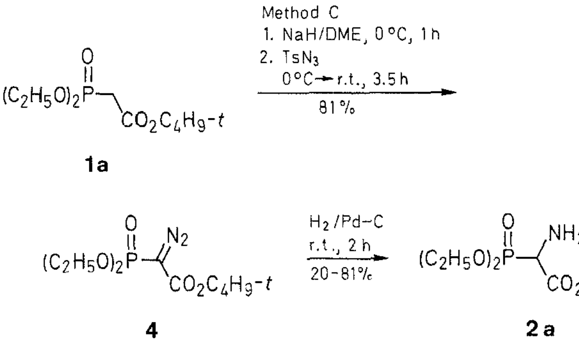


Table 2. Formation of Oxime **3** from **1a** Using Nitrites (Method B)

Reaction Conditions				Yield (%)
Nitrite	Solvent	Temp.	Base	
C_2H_5ONO	t-C_4H_9OH	r.t.	t-C_4H_9OK	trace[a]
C_2H_5ONO	THF/H_2O	r.t.	NaH	trace
C_2H_5ONO	DME	r.t.	NaH	trace
C_2H_5ONO	DME/ t-C_4H_9OH	r.t.	NaH	17
C_2H_5ONO	DME/ t-C_4H_9OH	0 °C	NaH	36
n-$C_5H_{11}ONO$	THF/H_2O	0 °C-r.t.	NaH	–
t-C_4H_9ONO	DME/ t-C_4H_9OH	r.t.	NaH	trace

[a] Not isolated. Identified with an authentic sample by TLC.

Table 3. Catalytic Hydrogenation of **4** (Method C)

Reaction Conditions				Yield (%)
Catalyst	Solvent	Pressure (psi)	Acid	
10 % Pd-C	ethanol	15[a]	–	20
Raney-Ni	ethanol	15	–	20
10 % Pd-C	acetic acid	15	–	57
10 % Pd-C	benzene	15	–	50
10 % Pd-C	ethanol	15	3N HCl[b]	61
10 % Pd-C	ethanol	15	PTSA[c]	76
10 % Pd-C	methanol	15	PTSA	61
10 % Pd-C	benzene	60	–	60
10 % Pd-C	methanol	60	PTSA	81

[a] Atmospheric pressure.
[b] Equivalent to **4**.
[c] p-Toluenesulfonic acid.

Table 1. Direct Amination with Chloramine (Method A)

Product[a,b]	Reaction Conditions			Yield (%)	IR (Neat)[c] ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J(Hz)
	Base	Solvent	Temp. (°C)			
2a	NaH	toluene	−78	84	3400, 2990, 1740, 1590	1.35 (t, 6H, J = 7); 1.50 (s, 9H); 1.78 (br s, 2H); 3.83 (d, 1H, J = 20); 4.20 (dq, 4H, J = 7, 7)
2a	NaH	THF	−30	48		
2a	NaH	DME	−30	32		
2a	NaH	toluene	−30	44		
2a	NaH	toluene	0	37		
2a	t-C_4H_9OK	toluene	0	46		
2b	NaH	DME	−30	37	3400, 3000, 1750	1.30 (t, 3H, J = 7); 1.93 (br s, 2H); 3.93 (d, 1H, J = 20); 4.23 (dq, 4H, J = 7, 7); 4.28 (q, 2H, J = 7)
2c	NaH	DME	−30	23	3300, 2990, 1765	1.37 (t, 6H, J = 7); 2.63 (br s, 2H); 3.93–4.50 (m, 5H); 4.88 (s, 2H)
2d	NaH	DME	−30	24	3400, 2990, 1745, 1505	1.27 (t, 6H, J = 7); 2.10 (br s, 2H); 3.97 (d, 1H, J = 20); 4.15 (dq, 4H, J = 7, 7); 5.25 (s, 2H); 7.38 (s, 5H)
2e	NaH	DME	−30	24	3400, 3000, 1750, 1610, 1530	1.30 (t, 6H, J = 7); 2.30 (br s, 2H); 3.92–4.40 (m, 5H); 5.33 (s, 2H); 7.54 (d, 2H, J = 9); 8.18 (d, 2H, J = 9)

[a] All the compounds were obtained as viscous oil.
[b] All the compounds are known (**2a**;[2] **2b**;[2,5] **2c**;[1] **2d**;[1,4] **2f**[1]) but no spectral data were reported, except for **2a**.
[c] Recorded on a Varian EM-390 NMR spectrometer.
[d] Recorded on a Jasco IR-810 IR spectrometer.

results of catalytic reduction of **4** are summarized in Table 3. *p*-Toluenesulfonic acid was found to be superior to hydrochloric acid or acetic acid in improving the yield. Palladium on carbon gave better results than Raney-nickel catalyst in terms of product complexity. Solvent seemed to play not so an important role on the yield, but the temperature affected the rate of reduction considerably. Reaction conducted at below 15 °C was very sluggish. Reaction of 10 g of **1a** gave, without purification of the intermediate diazo derivative, the amine **2a** in 62% overall yield. It also became possible to prepare *tert*-butyl 2-amino-2-diethoxyphophorylacetates in kilogram scale.

