Tetrahedron Vol. 48, No. 9, pp. 1707-1714, 1992
Printed in Great Britain

0040-4020/92 $3.00+.00

Conjugated azoalkenes. Part XI. Direct synthesis of substituted pyrazoles and 4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones by heterocyclization of some zwitterionic 1,4-adducts between conjugated azoalkenes and triphenylphosphine

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(*Received in UK* 13 *January* 1992)

Abstract - The simple and direct synthesis in good yields of substituted pyrazoles and 4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones is reported. These products have been prepared by heterocyclization under different reaction conditions of some 1,5-zwitterionic species obtained from the 1,4-conjugate addition of triphenylphosphine to the azo-ene system of conjugated azoalkenes.

INTRODUCTION

In previous investigations we studied some Wittig-like reactions of conjugated azoalkenes with phosphorus ylides.[1-3] In particular, the reaction between conjugated azoalkenes and carboalkoxymethylene triphenylphosphoranes produces α,ß-unsaturated 4-carboxyhydrazones or 1-amino-3-triphenylphosphoranylidene-2,3-dihydropyrrol-2-ones,[1,2] while the reaction between the same reagents and α-oxotriphenylphosphoranes provides α,ß-unsaturated 4-oxohydrazones and 3-unsubstituted 1-aminopyrroles.[3] In both cases the reactions occur via a common 1,6-zwitterionic intermediate arising from the 1,4-conjugate addition of the phosphorus ylides to the azo-ene system to give interesting molecular functionalization by carboxy-[1,2,4] or carbonyl-olefination,[3,4] as well new and useful five-membered heterocyclic derivatives.[2,3]

Recently, we observed the ready 1,4-conjugate addition (Michael-like) of

triphenylphosphine to the azo-ene system of conjugated azoalkenes to provide isolable adducts able to mainly afford substituted 1-carboxy-5-alkoxypyrazoles and unusual 1-carboxy-4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones in acetonitrile or methanol under reflux, respectively. However, these compounds exhibited an easy hydrolitic cleavage of the N-CO bond also in the same reaction medium with the result that some times from these reactions were directly obtained the corresponding pyrazol derivatives.

RESULTS AND DISCUSSION

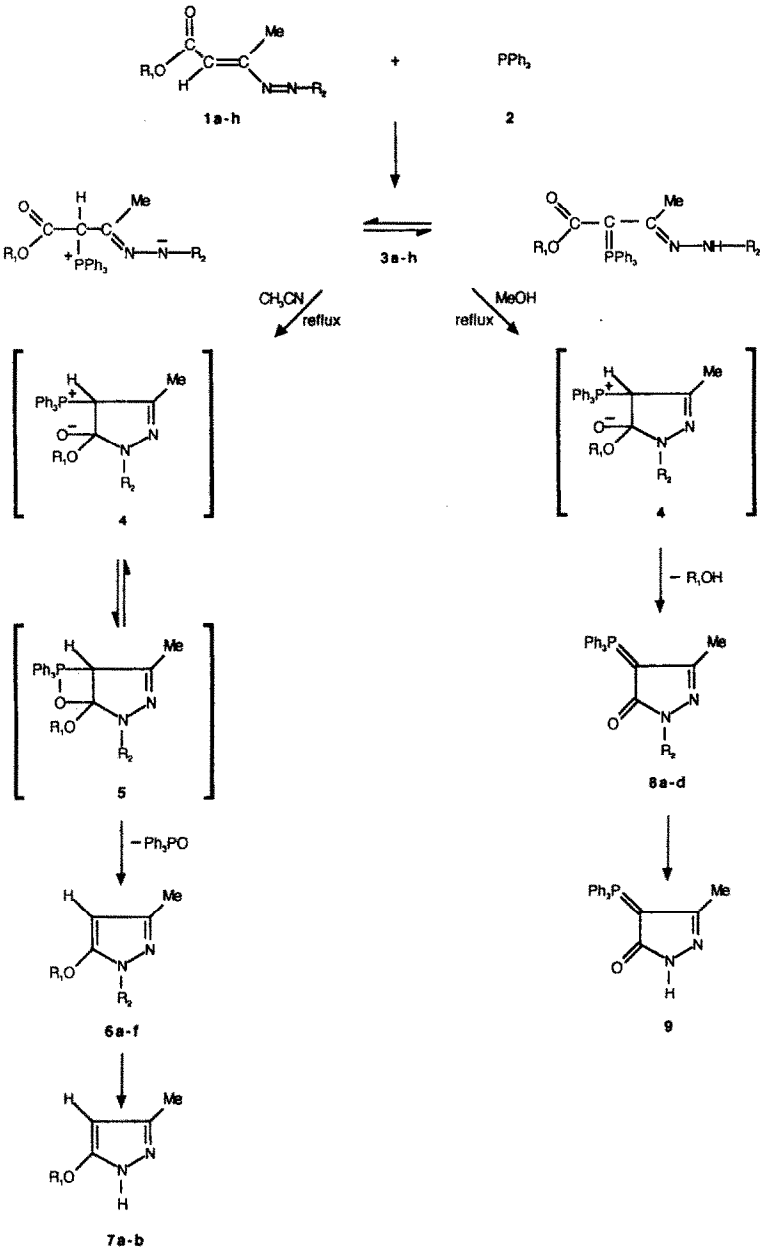
Conjugated azoalkenes (**1a-h**) promptly react with triphenylphosphine (**2**) at room temperature under magnetic stirring in ethyl acetate to give in good yield the stable 1,4-adducts (**3a-h**), as white precipitate. The 1,5-zwitterionic form produced initially by nucleophilic attack of triphenylphosphine to the azo-ene system of conjugated azoalkenes can tautomerize into corresponding hydrazonic form, as pictured in Scheme. Chemical and spectroscopical evidences support the existence of this tautomerism.

