

# Triphenylphosphine catalyzed vinyl amides: a mild, stereoselective and general synthesis

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## Abstract

The reaction of triphenylphosphine with dialkyl acetylenedicarboxylate in the presence of N-H of amides catalyzed stereoselective conversion of amides to (E)-isomer of vinyl amides. In these cases, phosphorus ylides are formed in-situ and converted to vinyl amides.

**Keywords:** Triphenylphosphine, amides, acetylenic esters, stereoselective, phosphorus ylides, catalyst, (E)-isomer, vinyl amides

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## Introduction

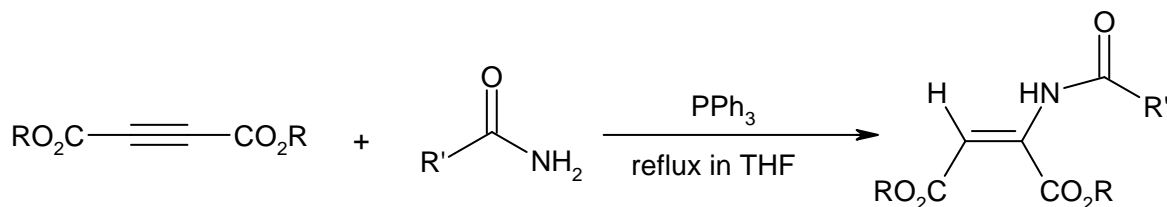
Amides are a very important class of organic compounds with a wide range of applications.<sup>1,2</sup> Some derivatives of amides exhibit biological properties such as antihelmintic, antihistamine, antifungal and antibacterial<sup>3-7</sup>.

6-*N*-(2-Hydroxy-3,5-dichlorophenyl)-2-hydroxy-3,5,6-trichlorobenzamide (oxyclozanide) was discovered in 1969 as an antihelmintic agent effective against *Fasciola hepatica* for the treatment of liver fluke infection<sup>3</sup>. 3,4-Dihydroxy-6-(*N*-ethylamino)benzamide is a natural product that has been found in green pepper (*Piper nigrum L.*) which demonstrated antibacterial activity<sup>5</sup>. Additionally, the benzamide derivative, BAS-118, has been found to be a novel anti-*Helicobacter pylori* agent with potent and selective antibacterial activity, which includes clarithromycin (CAM)- and metronidazole (MNDZ)-resistant isolates<sup>7</sup>.

Phosphorus ylides are reactive systems, which take part in many chemical reactions<sup>8,9</sup>. These ylides are usually prepared by treatment of phosphonium salt with a base, and phosphonium salts are usually prepared from the phosphine and an alkyl halide<sup>10,11</sup>. Phosphonium salts are also prepared by Michael addition of phosphorus nucleophiles to activated alkenes among other methods.

$\beta$ -Addition of nucleophiles to the vinylic phosphonium salts leading to the formation of new alkylidenephosphoranes which has attracted much attention as a convenient and synthetically useful method in organic synthesis. Organophosphorus compounds have been extensively used

in organic synthesis as useful reagents as well as ligands of a number of transition metal catalysts<sup>9-11</sup>. However, there are few reactions in which organophosphorus (III) species act as catalysts<sup>12-14</sup>. In this paper, we wish to describe a new method for the conversion of amides to vinylamides by use of a catalytic amount of triphenylphosphine via in situ generated stable phosphorus ylides (Scheme 1).



