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Efficient method to prepare diethylphosphonacetamides

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ABSTRACT

An efficient and versatile synthetic method is described to synthesize diethylphosphonacetamides in a single step.

Phosphonacetamides are very useful intermediates for accessing α,β-unsaturated amides as synthetic precursors in natural product synthesis.[1] The routine method to prepare phosphonacetamides is the Arbuzov reaction.[2] This method is also applied in the literature to prepare the diethylphosphonacetamides **2**[3] from (1*R*,2*S*)-(+)-10,2-camphorsultam. However, the Arbuzov synthesis is a two-step route and does not allow for adequate diversity of the amide side chains, mainly due to the limited availability of the amines. Another widely reported approach describes the synthesis of phosphonacetamides starting from the commercially available diethylphosphonoacetic acid **1** via a peptide coupling procedure, using carbodiimides with or without additives such as HOBT and 4-DMAP.[4] Also Melmam and co-worker[5] described an efficient acylation of sterically hindered alcohols of diethylphosphonoacetic acid through ketene intermediates promoted by the presence of DCC.

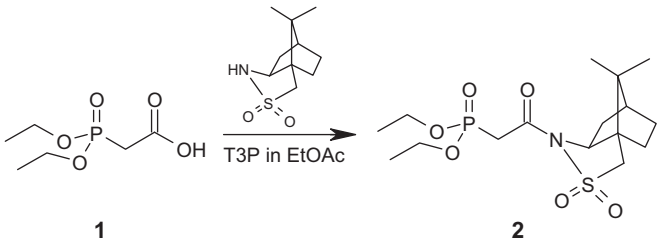
In our view, the latter approach is the most suitable for a large-scale synthesis.

Herein, we report an efficient, simple and practical method for accessing diethylphosphonacetamides using 1-propanephosphonic acid cyclic anhydride (T3P) as the coupling reagent.

In the initial attempts, the camphorsultam was treated with DCC and a solution of diethylphosphonoacetic acid **1** in dichloromethane at room temperature, leading to the formation of a complex mixture within which the desired product **2** was identified. These promising results encouraged us to investigate other coupling agents in order to improve the reaction profile. Boronic acids and T3P were screened and the results are shown in Table 1.

The formation of **2** was achieved with the use of T3P. Notably, the use of triethylamine at room temperature did not lead to complete conversion (Table 1, entry 5) and, moreover, the removal of the base did not have an impact on the reaction behaviour (Table 1, entry 6). The conversion was improved by heating the reaction mixture to reflux (Table 1, entry 7) and it was brought to completion by increasing the amount of the coupling agent (Table 1, entry 8). After a mild basic aqueous wash, which allowed the selective removal of the by-products of the T3P, **2** was isolated as a white solid in 93% yield.

We explored the scope and versatility of the coupling reaction involving T3P, without a base as additive, by applying this unprecedented methodology to a wide range of substrates containing NH group. The results are summarized in Table 2. Reactions were first carried out at room temperature to confirm the need for heating; as a general trend, the reaction takes place immediately after the



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Scheme 1.

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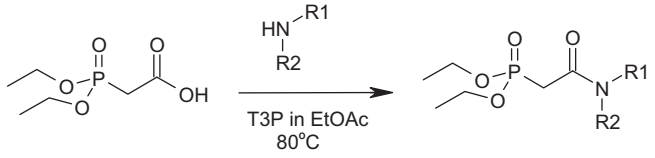
Table 1
Coupling reagents screening via Scheme 1

Entry	Coupling agents	Conditions	Results
1	DCC	DCC (1.1 equiv), DCM, 20 °C	Complex mixture
2	$B(OH)_3$	$B(OH)_3$ (0.2 equiv), toluene, Dean–Stark	No reaction
3	$PhB(OH)_2$	$PhB(OH)_2$ (0.2 equiv), toluene, Dean–Stark	No reaction
4	2-BrPhB(OH)_2	2-BrPhB(OH)_2 (0.2 equiv), toluene, Dean–Stark	No reaction
5	T3P	T3P (1.1 equiv), Et_3N (2 equiv), EtOAc, 20 °C	Incomplete conversion
6	T3P	T3P (1.1 equiv), EtOAc, 20 °C	Incomplete conversion
7	T3P	T3P (1.1 equiv), EtOAc, 80 °C	Almost complete conversion
8	T3P	T3P (1.1 equiv + 0.35 equiv), EtOAc, 80 °C	Complete conversion

