SHORT PAPER

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An easy route to functionalised tetrahydropyridazines†

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A one-pot synthesis of dialkyl 5-ethoxy-6-oxo-1,2-diphenyl-1,2,5,6-tetrahydro-pyridazine-3,4-dicarboxylates by reaction of ethyl 2-(1,2-diphenylhydrazino)-2-oxoacetate, dialkyl acetylenedicarboxylate, and triphenylphosphine in good yields is reported.

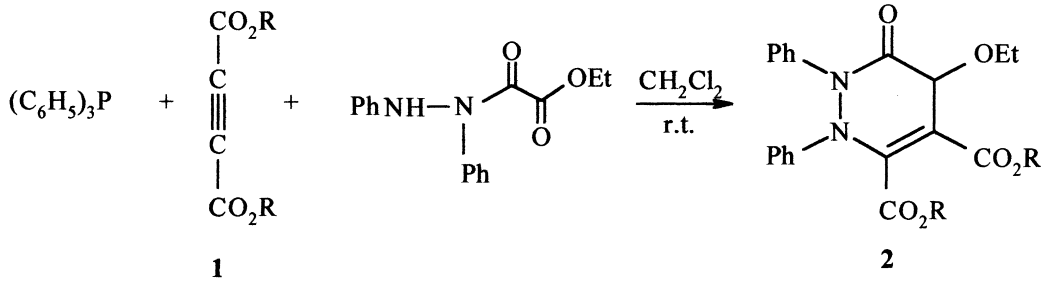
Keywords: intramolecular Wittig reaction; triphenylphosphine; acetylenic esters, pyridazines

Pyridazines are of interest because they constitute an important class of heterocyclic compounds, many of which exhibit useful biological activity.[1–3] The interest in pyridazine ring systems stem from the appearance of saturated and partially saturated pyridazine rings in many biologically active compounds. The expansion of work in this area following the commerical introduction of derivatives such as the antihypertensive hydralazine, the herbicide maleic hydrazide, and antibacterial sulfamethoxypyridazine in the middle of twentieth century has continued, and new selective herbicides and pharmaceuticals have been developed.[1–3] Herein we describe a simple synthesis of dialkyl 5-ethoxy-6-oxo-1,2-diphenyl-1,2,5,6-tetrahydropyridazine-3,4-dicarboxylates **2**. Thus, reaction of ethyl 2-(1,2-diphenylhydrazino)-2-oxoacetate with dialkyl acetylenedicarboxylate **1** in the presence of triphenylphosphine leads to **2** in 78–95% yields (see Scheme 1).

Reactions are known in which an unsaturated heterocyclic compound is produced from a phosphorane connected with a carbonyl group by a chain containing a heteroatom.[4–9] Thus, the tetrahydropyridazine **2** may be regarded as the product[10] of an intramolecular Wittig reaction. Such addition-cyclisation products apparently result from an initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct by ethyl 2-(1,2-diphenylhydrazino)-2-oxoacetate. Then, the positively charged ion is attacked by the nitrogen atom of the conjugate base of the NH-acid to form the phosphorane 3, which is converted into the 1,2,3,6-tetrahydropyridazine derivative **4**. Compound **4** apparently isomerizes under the reaction conditions employed to produce the 1,2,5,6-tetrahydropyridazine isomer **2** (see Scheme 2).

Structure **2** was assigned to the isolated products on the basis of their elemental analysis and IR, ^{1}H, ^{13}C NMR and mass spectral data. The mass spectra of compounds **2a–c** were fairly similar and displayed molecular ion peaks at m/z = 410, 438, and 494, respectively. ^{13}C NMR spectroscopy was used to distinguish structure **2** from the primary product, 1,2,3,6-tetrahydropyridazine derivative **4.** Thus, the ^{13}C NMR spectrum of each of the isolated products exhibited a methine carbon resonance at about δ = 72.8–74.7. The chemical shift for the methine carbon in **4** is expected to appear at about δ = 52–56.[10,11] Similarly, the five-membered ring pyrazole derivative **5** is ruled out.

The ^{1}H NMR spectrum of **2a** exhibited three single sharp lines, readily recognized as arising from methoxy (δ = 3.70 and 3.88) and methine (δ = 5.10) protons, along with characteristic multiplets for the ethoxy and phenyl groups. The ^{13}C NMR spectrum of **2a** showed 18 distinct resonances in agreement with the 1,2,5,6-tetrahydropyridazine structure. The ^{1}H and ^{13}C NMR spectra of **2b** and **2c** are similar to those of **2a**, except for the ester moieties, which exhibited characteristic resonances with appropriate chemical shifts.[10]