**Scheme 1**

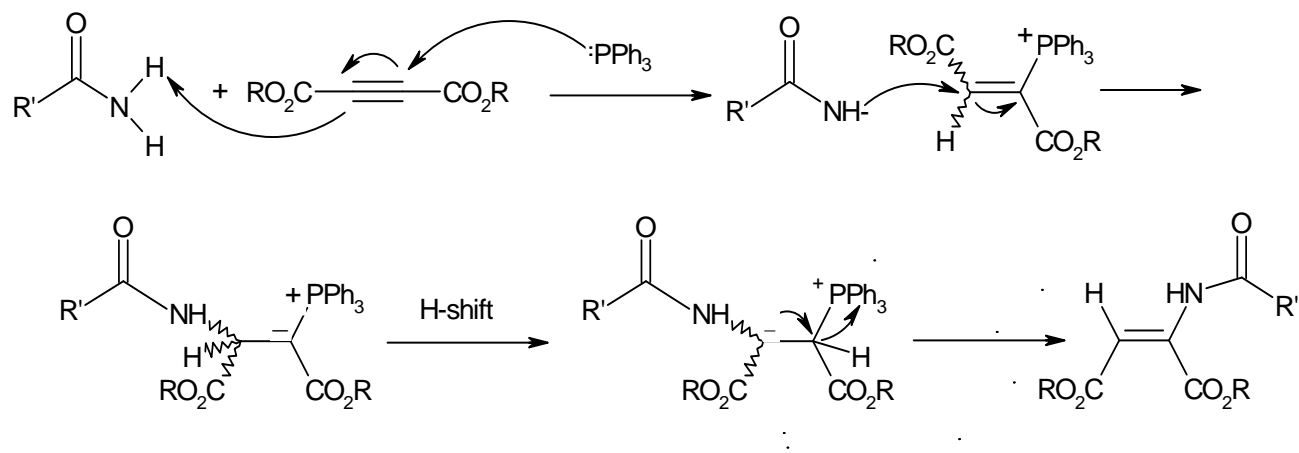
## Results and Discussion

Compounds apparently result from the initial addition of triphenylphosphine to the acetylenic ester and concomitant protonation of the reactive adducts. Then positively charged ion is attacked by the nitrogen of the conjugate base of the NH-acid to form phosphorus ylides. These ylides undergo a [1,2] proton shift and then the intermediates so-formed rapidly convert to vinyl amides (Scheme 2).

Structures of products were assigned on the basis of their IR, Mass, <sup>13</sup>CNMR and <sup>1</sup>HNMR spectra. GC data and Mass spectra showed that only one product was produced during the reactions. IR and <sup>1</sup>HNMR spectroscopy were applied to differentiate between vinyl amide or imines forms of products. As was shown in Table 2, vinyl amides are the single products of the reactions.

The assignment of the E and Z configurations of the products are based on the chemical shifts of vinylic protons, as the vinylic protons of the Z isomer appears at lower field as a result of anisotropic deshielding of the ester carbonyl groups<sup>15</sup>. It was shown in our previous work that the chemical shift of vinylic proton in the Z isomer is 6.94 ppm and it is 7.04 for the E isomer<sup>16</sup>.

As the spectral data showed, triphenylphosphine catalyzed stereoselective conversion of amides to the (E)-isomer of vinyl amides. In all cases complete conversion of reagents was obtained from GC spectra and product were obtained in good yields.



Scheme 2

## Experimental Section

**General Procedures.** All products were identified by their spectra. IR spectra were recorded on the FT-IR Bruker Tensor 27 spectrometer. <sup>1</sup>HNMR spectra were recorded on a Bruker AQS 300 MHz Avance Spectrometer in DMSO-*d*<sub>6</sub> (Chemical Shifts are given as  $\delta$  in ppm), Mass spectra were recorded on MS 5973 Network Mass Selective detector. All the yields were calculated from isolated products, and GC was used to establish their purities.

### Acetylamino-but-2-enedioic acid dimethyl ester (1). General procedure

Dialkyl acetylenedicarboxylate (1 mmol), was added drop wise during a few minutes to 0.03 mmol of triphenylphosphine at 0°C. A solution of amides (1 mmol) in 5 mL THF was then added via syringe and mixture refluxed for 2h. After completion of reaction (monitored by thin layer chromatography (TLC)) the solvent was evaporated and vinyl amides derivatives were obtained in good yields. More purification was obtained by column chromatography (Table 1).

<sup>1</sup>HNMR (300 MHz, DMSO, *d*<sub>6</sub>,  $\delta$ ): 2.02 (3H, s), 3.71 (3H, s), 3.74 (3H, s), 6.80 (1H, s), 10.51 (1H, s) ppm; <sup>13</sup>CNMR (300 MHz, DMSO, *d*<sub>6</sub>,  $\delta$ ): 23.58 (CH<sub>3</sub>), 50.61 (OCH<sub>3</sub>), 51.73 (OCH<sub>3</sub>), 123.75 (C=C), 128.35 (C=C), 158.43 (C=O (CO<sub>2</sub>CH<sub>3</sub>)), 164.86 (C=O (CO<sub>2</sub>CH<sub>3</sub>)), 168.78 (C=O (CONH)) ppm; FT-IR : 3427.35 (NH), 1691.10 (CONH), 1726.71 (COMe), 2958.98, 3024.43 (CH) cm<sup>-1</sup>; MS: *m/z* 201 [M<sup>+</sup>]. Oily and viscous liquid.

