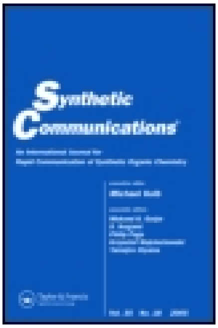

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Propane Phosphonic Acid Anhydride: A Mild Reagent for β-Lactam Synthesis

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PROPANE PHOSPHONIC ACID ANHYDRIDE: A MILD REAGENT FOR β-LACTAM SYNTHESIS

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The use of propane phosphonic acid anhydride (T3P®) as an acid activating reagent was demonstrated in the syntheses of *cis* β-lactams from the reactions of a glycine Dane salt and various imines.

In recent years there has been a renewed interest in the development of efficient methods for the production of *cis*-3-amino 2-azetidinones because of their importance in penicillin, cephalosporin and carbacephalosporin antibiotics.[1] The construction of the β-lactam ring system can be accomplished by the reaction of an activated carboxylic acid with an imine in the presence of a tertiary base.[2] This

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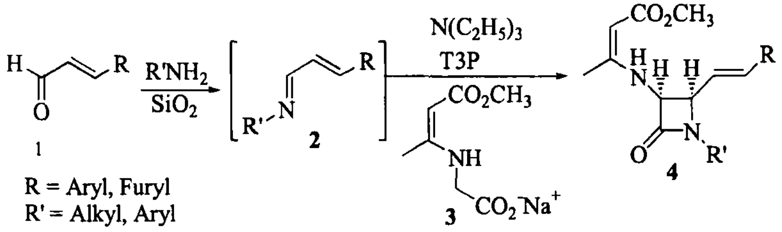
[*] To whom correspondence should be addressed.

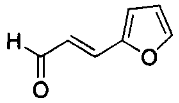
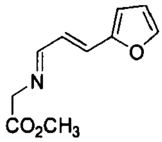
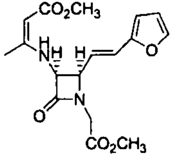
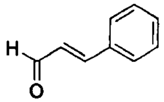
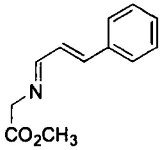
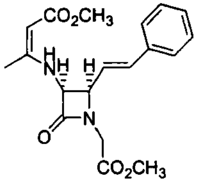
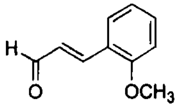
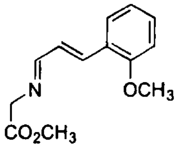
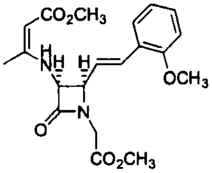
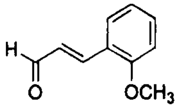
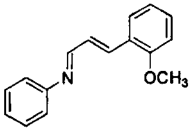
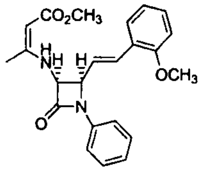
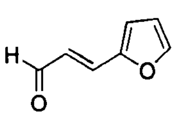
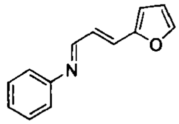
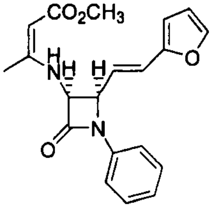
reaction is most often referred as the Staudinger [1,3,4] reaction and proceeds with good stereoselectivity depending upon the reaction conditions[5] and substituents.[6] A variety of acid activating reagents such as ethyl chloroformate,[7] p-toluenesulfonyl chloride,[8] trifluoroacetic anhydride,[9] phosphorous derived reagents,[10] N,N-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride,[11] 1-methyl-2-halopyridinium salts[12] and cyanuric chloride[13] have been used in the synthesis of β-lactams. The use of propane phosphonic acid anhydride (T3P®) as an acid activating reagent in acylation reactions has been reported.[14] We now report the synthesis of *cis* β-lactams using T3P® as an acid activating agent in Staudinger reactions as described in Scheme 1.



Scheme 1

In a typical reaction, T3P® and **2** were simultaneously added to a slurry of glycine Dane salt, triethylamine and methylene chloride to afford 2-azetidinones **4** as illustrated in Scheme 1. An analysis of the [2+2]cycloaddition product verified the presence of 2-azetidinones **4**. In the ^{1}H NMR spectra, the resonances of the protons in the C-3 and C-4 positions of the β-lactam showed a coupling constant of 5.1 Hz indicating the *cis* β-lactam.[15] The scope of the T3P® reagent was explored by synthesizing *cis* 3-[(1-methyl-2-methoxycarbonyl)ethenyl]-amino-4,1-substituted-2-azetidinones using glycine Dane salt **3** and imines **2** with various structural features (Table 1). Imines **2** were prepared from the reactions of unsaturated aldehydes **1** with amines in the presence of silica gel.