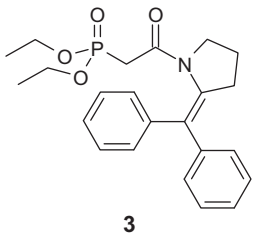
Table 2
Preparation of diethylphosphonacetamides with T3P



Entry	Amine	Yield (%)
1	Benzylamine[8]	80[a]
2	*iso*-Propylamine	56[a]
3	*tert*-Butylamine[9]	53[b]
4	(1*R*)-1-Phenylethanamine	91[b]
5	2-Phenylcyclohexylamine	84[b]
6	(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidine	40[a]
7	(2*S*)-2-{Diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidine[c]	70[a]
8	Aniline	89[b]
9	3,5-Bis(trifluoromethyl)aniline	83[a]
10	2-Aminopyridine	78[b]
11	6-Amino-5-iodo-3-pyridinecarbonitrile	58[a]
12	5-Fluoro-3-methyl-2-pyridinamine	85[b]
13	(1*R*,2*S*)-(+)-10,2-Camphorsultam	93[a]
14	(4*R*)-4-Phenyl-1,3-oxazolidin-2-one[10]	80[a]

[a] Isolated as a solid.
[b] Isolated as an oil, contaminated by triethylphosphono acetate already present in the purchased diethylphosphonoacetic acid.
[c] Reaction carried out at 20 °C.

addition of the coupling agent but it tends to stall until heated to 80 °C. Generally, the resulting diethylphosphonacetamides were obtained in moderate to high yields. The variability was probably due to the solubilities of the final compounds in water, which cause partial losses in the aqueous media used during the work-up. This appeared to be of particular relevance for alkyl primary amines (Table 2, entries 2 and 3). As a matter of fact, we included in our investigation one of the widely known organic catalysts, Jørgensen's (2*S*)-2-{diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidine[6] (Table 2, entry 6). Even if it reacted well, the isolated product was exclusively **3** resulting from the –OTMS elimination and consequent loss of the chirality. When the reaction was carried out under milder condition (Table 2, entry 7) no elimination occurred but TMS hydrolysis to **4** was observed. The highly hindered OH did not interfere and the reaction proceeded selectively on the nitrogen.



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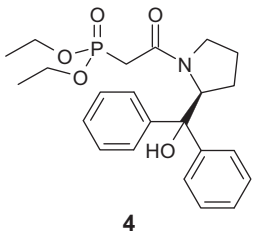

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Furthermore, unprecedented diethylphosphonacetamides deriving from amino pyridines were obtained in moderate to high yields (Table 2, entries 10–12). Finally, camphorsultam as sulfonamide and oxazolidinone[7] were successfully converted into the corresponding diethylphosphonacetamides (Table 2, entries 13 and 14).

A representative procedure using benzylamine is described. Diethylphosphonoacetic acid (3.08 mmol, 1.1 equiv) was added to a solution of benzylamine (2.8 mmol, 1 equiv) in ethyl acetate (3 mL) under nitrogen. A solution of T3P in ethyl acetate (50 wt %, 4.06 mmol, 1.45 equiv) was added dropwise over 5 min. The resulting solution was heated to 80 °C and stirred overnight. The reaction progression was followed by HPLC or LC/MS. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (3 mL) and water (3 mL). The biphasic system was then basified to pH 6 with 12 N aqueous NaOH, stirred for 1 h, then the two layers were allowed to settle and separate. The organic layer was washed with water (3 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to a solid which was triturated with heptane to yield 640 mg of benzyl diethylphosphonacetamides (80%).[11]

In conclusion, we have developed an efficient, simple and practical synthesis of diethylphosphonacetamides using T3P as the coupling agent.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.125 and new chemical entities can be downloaded from http://www.elsevier.com/wps/find/journaldescription.cws_home/233/description#description.

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11. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.19–7.42 (m, 5H), 7.09 (br s, 1H), 4.47 (d, J = 5.71 Hz, 2H), 4.00–4.20 (m, 4H), 2.89 (d, J = 20.64 Hz, 2H), 1.31 (td, J = 7.03, 1.32 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 163.79, 137.90, 128.61, 127.63, 127.42, 62.74 (d, J = 6.13 Hz), 43.79, 35.08 (d, J = 130.36 Hz), 16.28 (d, J = 6.13 Hz). HRMS (ES+) calcd for $C_{13}H_{20}NO_4P$ $[M+H]^+$: 286.1208; found: 286.1219.