**2-Propionylamino-but-2-enedioic acid dimethyl ester (2).** <sup>1</sup>HNMR (300 MHz, DMSO, *d*<sub>6</sub>,  $\delta$ ): 1.15 (3H, t, <sup>3</sup>J<sub>HH</sub> = 7.2 Hz), 2.24 (2H, q, <sup>3</sup>J<sub>HH</sub> = 7.2 Hz), 3.73 (3H, s), 3.76 (3H, s), 6.82 (1H, s), 11.91 (1H, s) ppm; <sup>13</sup>CNMR (300 MHz, DMSO, *d*<sub>6</sub>,  $\delta$ ): 9.18 (CH<sub>3</sub>), 31.58 (CH<sub>2</sub>), 50.58 (OCH<sub>3</sub>), 51.71 (OCH<sub>3</sub>), 123.81 (C=C), 128.74 (C=C), 159.23 (C=O (CO<sub>2</sub>CH<sub>3</sub>)), 165.32 (C=O (CO<sub>2</sub>CH<sub>3</sub>)), 170.68 (C=O (CONH)) ppm; FT-IR : 3448.12 (NH), 1671.69 (CONH), 1710.62 (COMe), 2934.58, 3057.81 (CH) cm<sup>-1</sup>; MS: *m/z* 215 [M<sup>+</sup>]. Oily and viscous liquid.

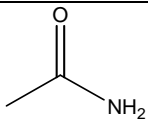
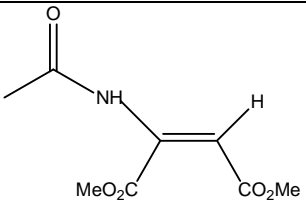
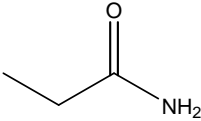
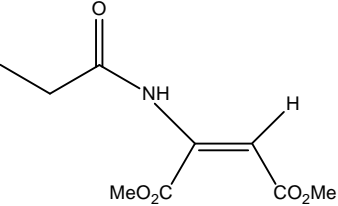
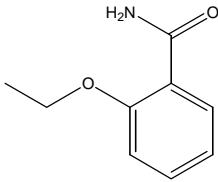
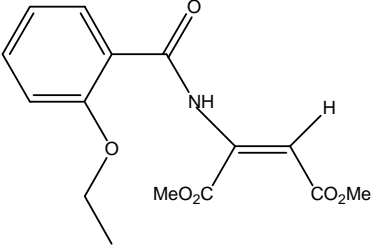
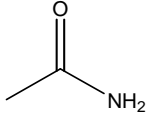
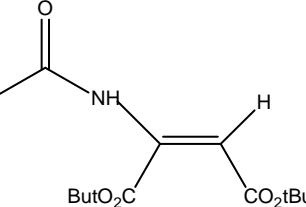
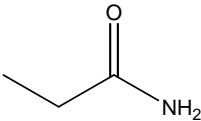
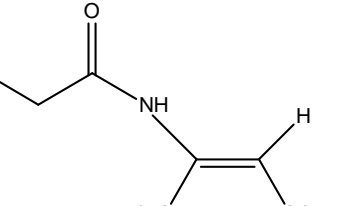
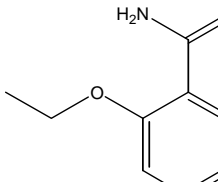
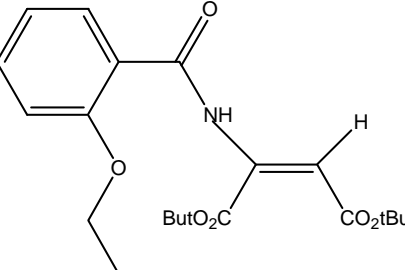
**2- (2-Ethoxy-benzoylamino) -but-2-enedioic acid dimethyl ester (3).**  $^1\text{H}$ NMR (300 MHz, DMSO, d6,  $\delta$ ): 1.37 (3H, t,  $^3J_{\text{HH}}=7.2\text{Hz}$ ), 4.01 (2H, q,  $^3J_{\text{HH}}=7.2\text{Hz}$ ), 3.74(3H,s), 3.76 (3H,s), 6.82 (1H,s); the chemical shift for phenyl is 6.95 -7.84 (4H, m), 10.37(1H,s) ppm;  $^{13}\text{C}$ NMR (300 MHz, DMSO, d6,  $\delta$ ): 14.98 (CH<sub>3</sub>), 49.58 (OCH<sub>3</sub>), 50.61 (OCH<sub>3</sub>), 64.71 (CH<sub>2</sub>), 123.74 (C=C), 127.51 (C=C), the chemical shift for phenyl is 117.49, 119.23, 123.85, 127.54, 134.31,159.63, 159.53 (C=O (CO<sub>2</sub>CH<sub>3</sub>)), 163.96 (C=O (CO<sub>2</sub>CH<sub>3</sub>)), 171.24 (C=O (CONH)) ppm. FT-IR : 3348.85 (NH), 1671.69 (CONH), 1728.17(COMe), 2938.98, 3019.51 (CH), 1571.28 (C=C) cm<sup>-1</sup>; MS: m/z 307[M<sup>+</sup>], mp 76-78 °C, Anal. Calcd for C<sub>15</sub>H<sub>17</sub>NO<sub>6</sub> (307): C, 58.63; H, 5.53; N, 4.56. Found: C, 58.58; H, 5.61; N, 4.48.

