Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 1655–1657
Tetrahedron Letters

Trapping of a phosphazide intermediate in the Staudinger reaction of tertiary phosphines with azides and its application to the synthesis of analogs of the marine alkaloid midpacamide

Pilar M. Fresneda,* Marta Castañeda, Miguel A. Sanz and Pedro Molina*

Departamento de Quimica Organica, Facultad de Quimica, Universidad de Murcia, Campus de Espinardo, E-30100 Murcia, Spain

Received 18 November 2003; revised 16 December 2003; accepted 19 December 2003

Abstract—A new method based on the reaction of an *E*-phosphazide, an intermediate in the Staudinger reaction between triphenylphosphine with an azide, with heterocumulenes allows the one-pot, two-component synthesis of a number of analogs of the pyrrole–imidazole marine alkaloid midpacamide. The procedure, which involves sequential treatment of the appropriate α-azido ester with triphenylphosphine and isothiocyanate leads to the thiohydantoin product after aqueous workup. The cyclization conditions can also be adapted to the synthesis of hydantoins by using isocyanates.

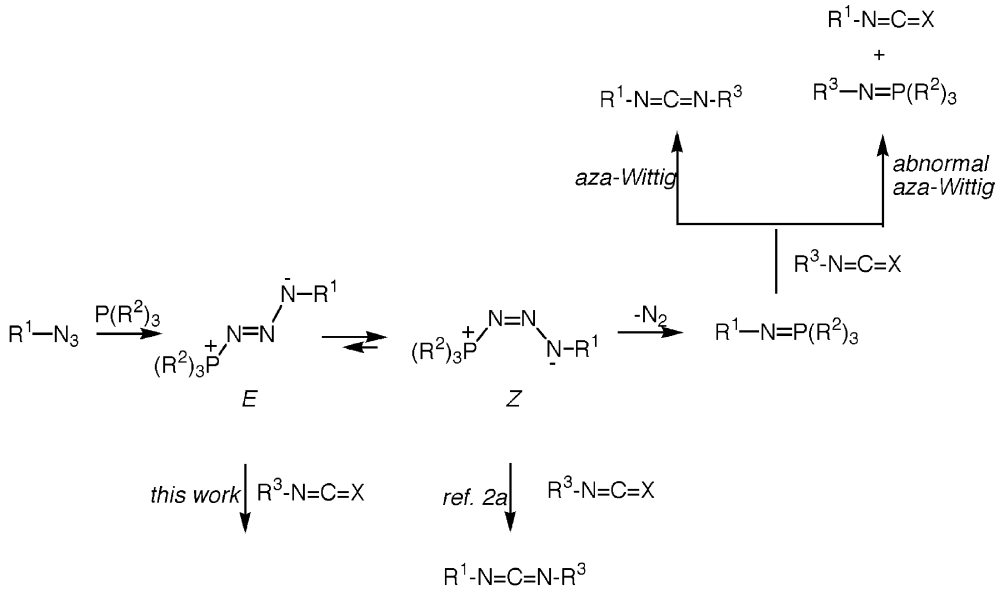
The reaction of a tertiary phosphine with an organic azide to produce an iminophosphorane after nitrogen evolution is known as the Staudinger reaction, and has proved to be a very useful reaction in synthetic organic chemistry.[1] The primary imination products, phosphazides (triazenophosphoranes or triazaphosphadienes), are sometimes isolable or stable,[2] or can be trapped either via intramolecular reactions,[2a,3] or through formation of a transition metal complex,[4] but as a rule they lose nitrogen at room temperature or at even lower temperatures to give the corresponding iminophosphoranes in practically quantitative yields. Mechanistic studies on the Staudinger reaction involving kinetic studies[5] revealed that the nucleophilic attack of the tertiary phosphine on the azide occurs with the formation of an *E*-phosphazide with zwitterionic character, in which the phosphorus atom has partial phosphonium character and the negative charge is on the N3 atom. After $E \rightarrow Z$ isomerization this decomposes rather easily into the iminophosphorane and nitrogen. This reaction can be described as an intramolecular nucleophilic attack of the negatively charged nitrogen atom, N3, onto the positively charged phosphorus atom.[6] In spite of the important role of iminophosphoranes in organic synthesis, they can react with a wide variety of carbonyl compounds containing polarized oxygen either via aza-Wittig[7] or abnormal aza-Wittig[8] pathways, little attention has been paid to their elusive precursors, phosphazides, primarily due to their rapid conversion to iminophosphoranes. It has been reported[2a] that an isolated *Z*-phosphazide reacts with isocyanates in a 'normal' aza-Wittig type fashion to give the expected carbodiimide.