Reaction times, yields, and melting points of the 1,4-adducts **3a-h** are listed in Table 1.

Heating of the 1,4-adducts (**3a-h**) in different solvents probably produces the common betaine intermediate (**4**) by internal nucleophilic attack of the nitrogen on the ester group. In acetonitrile under reflux, the betaine intermediate (**4**) cyclises to a four-centre oxaphosphetane intermediate (**5**), as reported in our previous paper[3] and in accordance with a typical Wittig reaction mechanism.[5] Loss of triphenylphosphine oxide then leads to 1-alkoxycarbonyl- (**6a-d**) and 1-aminocarbonyl-5-alkoxypyrazoles (**6e** and **6f**). In the case of 1,4-adducts **3e** and **3f**, 5-alkoxypyrazoles (**7a** and **7b**) deriving from the hydrolitic N-CO bond cleavage were directly isolated instead of the expected pyrazole derivatives **6**, while in the case of the other 1,4-adducts the 5-alkoxypyrazoles **7** were detected only in traces. Indeed, all the 1-carboxy-5-alkoxypyrazole derivatives **6** may be easily converted in almost quantitative yields by simple hydrolitic cleavage at room temperature into relevant 5-alkoxypyrazoles **7**.

Reaction times, yields, and melting points of 1-alkoxycarbonyl-5-alkoxypyrazoles **6a-d**, 1-aminocarbonyl-5-alkoxypyrazoles **6e** and **6f**, and 5-alkoxypyrazoles **7a** and **7b** are listed in Table 2.

When the reaction is carried out in methanol under reflux elimination of an alcohol



R_1 = Me, Et R_2 = COOEt, $COOCMe_3$, $CONH_2$, CONHPh

Scheme

Table 1 - Reaction times, yields, and melting points of the 1,4-adducts **3a-h**.

1,4-Adduct (3)	R_1	R_2	Reaction time (h)	Yield[a] (%)	Mp[b] (°C)
3a	Me	COOEt	0.2	75	137-139
3b	Et	COOEt	0.3	74	133-135
3c	Me	$COOCMe_3$	0.2	76	140-142
3d	Et	$COOCMe_3$	0.3	73	135-137
3e	Me	$CONH_2$	0.2	76	157-160
3f	Et	$CONH_2$	0.1	88	163-166
3g	Me	CONHPh	0.1	87	162-164
3h	Et	CONHPh	0.1	80	167-170

[a]Yield of pure isolated product. [b]Melting points are uncorrected.