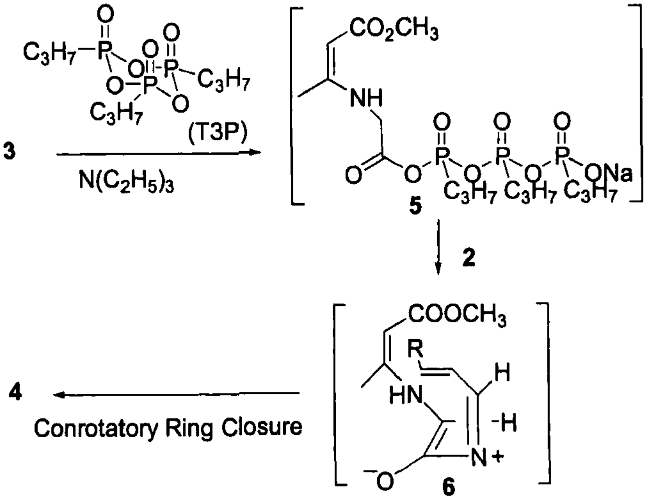
Table 1. Various 2-azetidinones synthesized using T3P® reagent.

Unsaturated aldehyde 1	Imine 2[a]	2-Azetidinone 4 (Yield)
 1a	 2a	 4a[16] (82 %)
 1b	 2b	 4b (78%)
 1c	 2c	 4c (75%)
 1d	 2d	 4d (90%)
 1e	 2e	 4e (80%)

a Imines **2** were prepared by reacting unsaturated aldehydes **1** with amines as indicated in the literature.[17]

Compounds 4b-e showed satisfactory elemental analysis (± 0.4%)

The possible pathway may proceed with the initial reaction of T3P® and **3** to form mixed carboxylic phosphoric anhydride **5**. The subsequent reaction with imines **2** may generate intermediate **6** and the conrotatory ring closure[4] of **6** may lead to the formation of 2-azetidinones **4** (Scheme 2).



Scheme 2

A simple work up of the reaction mixture, low toxicity[18] of the T3P® reagent, solubility of by-products in water and high yields of 2-azetidinones (4a-e) makes T3P® a reagent of choice in Staudinger reaction. In conclusion, ®T3P was shown to be an effective acid activating reagent in the synthesis of *cis* β-lactams.

Experimental: Unsaturated aldehydes **1** were purchased from Aldrich. Dane salt was purchased from Eastman. T3P® reagent was obtained from Clariant (Hoechst High Chem. Fine Chemicals). All melting points are uncorrected. ^{1}H NMR spectra were recorded at 400MHz on a Bruker DPX-400 in $CDCl_3$. IR spectra were recorded on a Nicolet 510P. Mass spectra were obtained by Flow Injection Analysis on a Micromass QTOF Mass Spectrometer.

General Preparation of Imines 2: Silica gel (5 g) was added to a solution of amine (0.032 moles) in dichloromethane at 0°C under nitrogen atmosphere. *trans*-Cunsaturated aldehyde (**1**, 0.031moles) was added to the reaction mixture and rinsed with CH_2Cl_2 (40 ml). The reaction mixture was stirred for approximately 2.75 hours at 0 to 3°C. The silica gel was removed *via* filtration and silica was rinsed with CH_2Cl_2 (30ml). Dichloromethane solution of Schiff base was concentrated to half of the volume and used as such in the [2+2]cycloaddition reaction.

General Procedure for the Preparation of 2-Azetidinones 4: To a mixture of glycine Dane salt (0.037 moles), triethylamine (0.063 moles) and CH_2Cl_2 (50 ml) at 0°C was added T3P (0.058 moles) and imine (0.031 moles) simultaneously over 45 minutes. The reaction mixture was stirred at 0 to 3°C for 4 hours. Chilled deionized water (40 ml) was added to the mixture and the pH was adjusted to 6.0-7.0 with sodium carbonate or HCl. The organic layer was separated and the solvent was evaporated to yield a solid or an oil. Enamines **4a-c** were purified using a Biotage column and ethylacetate/hexanes (70:30) containing 1% triethylamine as an eluent.