**2- Acetylamino-but-2-enedioic acid di- tert- butyl ester (4).**  $^1\text{H}$ NMR (300 MHz, DMSO, d6,  $\delta$ ): 1.40 (9H,s), 1.43(9H,s), 2.13 (3H,s) 6.81 (1H,s), 10.25(1H,s) ppm ;  $^{13}\text{C}$ NMR (300 MHz, DMSO, d6,  $\delta$ ):23.63 (CH<sub>3</sub>), 28.17 (CH<sub>3</sub> (C(CH<sub>3</sub>)<sub>3</sub>)), 81.73 (C), 83.91 (C), 124.75 (C=C), 128.15 (C=C), 159.73 (C=O (CO<sub>2</sub>CH<sub>3</sub>)), 164.38 (C=O (CO<sub>2</sub>CH<sub>3</sub>)), 169.28 (C=O (CONH)) ppm; FT-IR : 3427.35 (NH), 1691.10 (CONH), 1726.71 (CotBu), 2958.98, 3024.43 (CH) cm<sup>-1</sup>; MS: m/z 285[M<sup>+</sup>], mp 62-64 °C, Anal. Calcd for C<sub>14</sub>H<sub>23</sub>NO<sub>5</sub> (285): C, 58.94; H, 8.07; N, 4.91. Found: C, 58.89; H, 8.13; N, 4.86.

**2- Propionylamino- but-2- enedioic acid di- tert- butyl ester (5).**  $^1\text{H}$ NMR (300 MHz, DMSO, d6,  $\delta$ ): 1.15 (3H, t,  $^3J_{\text{HH}}=7.2\text{Hz}$ ), 1.39(9H,s) 1.41 (9H,s), 2.24 (2H, q,  $^3J_{\text{HH}}=7.2\text{Hz}$ ), 6.82 (1H,s), 11.85(1H,s) ppm;  $^{13}\text{C}$ NMR (300 MHz, DMSO, d6,  $\delta$ ): 9.34 (CH<sub>3</sub>), 28.17 (CH<sub>3</sub> (C(CH<sub>3</sub>)<sub>3</sub>)), 33.10 (CH<sub>2</sub>), 81.50 (C), 83.71 (C), 125.75 (C=C), 128.65 (C=C), 160.43 (C=O (CO<sub>2</sub>CH<sub>3</sub>)), 164.35 (C=O (CO<sub>2</sub>CH<sub>3</sub>)), 170.23 (C=O (CONH)) ppm; FT-IR : 3448.12 (NH), 1671.69 (CONH), 1710.62 (CotBu), 2934.58, 3057.81 (CH) cm<sup>-1</sup>; MS: m/z 299[M<sup>+</sup>], mp 52-54 °C, Anal. Calcd for C<sub>15</sub>H<sub>25</sub>NO<sub>5</sub> (299): C, 60.20; H, 8.36; N, 4.68. Found: C, 60.18; H, 8.31; N, 4.71.

**2- (2-Ethoxy-benzoylamino) -but-2-enedioic acid di- tert- butyl ester (6).**  $^1\text{H}$ NMR (300 MHz, DMSO, d6,  $\delta$ ): 1.33 (3H, t,  $^3J_{\text{HH}}=7.2\text{Hz}$ ), 1.38(9H,s),1.40 (9H,s), 3.98 (2H, q,  $^3J_{\text{HH}}=7.2\text{Hz}$ ), 6.82 (1H,s); the chemical shift for phenyl is 6.95 -7.84 (4H, m), 10.31(1H,s) ppm;  $^{13}\text{C}$ NMR (300 MHz, DMSO, d6,  $\delta$ ): 15.21 (CH<sub>3</sub>), 28.31 (CH<sub>3</sub> (C(CH<sub>3</sub>)<sub>3</sub>)), 64.73 (CH<sub>2</sub>), 81.48 (C), 83.65 (C), 124.74 (C=C), 128.91 (C=C), the chemical shift for phenyl is 117.85, 120.13, 123.65, 126.54, 134.26, 159.43, 161.10 (C=O (CO<sub>2</sub>CH<sub>3</sub>)), 164.21 (C=O (CO<sub>2</sub>CH<sub>3</sub>)), 171.28 (C=O (CONH)) ppm; FT-IR : 3348.85 (NH), 1671.69 (CONH), 1728.17(CotBu), 2938.98, 3019.51 (CH), 1571.28 (C=C) cm<sup>-1</sup> MS: m/z 391[M<sup>+</sup>], mp 116-118 °C, Anal. Calcd for C<sub>21</sub>H<sub>29</sub>NO<sub>6</sub> (391): C, 64.45; H, 7.41; N, 3.58. Found: C, 64.51; H, 7.43; N, 3.54.