Table 2 - Reaction times, yields, and melting points of the 1-alkoxycarbonyl-5-alkoxypyrazoles **6a-d**, 1-aminocarbonyl-5-alkoxypyrazoles **6e** and **6f**, and 5-alkoxypyrazoles **7a** and **7b**.

Pyrazole (6) and (7)	R_1	R_2	Reaction time (h)	Yield[a] (%)	Mp[b] (°C)
6a	Me	COOEt	2.0	93	21-24
6b	Et	COOEt	2.0	92	22-25
6c	Me	$COOCMe_3$	3.0	78	85-86
6d	Et	$COOCMe_3$	2.0	96	62-64
6e	Me	CONHPh	3.0	75	52-54
6f	Et	CONHPh	2.5	82	81-82
7a	Me	H	2.5	80	48-50
7b	Et	H	2.0	85	60-62

[a]Yield of pure isolated product. [b]Melting points are uncorrected.

molecule from the betaine intermediate (**4**) becomes operative, in agreement with our previous findings.[2] This behaviour determines the formation from the 1,4-adducts **3a** and **3b**, or **3c** and **3d**, of the same 1-alkoxycarbonyl-4-triphenylphosphoranylidene-4,5-di-

hydropyrazol-5-ones **8a** or **8b**, respectively. Analogously, starting from the 1,4-adducts **3e** and **3f**, or **3g** and **3h**, were prepared the same 1-aminocarbonyl-4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones **8c** or **8d**, respectively. However, while **8c** and **8d** were produced in high yields (nearly 90%), **8a** and **8b** were revealed in lower yields (nearly 50%) due to the presence in almost equimolecular ratio of the relative 1-alkoxycarbonyl-5-alkoxypyrazoles **6a-d**, respectively. Also in this case, 4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-one **9**, coming from the hydrolysis of the N-CO bond, was detected in traces. Indeed, this compound may be readily synthesized in almost quantitative yields by simple hydrolitic treatment at room temperature of the 1-carboxy-4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones **8a-d**.

Reaction times, yields, and melting points of 1-alkoxycarbonyl-4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones **8a** and **8b**, 1-aminocarbonyl-4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones **8c** and **8d**, and 4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-one **9** are listed in Table 3.

Table 3 - Reaction times, yields, and melting points of the 1-alkoxycarbonyl-4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones **8a** and **8b**, 1-aminocarbonyl-4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones **8c** and **8d**, and 4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-one **9**.

Pyrazole (8) and (9)	R_2	Reaction time (h)	Yield[a] (%)	Mp[b] (°C)
8a	COOEt	12.0	40	227-230
8b	$COOCMe_3$	10.0	42	334-336
8c	$CONH_2$	10.0	82	336-337
8d	CONHPh	11.0	90	273-275
9	H			336-338

[a]Yield of pure isolated product. [b]Melting points are uncorrected.

The products here reported are not easily synthesizable by other methods and should merit of tests on some pharmaceutical activities.[6] The present investigation represents a further confirmation that conjugated azoalkenes are attractive products and versatile intermediates in organic chemistry, and especially in the synthesis of heterocycles.[7]