1 **2**

1, 2		% yield of 2
a	Me	95
b	Et	80
c	^{t}Bu	78

Scheme 1

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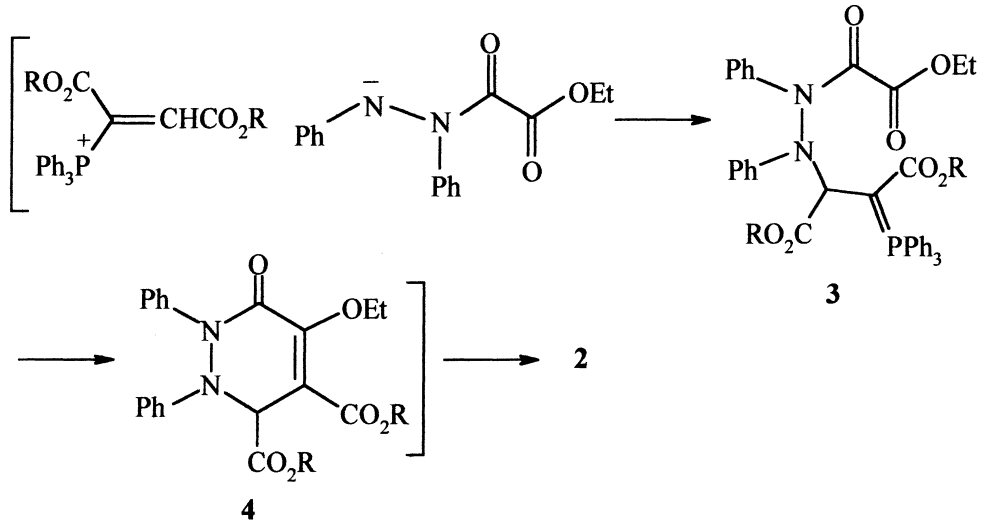
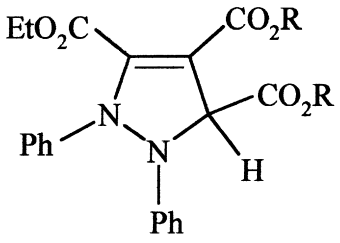
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 2



5

In summary, the reaction of ethyl 2-(1,2-diphenylhydrazino)-2-oxoacetate with dialkyl acetylenedicarboxylates in the presence of triphenylphosphine provides a one-pot entry into the synthesis of polyfunctionalised 1,2,5,6-tetrahydropyridazine derivatives of potential synthetic interest. Further applications of this type of addition-cyclization to the synthesis of interesting heterocycles will be reported in due course.

Experimental

Dialkyl acetylenedicarboxylates, triphenylphosphine, ethyl oxalyl chloride and diphenylhydrazine were obtained from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H and N were performed using a Heraus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionisation potential of 70 eV. ^{1}H and ^{13}C NMR spectra were measured of $CDCl_3$ solutions with a Brucker DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Aldrich silica gel 70-230 mesh.

Ethyl 2-(1,2-diphenylhydrazino)-2-oxoacetate was prepared in 95% yield from 1,2-diphenylhydrazine and ethyl oxalyl chloride in the presence of triethylamine. The product was recrystallised from ethanol to yield colourless crystals, m.p. 128–130°C, IR (KBr) (ν_{max}/cm^{-1}): 3255 (N–H), 1733 (C = O ester), 1654 (C = O amide). ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.1 (3 H, t, *J* 7.1 Hz, CH_3), 4.2 (2 H, q, *J* 7.1 Hz, OCH_2), 6.8–7.8 (11 H, m, 2 C_6H_5, NH).

The procedure for the preparation of dimethyl 5-ethoxy-6-oxo-1,2-diphenyl-1,2,5,6-tetrahydropyridazine-3,4-dicarboxylate **2a** is described here as an example. To a magnetically stirred solution of triphenylphosphine (0.252 g, 1 mmol) and ethyl 2-(1,2-diphenylhydrazino)-2-oxoacetate (0.284 g, 1 mmol) in dichloromethane (3 ml) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.142 g, 1 mmol) in dichloromethane (2 ml) at –5°C for 10 min. The reaction mixture was then allowed to warm to room temperature and stirred for 6 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography using hexane-ethyl acetate (2:1) as eluent. The solvent was removed under reduced pressure and the product was recrystalised from hexane-ethyl acetate (1:1).

2a: pale yellow crystals, m.p. 103–105°C (from 1:1 hexane-ethyl acetate), yield 0.38 g, 95%. IR (KBr) (ν_{max}/cm^{-1}): 1740 (C = O ester) and 1702 (C = O amide). MS, *m*/*z* (%): 410 (M$^+$, 2), 352 (14), 247 (6), 144 (35), 104 (40), 77 (100). Anal. Calcd. for $C_{22}H_{22}N_2O_6$ (410.43): C, 64.38; H, 5.40; N, 6.82. Found: C, 64.3; H, 5.3; N, 6.7%. ^{1}H NMR: δ 1.26 (3 H, t, *J* 7.1 Hz, CH_3), 3.70, 3.88 (6 H, 2 s, 2 OCH_3), 4.34 (2 H, 2 dq, $^2J_{HH}$ 10.8 Hz and $^3J_{HH}$ 7.1 Hz, ABX_3 system, OCH_2CH_3), 5.10 (1 H, s, OCH), 7.03 (1 H, tt, $^3J_{HH}$ 7.2 Hz and $^4J_{HH}$ 1 Hz, C^{p}H), 7.16 (1 H, tt, $^3J_{HH}$ 7.4 Hz and $^4J_{HH}$ 1 Hz, C^{p}H), 7.24 (2 H, dd, $^3J_{HH}$ 7.6 Hz and $^4J_{HH}$ 1 Hz, 2 C^{o}H), 7.30 (4 H, m, 4 C^{m}H), 7.38 (2 H, dd, $^3J_{HH}$ 7.6 Hz and $^4J_{HH}$ 1 Hz, 2 C^{o}H). ^{13}C NMR: δ 13.37 (CH_3), 51.22 and 52.45 (2 OCH_3), 62.33 (OCH_2), 72.79 (OCH), 102.49 (N–C = C), 116.27, 121.37, 122.96, 125.98, 128.85 and 128.87 (10 CH), 142.25, 147.63 and 150.30 (3 C), 160.66, 162.09 and 169.97 (3 C = O)

