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The reaction of (*N*-isocyanimino)triphenylphosphorane with dialkyl acetylenedicarboxylates in the presence of 1,3-diphenyl-1,3-propanedione: a novel three-component reaction for the stereoselective synthesis of dialkyl (*Z*)-2-(5,7-diphenyl-1,3,4-oxadiazepin-2-yl)-2-butenedioates

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Abstract—Reactions of dialkyl acetylenedicarboxylates with (*N*-isocyanimino)triphenylphosphorane in the presence of 1,3-diphenyl-1,3-propanedione proceed smoothly at room temperature to afford dialkyl (*Z*)-2-(5,7-diphenyl-1,3,4-oxadiazepin-2-yl)-2-butenedioates in high yields. The stereochemistry of the final products were confirmed by single crystal X-ray structure determination. The reaction is completely stereoselective.

1. Introduction

Compounds containing the oxadiazepine skeleton[1–5] have attracted interest in bio-organic, natural products and medicinal chemistry. They are an important class of heterocyclic compounds that have pharmaceutical and biological activities including antimicrobial, antifungal, and anticancer.[1–4]

For several years acetylenic esters have attracted the attention of organic chemists and are reactive systems that can take part in many chemical syntheses,[6] for example, as Michael acceptors.[7] In recent years, there has been increasing interest on the applications of acetylenic esters in the multi-component[8–11] synthesis. Due to the atom economy, convergent character and simplicity of one-pot procedures, multi-component condensation reactions (MCRs) have an advantageous position among other reactions. The development of novel MCRs is receiving growing interest from industrial chemistry research groups and represents a challenge for organic chemists.[12,13]

A few methods have been reported in the literature for the synthesis of oxadiazepine heterocycles which are multi-step in nature.[14,15] Based on our literature survey, reports on the synthesis of 1,3,4-oxadiazepine heterocycles are rare.[14,15]

In recent years, several synthetic methods have been reported for the preparation of (*N*-isocyanimino)triphenylphosphorane ($CNNPPh_3$) **1** (Scheme 1), there are several reports on the use of **1** in the synthesis of metal complexes.[16,17] However, application of **1** in the synthesis of organic compounds is rare.[18,19] As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds,[20–22] we sought to develop a convenient preparation of dialkyl 2-(5,7-diphenyl-1,3,4-oxadiazepin-2-yl)-2-butenedioates **7**. Herein we report a hitherto unknown, one-pot three-component reaction, which, starting from readily available dialkyl acetylenedicarboxylates **2** affords dialkyl (*Z*)-2-(5,7-diphenyl-1,3,4-oxadiazepin-2-yl)-2-butenedioates **7**.

Keywords: Acetylenic ester; (*N*-Isocyanimino)triphenylphosphorane; 1,3-Diphenyl-1,3-propanedione; 1,3,4-Oxadiazepine; Aza-Wittig reaction.
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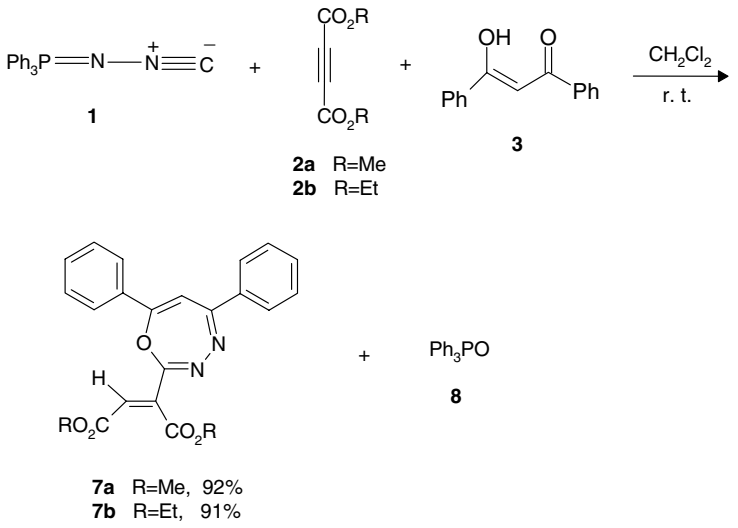
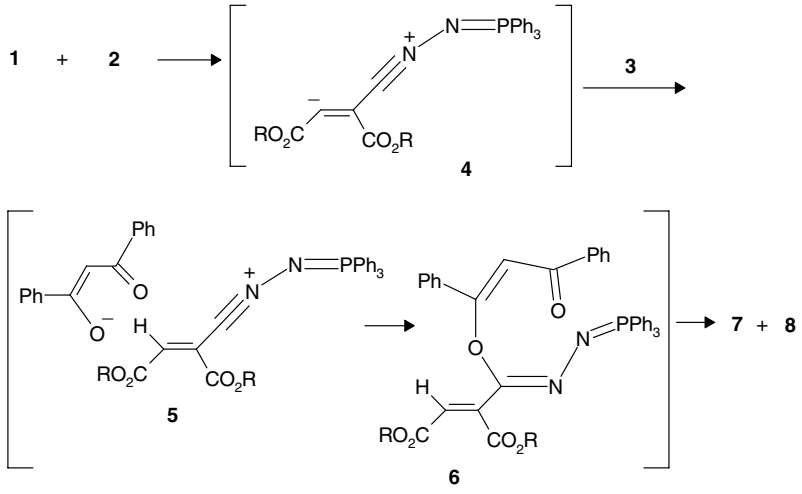