4a[16]: oil; IR ($CHCl_3$, cm^{-1}), 1769 (s), 1749 (s), 1659 (s), 1616 (s), 1488 (m), 1439 (m), 1414 (m), 1267 (s), 1165 (s); ^1H NMR (400 MHz, $CDCl_3$), 1.9 (s, 3H), 3.5 (s, 3H), 3.6 (d, 1H), 3.7 (s, 3H), 4.3 (d, 1H) 4.6 (s, 1H), 4.7 (dd, J = 5.1 Hz, 1H), 5.1 (dd, J = 5.1 Hz, 1H), 6.2 (dd, 1H), 6.4-6.5 (m, 1H), 6.6 (d, 1H), 7.3-7.4 (m, 2H), 8.9 (d, 1H); MS calculated for $C_{17}H_{20}N_2O_6$ is 348.3, [M+H]: 349.3, 317.1, 194.2.

4b: oil; IR ($CHCl_3$, cm^{-1}), 1768 (s), 1748 (s), 1657 (s), 1617 (s), 1439 (m), 1267 (s), 1166 (s); ^1H NMR (400 MHz, $CDCl_3$), δ 1.9 (s, 3H), 3.6 (s, 3H), 3.7 (d, 1H), 3.8 (s, 3H), 4.3 (d, 1H), 4.6 (br s, 1H), 4.7 (dd, J = 5.1 Hz, 1H), 5.1 (dd, J = 5.1 Hz, 1H), 6.2 (dd, 1H), 6.7 (d, 1H), 7.3-7.4 (m, 3H), 7.4-7.5 (m, 2H), 9.0 (br s, 1H); MS calculated for $C_{19}H_{22}N_2O_5$ is 358.4, [M+H]: 359.2, 360.3, 327.2, 204.2.

4c: oil; IR ($CHCl_3$, cm^{-1}), 1767 (s), 1748 (s), 1657 (s), 1616 (s), 1490 (s), 1439 (s), 1266 (s), 1248 (s), 1164 (s); ^1H NMR (400 MHz, $CDCl_3$), δ 1.9 (s, 3H), 3.6 (s, 3H), 3.7, (d, 1H), 3.8 (s, 3H), 3.9 (s, 3H), 4.3 (d, 1H), 4.6 (s, 1H), 4.7 (dd, J = 5.1 Hz, 1H), 5.1 (dd, J = 5.1 Hz, 1H), 6.2 (dd, 1H), 6.8-6.9 (m, 2H), 7.0 (d, 1H), 7.3 (d, 1H), 7.5 (d, 1H), 9.0 (d, 1H); MS calculated for $C_{20}H_{24}N_2O_6$ is 388.4, [M+H]: 389.3, 234.1.

4d: yellow solid (M. P. = 140-142°C); IR ($CHCl_3$, cm^{-1}), 1756 (s), 1658 (s), 1617 (s), 1600 (s), 1499 (s), 1491 (s), 1380 (s), 1267 (s), 1249 (s), 1164 (s); ^1H NMR (400 MHz, $CDCl_3$), δ 1.9 (s, 3H), 3.6 (s, 3H), 3.8 (s, 3H), 4.7 (br s, 1H), 4.9 (dd, J = 5.1 Hz, 1H), 5.1 (dd, J = 5.1 Hz, 1H), 6.3 (dd, 1H), 6.8-6.9 (m, 2H), 7.2 (d, 1H), 7.2-7.3 (m, 2H), 7.3 (d, 1H), 7.3-7.4 (m, 1H), 7.5 (d, 1H), 7.5-7.6 (m, 2H), 9.2 (br s, 1H); MS calculated for $C_{23}H_{24}N_2O_4$ is 392.5, [M+H]: 393.2, 238.1.

4e: yellow solid (M. P. = 116-118°C); IR ($CHCl_3$, cm^{-1}), 1757 (s), 1661(s), 1618 (s), 1600 (s), 1498 (s), 1380 (s), 1267 (s), 1165 (s); ^1H NMR (400 MHz, $CDCl_3$), δ 1.9 (s, 3H), 3.5 (s, 3H), 4.6 (s, 1H), 4.9 (dd, J = 5.1 Hz, 1H), 5.1 (dd, J = 5.1 Hz, 1H), 6.2 (dd, 1H), 6.3-6.4 (m, 1H), 6.6 (d, 1H), 7.1-7.2 (m, 2H), 7.3-7.4 (m, 3H), 7.4-7.5 (m, 2H), 9.0 (d, 1H); MS calculated for $C_{20}H_{20}N_2O_4$ is 352.4, [M+H]: 353.4, 321.1, 198.1, 189.4, 147.1.

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