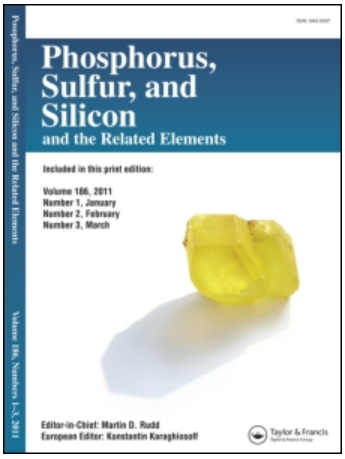

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A Novel Synthesis of 1-Aminoalkanephosphonic Acid Derivatives from 1-(*N*-Acylamino)- alkyltriphenylphosphonium Salts

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A NOVEL SYNTHESIS OF 1-AMINOALKANEPHOSPHONIC ACID DERIVATIVES FROM 1-(*N*-ACYLAMINO)-ALKYLTRIPHENYLPHOSPHONIUM SALTS

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Efficient and convenient procedures for the α-amidoalkylation of trialkylphosphites with 1-(N-acylamino)alkyltriphenylphosphonium salts followed by a Michaelis–Arbuzov-type reaction to afford 1-(N-acylamino)alkanephosphonic acid esters have been developed. High yields and simple isolation and purification protocols are the main advantages of this method.

Keywords 1-(*N*-Acylamino)alkanephosphonic acid esters; 1-(*N*-acylamino)alkyltriphenylphosphonium salts; α-amidoalkylation; Michaelis–Arbuzov rearrangement; phosphorus mimetics of α-amino acids

INTRODUCTION

1-Aminoalkanephosphonic acids, as structural analogues and mimetics of α-amino acids, display a broad spectrum of biological activity, and therefore are currently of significant interest to the chemical and biological communities.[1–3] Various methods for their synthesis have been reported. One of the most important approaches to 1-aminoalkanephosphonic acids consists in the Michaelis–Arbuzov reaction of trialkyl phosphites with amidoalkylating agents.[1,4–9]

Recently, we described simple and effective syntheses of 1-(*N*-acylamino)alkyltriphenylphosphonium salts **3**[10,11] from easily accessible 4-phosphoranylidene-5(4*H*)-oxazolones **1**[12] or their alkylation products **2**[13] (Scheme 1). The obtained phosphonium salts are stable, crystalline compounds and can be prepared on kilogram scale using these procedures. We have also demonstrated that 1-(*N*-acylamino)alkyltriphenylphosphonium salts can be considered as *N*-acylimine precursors, and therefore, strong α-amidoalkylating agents that are able to react with a wide variety of nucleophiles.[14]

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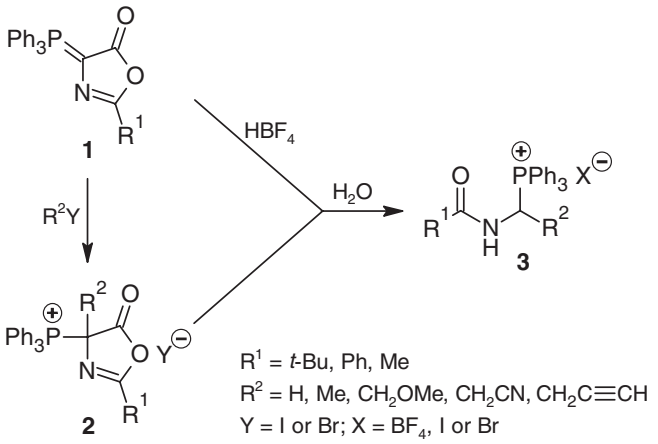
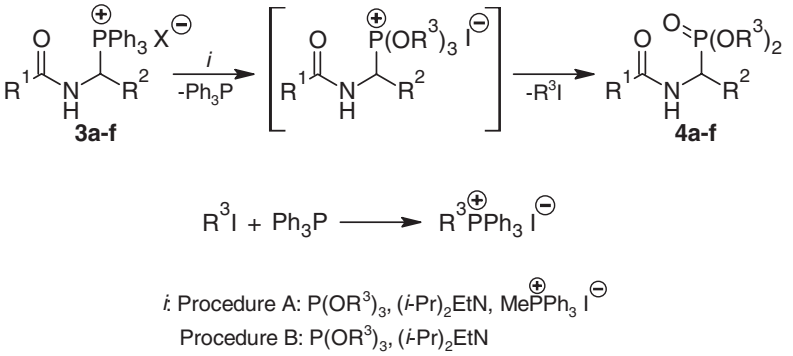