Scheme 1.

(*N*-Isocyanimino)triphenylphosphorane **1**, dialkyl acetylenedicarboxylates **2**, and 1,3-diphenyl-1,3-propanedione **3** were reacted in a 1:1:1 ratio in dichloromethane at room temperature to give dialkyl (*Z*)-2-(5,7-diphenyl-1,3,4-oxadiazepin-2-yl)-2-butenedioates **7** and triphenylphosphine oxide **8** (Scheme 1). The reaction proceeded smoothly and cleanly under mild conditions and no side reactions were observed. The mechanism of the three-component reaction between **1**, **2**, and **3** has not been established experimentally, however, a possible explanation is proposed in Scheme 2. On the basis of the well established chemistry of isocyanides,[6,23] it is reasonable to assume that compound **7** could result from the initial addition of **1** to acetylenic ester **2** followed by protonation of 1:1 adduct **4** by 1,3-diphenyl-1,3-propanedione **3**. Subsequent attack of the enolate anion on the positively charged ion **5** forms iminophosphorane **6**, which undergoes an intramolecular aza-Wittig[24] reaction under the conditions employed, to produce dialkyl (*Z*)-2-(5,7-diphenyl-1,3,4-oxadiazepin-2-yl)-2-butenedioates **7** and triphenylphosphine oxide **8** (Scheme 2). Based on TLC monitoring of the reaction and NMR analyses of the products, only *Z* stereoisomers (**7a** and **7b**) were observed.

The structures of products **7a**–**b** were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m*/*z* values. The ^{1}H NMR spectrum of **7b** consisted of two triplets for the methyl groups (OCH_2CH_3, $\delta = 1.25$ and 1.36 ppm), two quartets for the methylene groups (OCH_2CH_3, $\delta = 4.17$ and 4.37 ppm), two singlets for the oxadiazepine ring and vinylic protons, $\delta = 6.56$ and 6.58 ppm and a multiplet for the aromatic ring ($\delta = 7.44$–7.80 ppm). The ^{1}H decoupled ^{13}C NMR spectrum of **7b** showed 20 distinct resonances, partial assignment of these resonances is given in Section 2. Finally, the structure of **7b** was confirmed unambiguously by single crystal X-ray analysis (Fig. 1).

We believe that the reported method offers a mild, simple and efficient route for the preparation of dialkyl (*Z*)-2-(5,7-diphenyl-1,3,4-oxadiazepin-2-yl)-2-butenedioates



Scheme 2.