This paper describes a case where a phosphazide intermediate may participate in a new cyclization process, thus bypassing the usual Staudinger pathway (nitrogen elimination to give the iminophosphorane. (Scheme 1).

During the course of our studies directed toward the synthesis of the pyrrole–imidazole marine alkaloids midpacamide and dispacamide,[9] we have reported the preparation of the N-acylated ethyl α-azido-ω-amino valerate **1**. Now, we have discovered that the reaction of triphenylphosphine with α-azido ester **1** is very slow with no detectable nitrogen evolution. When methyl isothiocyanate was added to this mixture and the resulting solution was stirred at room temperature no triphenylphosphine sulfide was detected. Surprisingly, after, aqueous workup the thiohydantoin **5**, instead of the expected urea derivative, was formed cleanly in 75% yield. The assignment of **5** as the product was determined by ^{1}H, and ^{13}C NMR and mass spectroscopy.

Keywords: Phosphazides; Isocyanates; Isothiocyanates; Hydantoins; Thiohydantoins.
* Corresponding authors. Tel.: +34-968-367496; fax: +34-968-364149; e-mail: pmolina@um.es

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.12.117

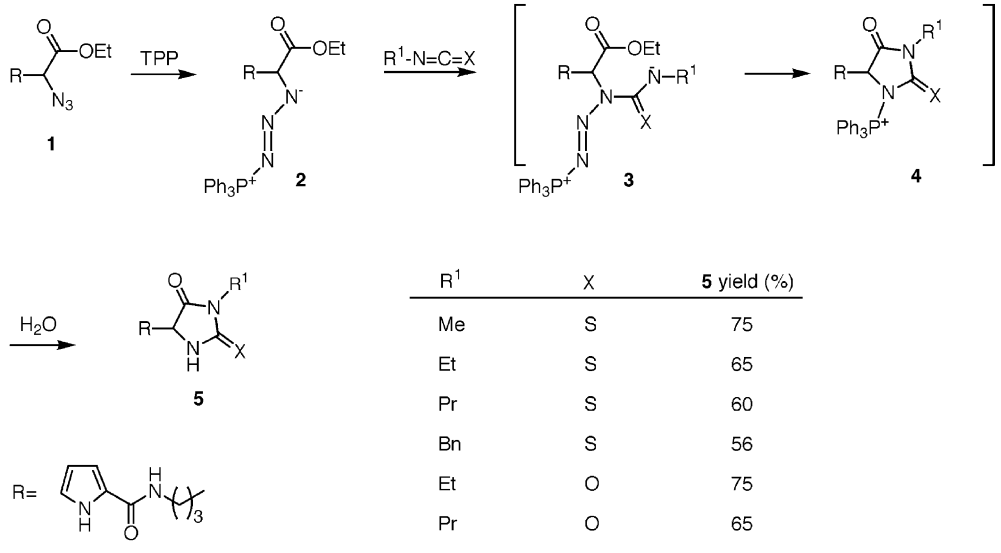


Scheme 1.

Similar results were obtained when ethyl-, propyl-, and benzyl isothiocyanate were used. We wished to determine if these cyclization conditions were suitable for the synthesis of hydantoins (Scheme 2, X = O). With the isocyanates employed, cyclization to hydantoins occurred under the same conditions as the thiohydantoins.[10]

We were intrigued by our inability to observe the uncyclized (thio)urea intermediates despite the mild and neutral reaction conditions employed. In the reaction of α-amino acid esters with isocyanates or isothiocyanates, cyclization usually involves heating, acid catalysis,[11] prolonged treatment with triethylamine at room temperature,[12] or treatment with sodium hydroxide.[9]