Scheme 1

In this article, we describe the application of 1-(*N*-acylamino)alkyltriphenyl phosphonium salts **3a–f** to the amidoalkylation of trialkylphosphites followed by a Michaelis–Arbuzov-type dealkylation that yields 1-(*N*-acylamino)alkanephosphonic acid esters **4a–f** (Scheme 2).



Scheme 2

RESULTS AND DISCUSSION

N-Acylaminomethyltriphenylphosphonium tetrafluoroborates **3a–c** (R^2 = H, X = BF_4) react smoothly with trialkylphosphites in dichloromethane in the presence of triphenylmethylphosphonium iodide (0.25 mol/mol of **3a–c**) and catalytic amounts of Hünig's base [$(i\text{-Pr})_2$EtN] at 50–60°C to give *N*-acylaminometanephosphonic acid esters **4a–c** in good to excellent yields (Table I, procedure A). The use of a catalytic base is crucial for obtaining high yields and accelerating the reaction. A substoichiometric amount of triphenylmethylphosphonium iodide, which was found to be the optimum iodide anion source, is necessary in order to transform the intermediate trialkoxyphosphonium salt into the phosphonic acid esters via a Michaelis–Arbusov-type dealkylation (Scheme 2). Obviously, no additional

Table I Synthesis and analytical data of *N*-acylaminoalkanephosphonic acid esters **4**

Phosphonium salt **3**				Reaction conditions			Product **4**				IR	Elemental analyses (calcd./found) [%]			
				Temp.					Yield	Mp					
No.	R^1	R^2	Y	Procedure	[°C]	Time	No.	R^3	[%]	[°C]	[CH_2Cl_2, cm^{-1}]	C	H	N	P
4a	*t*-Bu	H	BF_4	A	60	12 h	**4a**	Me	99	74–74.5	3460m, 1668vs, 1520s, 1240s, 1040vs	43.05/43.13	8.05/8.07	6.28/6.28	13.88/13.85
4b	Ph	H	BF_4	A	60	4 h	**4b**	Me	69	110–111[a]	3444m, 1664vs, 1520s, 1240s, 1036vs	—	—	—	–
4c	Me	H	BF_4	A	50	10 h	**4c**	Et	87[b]	Oil[c,d]	3440m, 1680vs,1520m, 1236s, 1032vs	—	—	—	–
4d	*t*-Bu	Me	I	B	60	30 min	**4d**	Me	91	128.5–129	3444m, 1668vs, 1510s, 1244s, 1036vs	45.57/45.38	8.50/8.53	5.90/5.96	13.06/13.06
4e	Ph	Me	I	B	60	30 min	**4e**	Et	70	63–64	3432m, 1664vs, 1512s, 1236s, 1028vs	54.73/54.82	7.07/7.02	4.91/4.92	10.86/10.48
4f	*t*-Bu	CH_2OMe	I	B	60	30 min	**4f**	Me	88	89–89.5	3452m, 1668vs, 1512s, 1244s, 1032vs	44.94/44.85	8.30/8.08	5.24/5.13	11.59/11.40

[a]Mp: 109–110°C.[15]
[b]The synthesis was carried out in a microwave reactor.
[c]Mp: 37–38°C.[4]
[d]The oily substance, solidifying in a refrigerator at about 0°C and melting at room temperature.