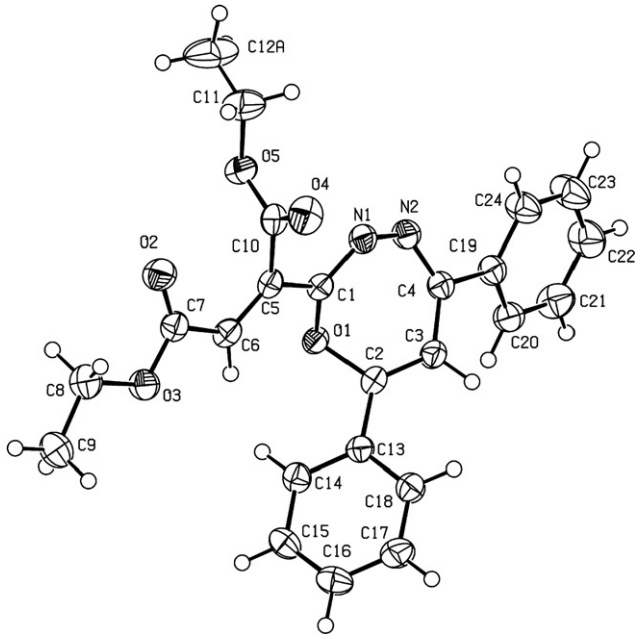


Figure 1. ORTEP diagram of the single crystal X-ray structure of **7b**. Selected interatomic distances (Å): O1–C1 = 1.389(2), O1–C2 = 1.4083(19), N1–C1 = 1.273(2), N1–N2 = 1.379(2), N2–C4 = 1.293(2), C1–C5 = 1.463(2), C2–C3 = 1.337(2), C2–C13 = 1.468(2), C3–C4 = 1.461(2), C4–C19 = 1.487(2), C5–C6 = 1.336(2), C5–C10 = 1.506(2), and C6–C7 = 1.479(2). Selected valence angles [°]: C1–O1–C2 = 109.12(12), C7–O3–C8 = 115.24(13), C1–N1–N2 = 121.93(15), C4–N2–N1 = 121.52(14), N1–C1–O1 = 124.50(16), N1–C1–C5 = 118.32(16), O1–C1–C5 = 117.06(14), C3–C2–O1 = 118.89(14), C3–C2–C13 = 127.23(15), O1–C2–C13 = 113.79(14), C2–C3–C4 = 122.59(15), N2–C4–C3 = 125.95(16), N2–C4–C19 = 114.97(14), C3–C4–C19 = 119.07(15), C6–C5–C1 = 123.16(16), C6–C5–C10 = 123.11(16), and C1–C5–C10 = 113.70(14). Selected torsion angles (°): C1–N1–N2–C4 = −47.4(2), N2–N1–C1–O1 = 3.4(2), N2–N1–C1–C5 = −172.38(14), C2–O1–C1–N1 = 67.87(19), C2–O1–C1–C5 = −116.27(15), C1–O1–C2–C3 = −64.7(2), C1–O1–C2–C13 = 118.29(15), O1–C2–C3–C4 = 1.3(3), C13–C2–C3–C4 = 177.80(16), N1–N2–C4–C3 = 8.1(3), N1–N2–C4–C19 = −171.61(15), C2–C3–C4–N2 = 34.6(3), C2–C3–C4–C19 = −145.62(18), N1–C1–C5–C6 = −175.10(15), O1–C1–C5–C6 = 8.8(2), N1–C1–C5–C10 = 2.7(2), O1–C1–C5–C10 = −173.40(13), C1–C5–C6–C7 = −175.85(15) and C10–C5–C6–C7 = 6.5(3).

7. The ease of work-up and high yields make it a useful addition to modern synthetic methodologies. Other aspects of this process are under investigation.

2. General procedure

To a magnetically stirred solution of (*N*-isocyanimino)triphenylphosphorane[17] **1** (0.302 g, 1 mmol) and 1,3-diphenyl-1,3-propanedione **3** (0.224 g, 1 mmol) in dry CH_2Cl_2 (10 ml) was added dropwise a solution of **2** (1 mmol) in CH_2Cl_2 (3 ml) at −10 °C over 15 min. The mixture was allowed to warm to room temperature and stirred for 72 h. The solvent was removed under reduced pressure and the viscous residue was purified by flash column chromatography (silica gel; light petroleum ether–ethyl acetate (5:1)). Characterization data are given below.