EXPERIMENTAL

Alkoxycarbonylazoalkenes **1a–d** (R_2=COOEt, $COOMe_3$),[8] and aminocarbonylazoalkenes **1e–h** (R_2=$CONH_2$, CONHPh)[9] were synthesized as previously reported and in accordance with the respective references. Triphenylphosphine **2** was commercial material (Farmitalia-Carlo Erba) and was used without further purification. The characterization of triphenylphosphine oxide was made in comparison with authentical commercial specimen (Aldrich). Mps up to 200 °C were determined in capillary tubes with a Büchi (Tottoli) apparatus, from 200 to 300 °C with a Reichert (Kofler) apparatus, and above 300 °C with an Electrothermal Digital Melting Point apparatus. Mps are uncorrected. The products often decompose at melting point. IR spectra were obtained in Nujol mull with a Perkin-Elmer 298 spectrophotometer. ^{1}H NMR spectra at 60 MHz were recorded on a Varian EM-360L spectrometer in $CDCl_3$, DMSO-d_6 or CD_3OD. Chemical shifts (δ) are reported in ppm downfield from internal TMS. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; D_2O ex, D_2O exchange. Merck precoated silica gel $60F_{254}$ plates (0.25 mm) were employed for analytical thin-layer chromatography (TLC), Merck silica gel PF_{254} plates (2.0 mm) for preparative TLC, and silica gel Kieselgel 60 (0.063–0.200 mm) for column chromatography. All the compounds prepared showed a satisfactory elemental analysis (C±0.35, H±0.30, N±0.30).

General procedure for the synthesis of the 1,4-adducts 3a–h. To a stirred solution of conjugated azoalkene (**1a–h**) (1 mmol), dissolved in ethyl acetate (3 ml), was added dropwise a solution of triphenylphosphine (**2**) (1 mmol) dissolved in ethyl acetate (3 ml), and the mixture was stirred (0.1–0.3 h) at room temperature until the conjugated azoalkene completely disappeared (monitored by silica gel TLC), and a white precipitate formed. The product **3** filtered off showed satisfactory purity and was used without further purification.

3a: IR 3370, 3240, 3130, 1690, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.12 and 1.23 (3H, 2t, J=7.0 Hz), 1.78 and 2.10 (3H, 2s), 3.30 and 3.43 (3H, 2s), 4.25 and 4.58 (2H, 2q, J=7.0 Hz), 7.17–8.87 (16H, m) ppm.

3b: IR 3380, 3250, 3150, 1695, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.80–1.48 (6H, m), 1.80 and 2.12 (3H, 2s), 3.67–4.78 (4H, m), 7.10–8.87 (16H, m) ppm.

3c: IR 3350, 3230, 3130, 1685, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.35 and 1.45 (9H, 2s), 1.83 and 2.05 (3H, 2s), 3.30 and 3.45 (3H, 2s), 7.17–8.57 (16H, m) ppm.

3d: IR 3350, 3235, 3130, 1685, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.97 (3H, t, J=7.0 Hz), 1.38 and 1.47 (9H, 2s), 1.83 and 2.10 (3H, 2s), 4.45 (2H, q, J=7.0 Hz), 7.10–8.63 (16H, m) ppm.

3e: IR 3480, 3305, 3190, 3115, 1740, 1685, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.75 and 2.15 (3H, 2s), 3.32 and 3.48 (3H, 2s), 4.60 and 5.38 (2H, 2 br s, D_2O ex), 7.20–8.37 (16H, m) ppm.

3f: IR 3480, 3300, 3200, 3120, 1735, 1680, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.82 (3H, t, J=7.0 Hz), 1.77 and 2.17 (3H, 2s), 4.33 (2H, q, J=7.0 Hz), 4.65 and 5.45 (2H, 2 br s, D_2O ex), 7.03–8.35 (16H, m) ppm.

3g: IR 3340, 3180, 3105, 1740, 1680, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.82 and 2.22 (3H, 2s),

3.32 and 3.45 (3H, 2s), 6.45–8.43 (17H, m) ppm.

3h: IR 3345, 3200, 3110, 1735, 1680, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) 0.82 (3H, t, J=7.0 Hz), 1.82 and 2.22 (3H, 2s), 4.33 (2H, q, J=7.0 Hz), 6.63–8.45 (17H, m) ppm.

General procedure for the synthesis of the 1-alkoxycarbonyl-5-alkoxypyrazoles 6a–d, 1-aminocarbonyl-5-alkoxypyrazoles 6e and 6f, and 5-alkoxypyrazoles 7a and 7b. A solution of 1,4-adduct (**3a–h**) (1 mmol), dissolved in acetonitrile (5 ml), was heated under reflux (2–3 h) until the 1,4-adduct completely disappeared (monitored by silica gel TLC). The solvent was evaporated under reduced pressure and the crude products were isolated by chromatography on a silica gel column (elution with methylene chloride and methylene chloride–ethyl acetate mixtures). The products **6** and **7** were further purified by crystallization from ethyl ether–petroleum ether (b.p. 40–60 °C).