**Table 1.** Conversion dialkyl acetylene dicarboxylate and amides into vinyl amides

Entry	Amides	Activated alkynes	Products	Yields (%)
1		$\text{MeO}_2\text{C}-\text{C}\equiv\text{C}-\text{CO}_2\text{Me}$		98
2		$\text{MeO}_2\text{C}-\text{C}\equiv\text{C}-\text{CO}_2\text{Me}$		96
3		$\text{MeO}_2\text{C}-\text{C}\equiv\text{C}-\text{CO}_2\text{Me}$		93
4		$\text{tBuO}_2\text{C}-\text{C}\equiv\text{C}-\text{CO}_2\text{tBu}$		97
5		$\text{tBuO}_2\text{C}-\text{C}\equiv\text{C}-\text{CO}_2\text{tBu}$		96
6		$\text{tBuO}_2\text{C}-\text{C}\equiv\text{C}-\text{CO}_2\text{tBu}$		92

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## References and Notes

1. North, M. *Contemp. Org. Synth.* **1994**, *1*, 475.
2. (a) Beckwith, A. L. J. In *The Chemistry of Amides: Synthesis of Amides*, Zabicky, J., Ed.; Interscience: New York, **1970**; (b) Hudson, D. *J. Org. Chem.* **1988**, *53*, 617.
3. Mrozik, H.; Jones, H.; Friedman, J.; Schwartzkopf, G.; Schardt, R. A.; Patchett, A. A.; Hol., D. R.; Yakstis, J. J.; Riek, R. F.; Ostlind, D. A.; Plischker, G. A.; Butler, R. W.; Cuckler, A. C.; Campbell, W. C. *Experientia.* **1996**, 883.
4. (a) White, G. A. *Pestic. Biochem. Physiol.* **1989**, *34*, 255; (b) Yalcin, I.; Kaymakcioglu, B. K.; Oren, I.; Sener, E.; Temiz, O.; Akin, A.; Altanlar, N. *Farmaco* **1997**, *52*, 685.
5. Pradhan, K. J.; Variyar, P. S.; Bandekar, J. R. *Lebensm. Wiss. U. Technol.* **1999**, *32*, 121.
6. (a) Aki-Sener, E.; Bingol, K. K.; Oren, I.; Temiz-Arpaci, O.; Yalcin, I.; Altanlar, N. *Farmaco.* **2000**, *55*, 469; (b) Aki-Sener, E.; Bingol, K. K.; Temiz-Arpaci, O.; Yalcin, I.; Altanlar, N. *Farmaco.* **2002**, *57*, 451; (c) Yildiz-Oren, I.; Aki-Sener, E.; Ertas, C.; Temiz-Arpaci, O.; Yalcin, I.; Altanlar, N. *Turk. J. Chem.* **2004**, *28*, 441.
7. Kobayashi, I.; Muraoka, H.; Hasegawa, M.; Saika, T.; Nishida, M.; Kawamura, M.; Ando, R. *J. Antimicrob. Chemother.* **2002**, *50*, 129.
8. Engel, R. *Synthesis of Carbon- Phosphorus Bond*, CRC Press, 1988.
9. Cadogan, J. I. G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press: New York, 1979.
10. Engel, R. *Synthesis of Carbon-phosphorus Bonds*, CRC Press: Boca Raton, FL, 1988.
11. Johnson, A. W. *Ylide Chemistry*, Academic Press: New York, 1966.
12. Amri, H.; Rambaud, M.; Villieras, J. *Tetrahedron Lett.* **1989**, *30*, 7381.
13. Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241.
14. Yavari, I.; Ramazani, A. *Synth. Commun.* **1997**, *27*, 1449.
15. Yavari, I.; Shaabani, A.; Soleimani, H.; Nourmohammadian, F.; Bijanzadeh, H. R. *Magn. Reson. Chem.* **1996**, *34*, 1003.
16. Yavari, I.; Hekmatshoar, R. *J. Sci. I. R. Iran.* **1999**, *2*, 108.