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A new application of the Mitsunobu reaction in the synthesis of phosphonium salts

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Abstract—The condensation of methanol or primary alcohols with triphenylphosphonium tetrafluoroborate in the presence of ethyl azodicarboxylate and triphenylphosphine in THF at room temperature gives the respective alkyltriphenylphosphonium salts in good yields. The reaction also worked for the conversion of *N*-acyl-2-hydroxyglycinates into *N*-acyl-2-triphenylphosphonioglycinates.
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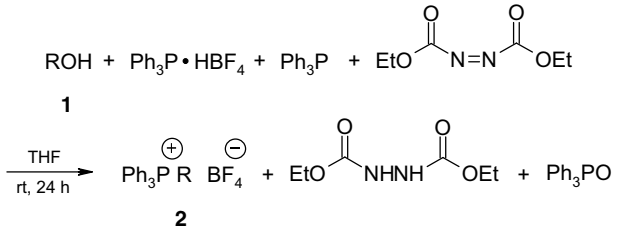
The Mitsunobu reaction can be described as the alkylation of a nucleophile NuH with an alcohol in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) or related reagents. A variety of nucleophiles have been employed in the reaction, for example, carboxylic acids, phenols, imides, thiols, thioamides and even carbon nucleophiles.[1] According to the best of our knowledge, our work, reported in this letter, is the first successful attempt to apply the Mitsunobu reaction for the *P*-alkylation of phosphorus nucleophiles, namely, for the alkylation of phosphines into alkylphosphonium salts. Such a reaction would be interesting as a method for the direct transformation of some labile alcohols into phosphonium salts, which are important precursors of phosphorus ylides for the Wittig reaction.

The Mitsunobu reaction requires the application of a nucleophile in its protonated form (NuH). Trying to alkylate triphenylphosphine in the Mitsunobu reaction, we decided to use it in the form of triphenylphosphonium tetrafluoroborate. The latter compound, when treated with the adduct of DEAD and triphenylphosphine and methyl alcohol or primary alcohols in THF at room temperature for 24 h, gives the expected alkyltriphenylphosphonium salts **2a–d** in good yields (Scheme 1, Table 1).



Scheme 1.

The phosphonium salts obtained were isolated by column chromatography;[†] their structure was confirmed by comparing their physical and spectroscopic properties (^{1}H and ^{13}C NMR)[5,6] with literature data.

Keywords: Mitsunobu reaction; Phosphines; *P*-alkylation; Alkyltriphenylphosphonium salts; *N*-acyl-2-triphenylphosphonioglycinates.
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[†] Procedure A: To a stirred solution of triphenylphosphine (0.524 g, 2 mmol) in THF (5 cm^3), triphenylphosphine tetrafluoroborate (0.700 g, 2 mmol), alcohol (1 mmol) and DEAD (0.315 cm^3, 2 mmol) were added under Ar at room temperature. The mixture was left for 24 h at room temperature without stirring, and after evaporating THF, the residue was extracted with hot toluene (5 × 2.5 cm^3). The crude product was purified by column chromatography on silica gel eluting with a mixture of toluene and methanol in a ratio of 4:1 and recrystallized from the same solvent.

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Table 1. Synthesis of phosphonium salts **2** via the Mitsunobu reaction

Starting alcohol **1**			Phosphonium salt **2**		
Entry	ROH	Procedure	Yield (%)	Mp (°C)	Lit. mp (°C)
1a	MeOH	A	92[b]	124–126	129–131[2]
1b	PrOH	A	83[a]	169–171	173–174[2]
1c	CH_2=$CHCH_2OH$	A	57[a]	164–166	161–162[3]
1d	$PhCH_2OH$	A	61[a]	209–210	215–216[4]
1e	*i*-PrOH	A	trace	—	—
1f	$MeOCONHCHOHCO_2Me$	B	77[b]	—	—
1g	*t*-$BuOCONHCHOHCO_2Me$	B	82[b]	—	—
1h	$PhCH_2OCONHCHOHCO_2Me$	B	77[b]	—	—

[a] Yield of isolated compound.
[b] Yield estimated from the ^{1}H NMR spectrum.