Table II ^{1}H and ^{13}C NMR spectroscopic data of *N*-acylaminoalkanephosphonic acid esters **4**

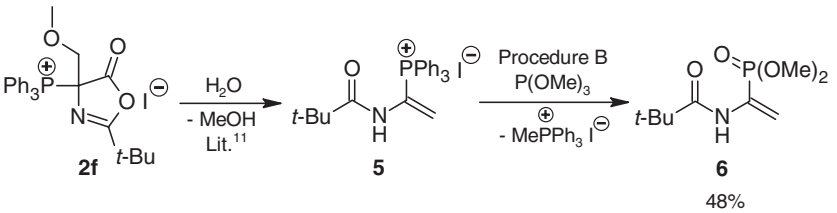
No.	^{1}H NMR [300 MHz, $CDCl_3$/TMS, δ (ppm)]	^{13}C NMR [75.5 MHz, $CDCl_3$/TMS, δ (ppm)/J_{PC} (Hz)]				
		O=C−NH	P−C_α	R^1	R^2	R^3
4a	6.0 (br, 1H, NH), 3.78 (d, J = 11.1 Hz, 6H, $P(OMe)_2$), 3.76 (dd, J_{PH} = 11.7 Hz, J_{HH} = 5.7 Hz, 2H, CH_2), 1.22 (s, 9H, *t*-Bu)	178.2/4.6	33.8/159.9	38.7 ($\underline{C}Me_3$) 27.3 ($C\underline{Me}_3$)	—	52.9/6.4
4b	7.83–7.39 (m, 5H, Ph), 7.08 (br, 1H, NH), 3.96 (dd, J_{PH} = 11.7 Hz, J_{HH} = 6.0 Hz, 2H, CH_2), 3.80 (d, J = 11.1 Hz, 6H, $P(OMe)_2$)	167.3/5.0	34.3/156.8	133.6, 131.8, 128.5, 127.1 (Ph: C_1, C_4, C_2, C_3)	—	53.1/6.5
4c	6.55 (br, 1H, NH), 4.14 (dq, J_{HH} = 7.9 Hz, J_{PH} = 7.2 Hz, 4H, $P(O\underline{C}H_2CH_3)_2$), 3.71 (dd, J_{PH} = 11.9 Hz, J_{HH} = 5.9 Hz, 2H, CH_2), 2.04 (d, J_{PH} = 1.2 Hz, 3H, Me), 1.34 (dt, J_{HH} = 7.2 Hz, J_{PH} = 0.6 Hz, 6H, $P(OCH_2\underline{C}H_3)_2$)	170.0/6.1	34.7/157.1	22.8 (CH_3)	—	62.6/6.7 ($\underline{C}H_2CH_3$), 16.3/5.8 ($CH_2\underline{C}H_3$)
4d	5.92 (br d, J_{HH} = 9.6 Hz, 1H, NH), 4.65–4.49 (m, 1H, CH), 3.77 (d, J_{PH} = 10.5 Hz, 3H, $P(OMe)_2$[a]), 3.76 (d, J_{PH} = 10.5 Hz, 3H, $P(OMe)_2$[a]), 1.38 (dd, J_{PH} = 16.8 Hz, J_{HH} = 7.5 Hz, 3H, Me), 1.21 (s, 9H, *t*-Bu)	177.7/5.0	40.1/156.4	38.7 ($\underline{C}Me_3$) 27.3 ($C\underline{Me}_3$)	15.6 (Me)	53.2/7.2[e] 52.9/6.5[e]
4e	7.83–7.42 (m, 5H, Ph), 6.61 (br d, J_{HH} = 8.7 Hz, 1H, NH), 4.83–4.67 (m, 1H, CH), 4.24–4.08 (m, 4H, $P(O\underline{C}H_2CH_3)_2$), 1.48 (dd, J_{PH} = 16.8 Hz, J_{HH} = 7.5 Hz, 3H, Me), 1,35 (dd, $J_1 = J_2$ = 7.0 Hz, 3H, $P(OCH_2\underline{C}H_3)_2$[b]), 1.29 (dd, $J_{HH} = J_{HH}$ = 7.0 Hz, 3H, $P(OCH_2\underline{C}H_3)_2$[b])	166.7/6.1	41.3/157.2	134.0, 131.7, 128.6, 127.0 (Ph: C_1, C_4, C_2, C_3)	15.8 (Me)	62.8/7.0 ($\underline{C}H_2CH_3$)[f], 62.5/6.7 ($\underline{C}H_2CH_3$)[f], 16.5/4.2 ($CH_2\underline{C}H_3$)[g], 16.4/4.3 ($CH_2\underline{C}H_3$)[g]
4f	6.11 (br d, J_{HH} = 9.6 Hz, 1H, NH), 4.74–4.62 (m, 1H, CH), 3.83–3.75 (m, 1H, $C\underline{H}_2OMe$[c,d]), 3.55 (ddd, J_{PH} = 25.5 Hz, J_{HH} = 10.1 Hz, J_{HH} = 3.9 Hz, 1H, $C\underline{H}_2OMe$[c]), 3.77 (d, J = 10.2 Hz, 3H, $P(OMe)_2$[a]), 3.76 (d, J = 10.2 Hz, 3H, $P(OMe)_2$[a]), 3.39 (s, 3H, $CH_2O\underline{C}H_3$), 1.22 (s, 9H, *t*-Bu)	177.8/5.3	45.3/154.4	38.7 ($\underline{C}Me_3$) 27.3 ($C\underline{Me}_3$)	70.8 ($\underline{C}H_2OCH_3$), 59.1 ($CH_2O\underline{C}H_3$)	53.1/6.4[h] 52.8/6.4[h]