Monitoring the reaction sequence by ^{31}P NMR revealed a number of details: (a) the spectrum recorded on the mixture of triphenylphosphine and compound **1** showed a signal at $\delta = 17.70$ ppm, which is in good agreement with the previously reported values for phosphazides,[2a] (b) the spectrum recorded after the addition of methyl isothiocyanate exhibited a signal at $\delta = 42.40$ ppm characteristic of aminotriphenylphosphonium salts, and (c) the spectrum recorded on the final solution after work-up showed a signal at $\delta = 26.12$ ppm due to triphenylphosphine oxide. In addition, the IR spectrum of



R^1	X	**5** yield (%)
Me	S	75
Et	S	65
Pr	S	60
Bn	S	56
Et	O	75
Pr	O	65
*i*Pr	O	58
Bn	O	55

Scheme 2.

the solution after addition of methyl isothiocyanate did not show the characteristic carbodiimide absorption bands.

Taking into account these observations, we believe that this process is likely to take place through the initially formed *E*-phosphazide **2**, which reacts with methyl isothiocyanate to give a betaine **3**, which undergoes cyclization with the ester functionality with concomitant nitrogen evolution. Finally, hydrolytic cleavage of the resulting cyclized phosphonium salt **4** provided the final product **5** and triphenylphosphine oxide (Scheme 2). The *Z*-phosphazide required for elimination of nitrogen and concurrent iminophosphorane formation is essentially never formed, perhaps due to steric hindrance.

Why under the same conditions the reaction with tosyl isocyanate follows the aza-Wittig pathway giving the expected carbodiimide[9] can be explained by delocalization of the negative charge on the nitrogen atom by the electron-withdrawing tosyl group, which consequently increases the stability of betaine **3** and decreases the nucleophilic character of the nitrogen atom. Under these circumstances $E \rightarrow Z$ isomerization takes place thus allowing the reaction course to follow the aza-Wittig pathway.

Acknowledgements

We thank the Dirección General de Investigación (MCYT, Spain) project number BQU2001-0014 and Foundation Seneca (CARM) project number PI-48/00740/FS/01.