In the case of the simplest secondary alcohol, isopropyl alcohol, we were able to detect only a trace amount of the expected phosphonium salt **2e** in the reaction mixture. Our attempts to use *N*-acyl-2-hydroxyglycinates in this reaction were, however, successful. Based on spectral evidence, we proved the formation in this reaction of the corresponding *N*-acyl-2-triphenylphosphonioglycinates **2f–h** in good yields. It seems that electron withdrawing acylamino and alkoxycarbonyl groups make the hydroxyglycine more reactive when compared with simple secondary alcohols.[‡]

N-Acyl-2-triphenylphosphonioglycinates have been proved to be valuable reagents for the synthesis of non-proteinogenic α-amino acids.[7,8] Unfortunately, our efforts to isolate pure *N*-acyl-2-triphenylphosphonioglycinates from the reaction mixture failed. Nevertheless, we have demonstrated that *N*-acyl-2-triphenylphosphonioglycinates obtained from *N*-acyl-2-hydroxyglycinates in the Mitsunobu reaction can be used directly, without isolation, for further transformations, for example, in the synthesis of *N*-acyl-2-(dialkoxyphosphoryl)-glycinates in a one-pot procedure, in good yields.[9] The latter compounds are important synthons for syntheses of α,β-dehydro-α-amino acids in the Wadsworth–Emmons reaction.

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5. ^{1}H NMR spectral data (300 MHz, $CDCl_3$, δ) of **2a**: 7.83–7.61 (m, 15H), 2.89 (d, $J_{H-P} = 13.7$ Hz, 3H); **2b**: 7.85–7.65 (m, 15H), 3.26 (m, 2H), 1.69 (m, 2H), 1.18 (dt, $J_{H-H} = 7.2$ Hz, $J_{H-P} = 1.8$ Hz, 3H); **2c**: 7.83–7.67 (m, 15H), 5.66 (m, 1H), 5.44 (dd, $J_{H-H} = 4.8$ Hz, $J_{H-P} = 26.4$ Hz, 1H), 5.40 (dd, $J_{H-H} = 4.4$ Hz, $J_{H-P} = 19.0$ Hz, 1H), 4.20 (dd, $J_{H-H} = 6.8$ Hz, $J_{H-P} = 15.2$ Hz, 2H); **2d**: 7.80–7.69 (m, 20H), 4.67 (d, $J_{H-P} = 14.2$ Hz, 2H); **2f**: 7.84–7.60 (m, 15H), 6.68 (s, 1H), 6.38 (dd, $J_{H-P} = 16.6$ Hz, $J_{H-H} = 8.6$ Hz, 1H), 3.61 (s, 3H), 3.39 (s, 3H); **2g**: 7.82–7.61 (m, 15H), 6.68 (s, 1H), 6.38 (dd, $J_{H-P} = 16.2$ Hz, $J_{H-H} = 8.1$ Hz, 1H), 3.58 (s, 3H), 1.16 (s, 9H); **2h**: 7.82–7.26 (m, 20H + Ph_3PO) 6.55 (s, 1H), 6.41 (dd, $J_{H-P} = 16.5$ Hz, $J_{H-H} = 7.5$ Hz, 1H), 4.85 (d, $J = 12.3$ Hz, 1H), 4.81 (d, $J = 12.6$ Hz, 1H), 3.61(s, 3H).
6. ^{13}C NMR spectral data (75 MHz, $CDCl_3$, δ (ppm)/J_{C-P} (Hz)) of **2a**: 135.1/3.0, 133.0/11.0, 130.4/13.1, 118.9/88.6, 9.0/58.4; **2b**: 135.1/3.0, 133.4/10.0, 130.5/13.0, 118.1/86.6, 23.6/50.4, 16.5/4.0, 15.0/17.1; **2c**: 135.2/3.0, 133.6/10.0, 130.4/13.0, 126.3/13.1, 122.7/9.1, 117.6/85.6, 28.0/51.4; **2d**: 135.1/3.0, 134.0/10.0, 131.2/8.2, 130.2/12.0, 129.0/4.0, 128.6/4.0, 126.7/8.3, 117.3/85.6, 30.2/48.3.
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[‡] Procedure B: To a stirred suspension of methyl *N*-acyl-α-hydroxyglycinate (1 mmol) in THF (5 cm^3), DEAD (0.2 cm^3, 1.25 mmol), triphenylphosphine (0.29 g, 1.1 mmol) and triphenylphosphine tetrafluoroborate (0.38 g, 1.1 mmol) were added under Ar at room temperature. The mixture was left for 3 days at room temperature without stirring, and then the THF was evaporated. The content of the *N*-acyl-2-triphenylphosphonioglycinate in the residue was estimated based on the ratio of the intensity of the characteristic signals of the OMe group of the product and the Me group of diethoxycarbonyl hydrazine in the ^{1}H NMR spectrum.