6a: IR 1755, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) 1.38 (3H, t, J=7.0 Hz), 2.18 (3H, s), 3.85 (3H, s), 4.32 (2H, q, J=7.0 Hz), 5.25 (1H, s) ppm.

6b: IR 1745, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) 1.43 (3H, t, J=7.0 Hz), 1.47 (3H, t, J=7.0 Hz), 2.20 (3H, s), 4.63 (2H, q, J=7.0 Hz), 4.97 (2H, q, J=7.0 Hz) 5.38 (1H, s) ppm.

6c: IR 1755, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) 1.57 (9H, s), 2.13 (3H, s), 3.75 (3H, s), 5.22 (1H, s) ppm.

6d: IR 1750, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) 1.38 (3H, t, J=7.0 Hz), 1.58 (9H, s), 2.12 (3H, s), 4.48 (2H, q, J=7.0 Hz), 5.18 (1H, s) ppm.

6e: IR 3370, 1735, 1610, 1600, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) 2.50 (3H, s), 3.77 (3H, s), 5.38 (1H, s), 6.57–7.53 (5H, m), 8.55 (1H, br s, D_2O ex) ppm.

6f: IR 3370, 1735, 1615, 1600, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) 1.32 (3H, t, J=7.0 Hz), 2.50 (3H, s), 4.50 (2H, q, J=7.0 Hz), 5.40 (1H, s), 6.63–7.45 (5H, m), 8.67 (1H, br s, D_2O ex) ppm.

7a: IR 3190, 3150, 3130, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) 2.18 (3H, s), 3.83 (3H, s), 5.38 (1H, s), 10.07 (1H, br s, D_2O ex) ppm.

7b: IR 3190, 3140, 3120, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) 1.33 (3H, t, J=7.0 Hz), 2.20 (3H, s), 4.63 (2H, q, J=7.0 Hz), 5.42 (1H, s), 10.55 (1H, br s, D_2O ex) ppm.

General procedure for the synthesis of the 1-alkoxycarbonyl-4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones 8a and 8b, 1-aminocarbonyl-4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones 8c and 8d, and 4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-one 9. A solution of 1,4-adduct (**3a–h**) (1 mmol), dissolved in methanol (5 ml), was heated under reflux (10–12 h) until the 1,4-adduct completely disappeared (monitored by silica gel TLC). The solvent was evaporated under reduced pressure and the crude products were isolated by chromatography on a silica gel column (elution with methylene chloride and methylene chloride–ethyl acetate mixtures). The products **8** and **9** were further purified by crystallization with methanol.

8a: IR 1745, 1625, 1465, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) 1.67 (3H, s), 1.67 (3H, t, J=7.0 Hz),

4.50 (2H, q, J=7.0 Hz), 7.45-8.05 (15H, m) ppm.

8b: IR 1745, 1615, 1460, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) 1.33 (3H, s), 1.58 (9H, s), 7.12-7.80 (15H, m) ppm.

8c: IR 3515, 3310, 1715, 1620, 1460, 1105 cm^{-1}; ^1H NMR (DMSO-d_6) 1.37 (3H, s), 6.05 (1H, br s, D_2O ex), 7.17-7.85 (15H, m), 8.38 (1H, br s, D_2O ex) ppm.

8d: IR 3410, 1715, 1630, 1460, 1105 cm^{-1}; ^1H NMR (DMSO-d_6) 1.33 (3H, s), 6.53-7.83 (21H, m) ppm.

9: IR 3210, 3130, 1600, 1460, 1105 cm^{-1}; ^1H NMR (CD_3OD) 1.38 (3H, s), 7.42-8.03 (16H, m) ppm.

ACKNOWLEDGMENT

This work was supported by financial assistance from Consiglio Nazionale delle Ricerche (CNR - Roma), Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST - Roma), and Regione Marche (Ancona).

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