Diethyl 5-ethoxy-6-oxo-1,2-diphenyl-1,2,5,6-tetrahydropyridazine-3,4-dicarboxylate (**2b**): pale yellow crystals, m.p. 78–80°C (from 1:1 hexane-ethyl acetate), yield 0.35 g, 80%. IR (KBr) (ν_{max}/cm^{-1}): 1744 (C = O ester) and 1695 (C = O amide). MS, *m*/*z* (%): 438 (M$^+$, 3), 366 (6), 248 (4), 144 (30), 116 (10), 77 (100). Anal. Calcd. For $C_{24}H_{26}N_2O_6$ (438.48): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.4; H, 5.9; N, 6.4%. ^{1}H NMR: δ 1.24, 1.25 and 1.34 (9 H, 3 t, *J* 7.2 Hz, 3 CH_3), 4.17 (2 H, m, ABX_3 system, OCH_2CH_3), 4.25–4.40 (4 H, 4 dq, $^2J_{HH}$ 10.7 Hz and $^3J_{HH}$ 7.2 Hz, 2 AMX_3 system, 2 OCH_2CH_3), 5.07 (1 H, s, OCH), 7.03 (1 H, tt, $^3J_{HH}$ 7.3 Hz and $^4J_{HH}$ 1 Hz, C^{p}H), 7.16 (1 H, tt, $^3J_{HH}$ 7.4 Hz and $^4J_{HH}$ 1.1 Hz, C^{p}H) , 7.23 (2 H, dd, $^3J_{HH}$ 8.8 Hz and $^4J_{HH}$ 1 Hz, 2 C^{o}H), 7.29 (4 H, m, 4 C^{m}H), 7.40 (2 H, dd, $^3J_{HH}$ 8.7 Hz and $^4J_{HH}$ 1.1 Hz, 2 C^{o}H). ^{13}C NMR: δ 13.77, 14.12 and 14.13 (3 CH_3), 60.51, 61.57 and 62.66 (3 OCH_2), 73.48 (OCH), 103.81 (N–C = C), 116.64, 121.94, 123.23, 126.33, 129.23 and 129.25 (10 CH), 143.07, 147.96 and 150.86 (3 C), 161.21, 162.09 and 169.95 (3 C = O).

Di-t-butyl 5-ethoxy-6-oxo-1,2-diphenyl-1,2,5,6-tetrahydropyridazine-3,4-dicarboxylate (**2c**): yellow oil, yield 0.38 g, 78%. IR (KBr)(ν_{max}/cm^{-1}): 1736 (C = O ester) and 1702 (C = O amide). MS, *m*/*z* (%): 494 (M$^+$, 2), 337 (6), 219 (8), 183 (10), 144 (10), 99 (20), 77 (37), 57 (100). Anal. Calcd. for $C_{28}H_{34}N_2O_6$ (494.60): C, 67.99; H, 6.93; N, 5.66. Found: C, 67.9; H, 6.9; N, 5.7%. ^{1}H NMR: δ 1.20 (3 H, t, *J* 7.1 Hz, CH_3), 1.45 and 1.54 [18 H, 2 s, 2 $C(CH_3)_3$], 4.30 (2 H, 2 dq, $^2J_{HH}$ 10.7 Hz and $^3J_{HH}$ 7.1 Hz, AMX_3 system, OCH_2CH_3), 6.07 (1 H, s, OCH), 6.70 and 7.07 (2 H, 2 br t, $^3J_{HH}$ 7.1 Hz and $^3J_{HH}$ 7.2 Hz, 2 C^{p}H), 7.25 (2 H, br d, *J* 8.9 Hz, 2 C^{o}H), 7.30 (4 H, m, 4 C^{m}H), 7.39 (2 H, br d, $^3J_{HH}$ 7.7 Hz, 2 C^{o}H). ^{13}C NMR: δ 13.75 (CH_3), 27.91 and 28.09 (2 $C(CH_3)_3$) 62.38 (OCH_2), 74.66 (OCH), 81.16 and 81.98 (2 CMe_3), 106.49 (N–C = C), 116.18, 121.83, 122.57, 126.08, 129.13 and 129.16 (10 CH), 143.71, 147.24 and 150.98 (3 C), 161.37, 161.47 and 168.99 (3 C = O).

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