[a,b]One of two diastereotopic methyl groups.
[c]One of two diastereotopic protons of the methylene group.
[d]Overlapping with the signal of the Me group of the $P(OMe)_2$ group.
[e,g,h]One of two diastereotopic carbon atoms of methyl groups.
[f]One of two diastereotopic carbon atoms of methylene groups.

iodide anion source was needed in the case of 1-(*N*-acylamino)alkyltriphenylphosphonium iodides **3d–f** ($R^2 \neq H$, X = I) (Table I, procedure B).

The 1-aminoalkanephosphonic acid esters were isolated from the reaction mixture and purified by evaporation of CH_2Cl_2, extraction of the crude product from the resulting residue with toluene, evaporation of toluene, and finally recrystallization of the product. Only in the case of diethyl 1-(*N*-benzoylamino)ethanephosphonate **4e** was additional column chromatography required.

In addition, we have also demonstrated the applicability of procedure B for the synthesis of the α-aminoethenephosphonic acid derivative **6** (Scheme 3); however, in this case the yield of the reaction was poor.



Scheme 3

The structures of all reported 1-(*N*-acylamino)alkanephosphonic acid esters were confirmed by their spectroscopic properties (IR, ^1H, and ^{13}C NMR). Satisfactory elemental analysis results were also obtained for all new compounds (Tables I and II).

CONCLUSION

In conclusion, procedures for α-amidoalkylation of trialkylphosphites with 1-(*N*-acylamino)alkyltriphenylphosphonium salts followed by a Michaelis–Arbuzov-type dealkylation have been developed. This protocol offers a convenient and effective entry into the synthesis of 1-(*N*-acylamino)alkanephosphonic acid esters. A simple procedure for the isolation and purification of the products is of particular value.

EXPERIMENTAL

Melting points are determined in capillary tubes in a Stuart Scientific SMP3 melting point apparatus, and are uncorrected. IR spectra were recorded on a Zeiss Specord M 80 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian UNITY INOVA-300 spectrometer at operating frequencies of 300 and 75.5 MHz or on a Varian 600 spectrometer at operating frequencies of 600 and 150.8 MHz, respectively, in the FT mode using TMS as an internal standard.