2.1. Dimethyl (*Z*)-2-(5,7-diphenyl-1,3,4-oxadiazepin-2-yl)-2-butenedioate 7a

Yellow crystals; mp: 148 °C. Yield: 92%. IR (KBr) (ν_{max}, cm^{-1}): 3015, 2939, 1739, 1631, 1269, 1169, 1023. ^1H NMR (250 MHz, $CDCl_3$) δ_H: 7.87–7.41 (m, 10H, arom.); 6.58 and 6.57 (2s, 2H, oxadiazepine and vinylic); 3.85 and 3.82 (s, 6H, $2OCH_3$).^{13}C NMR (62.5 MHz, $CDCl_3$) δ_C: 164.21 and 161.99 (2C=O); 164.77, 159.87, and 146.39 (3C, oxadiazepine), 140.68 (1C, vinylic); 136.56 and 132.23 (2C, arom.); 131.34, 130.94, 129.04, 128.62, 127.61, and 126.50 (10CH, arom.); 123.30 (1CH, vinylic); 106.89 (1CH, oxadiazepine); 53.06 and 52.39 (2C, $2OCH_3$). Anal. Calcd for $C_{22}H_{18}N_2O_5$ (390.39): C, 67.69; H, 4.65; N, 7.18; found: C, 67.77; H, 4.70; N, 7.26. MS: *m*/*z* (%) (EI) 390 (M^+, 8), 331 (11), 302 (10), 287 (9), 220 (14), 165 (12), 105 (100), and 77 (58).

2.2. Diethyl (*Z*)-2-(5,7-diphenyl-1,3,4-oxadiazepin-2-yl)-2-butenedioate 7b

Yellow crystals; mp: 138 °C. Yield: 91%. IR (KBr) (ν_{max}, cm^{-1}): 3008, 2931, 1739, 1631, 1185. ^1H NMR (250 MHz, $CDCl_3$) δ_H: 7.80–7.44 (m, 10H, arom.); 6.58 and 6.56 (2s, 2H, oxadiazepine and vinylic); 4.37 and 4.17 (2q, 4H, $^3J_{HH} = 7.0$ Hz, $2OCH_2$); 1.36 and 1.25 (2t, 6H, $^3J_{HH} = 7.0$ Hz, $2CH_3$).^{13}C NMR (62.5 MHz, $CDCl_3$) δ_C: 163.72 and 162.00 (2C=O); 164.38, 159.87, and 146.49 (3C, oxadiazepine); 140.41 (1C, vinylic); 136.63 and 132.25 (2C, arom.); 131.30, 130.90, 129.02, 128.61, 127.62, and 126.52 (10CH, arom); 123.77 (1CH, vinylic); 106.90 (1CH, oxadiazepine); 62.31 and 61.46 (2C, OCH_2); 14.00 and 13.86 (2C, $2CH_3$). Anal. Calcd for $C_{24}H_{22}N_2O_5$ (418.45): C, 68.89; H, 5.30; N, 6.69; found: C, 68.79; H, 5.36; N, 6.64. MS: *m*/*z* (%) (EI) 418 (M^+, 6), 345 (9), 220 (15), 105 (100), and 77 (43).

2.3. Preparation of single crystals of diethyl (*Z*)-2-(5,7-diphenyl-1,3,4-oxadiazepin-2-yl)-2-butenedioate (7b)

Yellow single crystals of **7b** were obtained from light petroleum ether–ethyl acetate (5:1) solution by slow evaporation at 20 °C over three days. The yellow single crystals were filtered, washed with a cold mixture of light petroleum ether–ethyl acetate (5:1) and dried at room temperature (mp 138 °C).

Crystal data for **7b** $C_{24}H_{22}N_2O_5$ (CCDC 631682): $M_W = 418.44$, monoclinic, space group $P21/c$, $a = 10.665(2)$ Å, $b = 9.843(2)$ Å, $c = 20.913(6)$ Å, $\alpha = 90.00°$, $\beta = 98.630(10)°$, $\gamma = 90.00°$, $V = 2170.5(9)$ Å^3, $Z = 4$, $D_c = 1.280$ mg/mm^3, $F(000) = 880$, crystal dimension $0.20 \times 0.15 \times 0.15$ mm, radiation, Mo K_α ($\lambda = 0.71070$ Å), $3.94 \leqslant 2\theta \leqslant 59.98$, intensity data were collected at 173(2) K with a Nonius KappaCCD diffractometer employing the $\omega/2\theta$ scanning technique, in the range of $-14 \leqslant h \leqslant 15$, $-13 \leqslant k \leqslant 10$, $-29 \leqslant l \leqslant 29$; the structure was solved by direct methods, all nonhydrogen atoms were positioned and anisotropic thermal parameters refined from 10,342 observed reflections with $R_{(int)} = 0.0412$ by a full matrix least-squares technique

converged to $R = 0.1356$ and $R_w = 0.1582$. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 631682. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033, e-mail: deposit@ccdc.cam.ac.uk and Web: www.ccdc.cam.ac.uk/data_request/cif].

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