References and notes

1. Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353–1406.
2. (a) Molina, P.; Lopez-Leonardo, C.; Llamas-Botía, J.; Foces-Foces, C.; Fernandez-Castaño, C. *Tetrahedron* **1996**, *52*, 9629–9642, and references cited therein; (b) Alajarín, M.; Molina, P.; Lopez-Lazaro, A.; Foces-Foces, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 67–70; (c) Velasco, M. D.; Molina, P.; Fresneda, P. M.; Sanz, M. A. *Tetrahedron* **2000**, *56*, 4079–4084.
3. (a) Molina, P.; Arques, A.; Vinader, M. V. *Tetrahedron Lett.* **1989**, *30*, 6237–6240; (b) Molina, P.; Arques, A.; Vinader, M. V. *J. Org. Chem.* **1990**, *55*, 4724–4731; (c) Molina, P.; Arques, A.; Cartagena, I.; Obón, R. *Tetrahedron Lett.* **1991**, *32*, 2521–2524; (d) D'Andrea, S. V.; Ghosh, A.; Wang, W.; Freeman, J.; Szmuszkovicz, J. *J. Org. Chem.* **1991**, *56*, 2680–2684.
4. (a) Hillhouse, G. L.; Haymore, B. L. *J. Organomet. Chem.* **1978**, *162*, C23–C26; (b) Hillhouse, G. L.; Goeden, G. V.; Haymore, B. L. *Inorg. Chem.* **1982**, *21*, 2064–2071; (c) Bieger, F.; Bonhádir, G.; Réau, R.; Dahan, F.; Bertrand, G. *J. Am. Chem. Soc.* **1996**, *118*, 1038–1044.
5. Leffer, J. E.; Temple, R. D. *J. Am. Chem. Soc.* **1967**, *89*, 5235–5246.
6. Wideaur, C.; Grützmacher, H.; Shevchenco, I.; Gramlich, V. *Eur. J. Inorg. Chem.* **1999**, 1659–1664.
7. Reviews: (a) Barluenga, J.; Palacios, F. *Org. Prep. Proced. Int.* **1991**, *23*, 1–65; (b) Gusar, N. I. *Russ. Chem. Rev.* **1991**, *60*, 146–161; (c) Gololobov, Y. G.; Kasukhin, L. *Tetrahedron* **1992**, *48*, 1353–1406; (d) Eguchi, S.; Matsushita, K.; Yamashita, K. *Org. Prep. Proced. Int.* **1992**, *24*, 209–243; (e) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197–1218; (f) Wammhoff, H.; Richardt, G.; Stölben, S. *Adv. Heterocycl. Chem.* **1999**, *64*, 159–249; (g) Eguchi, S.; Okano, T.; Okawa, T. *Rec. Res. Dev. Org. Chem.* **1997**, *1*, 337–346.
8. (a) Itoh, K.; Okamura, M.; Yshii, Y. *J. Organomet. Chem.* **1974**, *65*, 327–334; (b) Bruché, L.; Garanti, L.; Zechi, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2177–2179; (c) Molina, P.; Conesa, C.; Alias, A.; Arques, A.; Velasco, M. D.; Llamas-Saiz, A. L.; Foces-Foces, C. *Tetrahedron* **1993**, *49*, 7599–7616; (d) Molina, P.; Alajarín, M.; Vidal, A. *Tetrahedron* **1990**, *46*, 1063–1078; (e) Alajarín, M.; Molina, P.; Sanchez-Andrada, P.; Foces-Foces, C. *J. Org. Chem.* **1999**, *64*, 1121–1130; (f) Hoesl, C. A.; Nefzi, A.; Hougten, R. A. *Tetrahedron Lett.* **2003**, *44*, 3705–3708.
9. Fresneda, P. M.; Molina, P.; Sanz, M. A. *Tetrahedron Lett.* **2001**, *42*, 851–854.
10. Typical procedure: To a solution of triphenylphosphine (0.47 g, 1.79 mmol) in dry diethyl ether (15 mL) at 0 °C a solution of the α-azido ester **1** (0.5 g, 1.79 mmol) in the same solvent (15 mL) was added dropwise under N_2. The resultant solution was allowed to warm to room temperature and stirred for 12 h. Then, it was cooled to 0 °C and a solution of the appropriate iso(thio)cyanate (1.79 mmol) was added. The resultant mixture was stirred at room temperature for 48 h and then THF/H_2O (9:1, v/v) (10 mL) was added. The solution was concentrated to dryness and the residue was chromatographed on a silica gel column using EtOAc as eluent to give **5**. Spectroscopic data for **5** (R^1 = Me, X = S): ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.50–1.90 (m, 4H, H-9+H-10), 3.06 (s, 3H, H-16), 3.22 (td, 2H, J = 6.0, 5.5 Hz, H-8), 4.24–4.33 (m, 1H, H-11), 6.05–6.09 (m, 1H, H-3), 6.74 (m, 1H, H-4), 6.83 (d, 1H, J = 0.9 Hz, H-2), 7.98 (t, 1H, J = 5.5 Hz, H-7), 10.34 (s, 1H, H-15), 11.36 (s, 1H, H-1). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 24.8 (C-9), 26.8 (C-16), 28.3 (C-10), 37.9 (C-8), 58.7 (C-11), 108.5 (C-3), 109.7 (C-4), 121.2 (C-2), 126.3 (C-5), 160.7 (C-6), 174.8 (C-12), 182.9 (C-14). IR (Nujol) v: 3375 (m), 3266 (m), 3163 (m), 1714 (s), 1632 (s) cm^{-1}. MS: m/z (%) (EI positive) 281 (M+1, 6), 280 (M, 44), 213 (24), 94 (100).
11. (a) Hemichart, J. P. *Synthesis* **1980**, 311–312; (b) Jacobsen, N.; Toelberg, J. *Synthesis* **1986**, 559–561; (c) Stella, V.; Higuchi, T. *J. Org. Chem.* **1973**, *38*, 1527–1534.
12. (a) Sim, M. M.; Ganesan, A. *J. Org. Chem.* **1997**, *62*, 3230–3235; (b) Zhang, W.; Lu, Y. *Org. Lett.* **2003**, *5*, 2555–2558.