Starting Materials

Commercial grade CH_2Cl_2 was distilled and dried over molecular sieves (4A). The following reagents trimethylphosphite and triethylphosphite were of commercial

quality (Aldrich). The 1-(*N*-acylamino)alkyltriphenylphosphonium salts **3** and the 1-(*N*-pivaloylamino)vinyltriphenylphosphonium iodide **5** were synthesized as described in the literature.[11,12]

Synthesis of *N*-Acylaminoalkanephosphonic Acid Esters 4a–c: (Procedure A)

Reactions were carried out in a glass vial sealed with a screw-cap. Triphenylmethylphosphonium iodide (0.2 g, 0.5 mmol), $(i\text{-Pr})_2$EtN (0.03 mL, 0.2 mmol), and trialkylphosphite (3 mmol) were added to a solution of *N*-acylaminomethyltriphenyl phosphonium tetrafluoroborate **3a–c** (2 mmol) in CH_2Cl_2 (3.6 mL). The mixture was kept at 60°C (**3a–c**) or heated at 50°C in a microwave reactor at a power of 8–10 W (**3c**, CEM Matthews) for the times shown in Table I. The progress of the reaction was monitored by ^{1}H NMR. Upon completion, the solvent was evaporated under reduced pressure, the residue was extracted with toluene, and the toluene was subsequently evaporated. The crude product was recrystallized from a mixture of toluene and hexane (**4a** and **4c**) or purified by dissolving in ethyl acetate and precipitation by addition of diethyl ether (**4b**).

Synthesis of *N*-Acylaminoalkanephosphonic Acid Esters 4d–f and α-Aminoethenephosphonic Acid Derivative 6 (Procedure B)

Reactions were carried out in a glass vial sealed with a screw-cap. $(i\text{-Pr})_2$EtN (0.03 mL, 0.2 mmol) and trialkylphosphite (3 mmol) were added to a solution of (*N*-acylamino)alkyltriphenylphosphonium iodide **3d–f** or 1-(*N*-pivaloylamino)vinyltriphe nylphosphonium iodide **5** (2 mmol) in CH_2Cl_2 (3.6 mL). The mixture was heated at 60°C for the time shown in Table I. In the case of compound **5**, the reaction time was 2 h. The progress of the reaction was monitored by ^{1}H NMR. The solvent was evaporated under reduced pressure, the residue was extracted with toluene, and the toluene was subsequently evaporated. The crude products **4d** and **4f** were recrystallized from a mixture of toluene and hexane. In the case of compounds **4e** and **6**, the crude product was purified by column chromatography (silica gel, toluene/AcOEt, 1:5 v/v for **4e** and toluene/MeOH, 20:1 v/v for **6**). Finally, the product **4e** was recrystallized from a mixture of toluene and hexane.

Spectral and analytical data for compound **6**: oil, IR (CH_2Cl_2, cm^{-1}) 3448m, 1688vs, 1512vs, 1505vs, 1272s. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.45 (br s, 1H, NH), 6.70 (d, J_{PH} = 42.3 Hz, 1H, C=CH), 5.50 (dd, J_{PH} = 19.4 Hz, J_{HH} = 1.0 Hz, 1H, C=CH), 3.78 (d, J_{PH} = 11.4 Hz, 6H, $P(OMe)_2$), 1.26 (s, 9H, *t*-Bu). ^{13}C NMR (150.8 MHz, $CDCl_3$, δ / J_{PC} (Hz)) = 177.8/9.2 (C=O), 130.0/198.3 ($\underline{C}$=CH_2), 113.2/9.2 (C=$\underline{C}H_2$), 53.2/5.5 ($P(O)(OMe)_2$), 39.7/1.9 ($\underline{C}Me_3$), 27.2 ($C\underline{Me}_3$). HR-EI-MS *m/z* for $C_9H_{18}NO_4P$ [M^+]: calcd 235.0973; found 235.0964.

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