Caution! Care should be taken in handling tosyl azide in large scale because of its potential explosiveness.

Amino(diethoxyphosphoryl)acetates 2a–e; General and Typical Procedures:

Method A; General Procedure:

A solution of **1** (30 mmol) in DME (25 mL) is added dropwise to a suspension of NaH (0.79 g, 33 mmol) in DME (25 mL) at −30 °C. The mixture is allowed to come up to −10 °C slowly, and then cooled to −30 °C. To this mixture is added a solution of $ClNH_2$ in ether (375 mL, 33 mmol) at that temperature, stirred overnight, and filtered. The filtrate is evaporated and the residue is dissolved in $CHCl_3$ (40 mL), extracted with 10% HCl solution (3 × 50 mL). The combined aqueous solution is washed with $CHCl_3$ (40 mL), neutralized with $NaHCO_3$, and extracted with $CHCl_3$ (3 × 100 mL). The organic layer is dried ($MgSO_4$) and evaporated to give **2** (Table 1).

The concentration of chloramine solution is analyzed by the Volhard method.[14]

Method B; *tert*-Butyl Amino(diethoxyphosphoryl)acetate (2a); Typical Procedure:

tert-Butyl Hydroxyimino(diethoxyphosphoryl)acetate (**3**): The ester **1a** (100 g, 0.396 mole) dissolved in dry DME (100 mL) is added dropwise in 1 h to a stirred suspension of NaH (0.96 g, 0.40 mol) in dry DME (400 mL). To this mixture, t-C_4H_9OH (100 mL) is added in one portion and then a sat. solution of ethyl nitrite in ether (300 mL) is added dropwise in 2 h. After stirring for 1.5 h at 0 °C, then for 2 h at 10 °C, AcOH (29.6 g) is added and the mixture is diluted with EtOAc, washed with brine three times and dried (Na_2SO_4). Filtration and evaporation gives an oily material, which is allowed to stand at 0 °C overnight; yield: 40.0 g (36%); mp 105–106 °C.

$C_{10}H_{20}No_6P$	calc.	C 42.71	H 7.17	N 4.98
(281.2)	found	42.49	7.25	4.71

^{1}H-NMR ($CDCl_3$): $\delta = 1.36$ (t, 6H, $J = 7$ Hz, CH_3); 1.54 (s, 9H, t-C_4H_9); 4.22 (dq, 4H, $J = 7$ Hz, $J = 7$ Hz, CH_2); 12.20 (br s, 1H, NOH).

MS: $m/z = 282$ (M + 1).

Conversion of **3** *to* **2a**: To a solution of **3** (8.0 g, 2.83 mmol) in AcOH (80 mL), is added zinc powder (4.8 g) in small portions in 30 min. After stirring for 1 h, the mixture is filtered and evaporated. The residue is dissolved in water and the pH is adjusted to 7.9 with sat. $NaHCO_3$ solution. The solution is extracted with $CHCl_3$ five times and the combined organic layer is washed with brine, dried (Na_2SO_4); and evaporated to give **2a** as a pale-yellow oil; yield: 7.6 g (100%).

Method C; *tert*-Butyl Amino(diethoxyphosphoryl)acetate (2a); Typical Procedure:

tert-Butyl Diazo(diethoxyphosphoryl)acetate (**4**): The ester **1a** (10.08 g, 40 mmol) is added dropwise to a stirred suspension of NaH (1.056 g, 44 mmol) in dry DME (40 mL) at 0 °C. After the addition has been completed (20 min), the mixture is stirred at 0 °C for 1 h. To this, a solution of tosyl azide (7.88 g, 40 mmol) in dry DME (10 mL) is added dropwise in 20 min. The mixture is stirred at room temperature for 3 h and the precipitate obtained is removed by filtration. The filtrate is evaporated and the residue is dissolved in ether (100 mL). The ether solution is washed with 0.5 N NaOH, water, brine, dried (Na_2SO_4) filtered and evaporated to give **4** as a red-brown oil; yield: 9.0 g (81%).

$C_{10}H_{19}N_2O_5P$	calc.	C 43.17	H 6.88	N 10.07
(278.2)	found	42.93	6.98	9.77

IR ($CHCl_3$): $\nu = 2150, 1705, 1310\ cm^{-1}$.

^{1}H-NMR ($CDCl_3$): $\delta = 1.37$ (t, 6H, CH_3); 1.50 (s, 9H, t-C_4H_9); 3.98–4.48 (m, 4H, CH_2).

Conversion of **4** *to* **2a**: The diazo compound **4** (9.0 g, 32 mmol) obtained as above is dissolved in MeOH (150 mL). To this solution, Pd-C (10%, 4 g) and *p*-TosOH (6.18 g, 32 mmol) are added. The mixture is hydrogenated at 60 psi hydrogen pressure in a Parr apparatus at room temperature. After hydrogenation for 2 h, the mixture is filtered, evaporated, and the residue is dissolved in 1 N HCl (250 mL). The aqueous solution is washed with EtOAc, neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ solution is washed with brine, dried (Na_2SO_4), and evaporated to afford **2a** as a pale-yellow oil: yield: 6.58 g (76%); overall yield from **1a**: 62% (Table 3).

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