A Novel Synthesis of 5-Chloro-3-methoxycarbonyl-1-arylpyrazoles from Arylazomethylenetriphenylphosphoranes

C. Baldoli, L. Lattuada, E. Licandro*, S. Maiorana and A. Papagni*

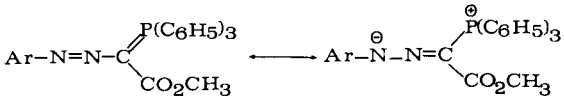
Dipartimento di Chimica Organica e Industriale, Universitá di Milano,
Via Golgi 19, 20133 Milano, Italy

Received July 19, 1988

The reaction of arylazomethoxycarbonylmethylenetriphenylphosphoranes **1** with chloroform and sodium hydroxide in the presence of benzyltriethylammonium chloride (TEBA) as phase transfer catalyst directly affords 5-chloro-3-methoxycarbonyl-1-arylpyrazoles **3**.

J. Heterocyclic Chem., **26**, 241 (1989).

During the last few years we have investigated the chemical behaviour of arylazomethylenetriphenylphosphoranes **1** towards electrophilic species, both in intermolecular [1-5] and intramolecular [2-4] reactions and we have found that the reactivity of compounds **1** is strictly related to the possibility of delocalizing the negative charge of the ylidic carbon atom on the azo group: this is in fact the preferred site of attack of electrophilic reagents.



1

We wish now to report the results of the reaction of the arylazomethoxycarbonylmethylenephosphoranes **1a-e** with chloroform and 50% aqueous sodium hydroxide under phase transfer conditions, using benzyltriethylammonium chloride (TEBA) as catalyst.

The reaction, run at room temperature, directly leads to the 5-chloro-3-methoxycarbonyl-1-arylpyrazoles **3a-e**, besides variable amounts of the corresponding acids **4a-e** (Scheme I). Purification by crystallization of compounds **4** was unsuccessful since they easily decarboxylate by heating, therefore they were retransformed into their methyl esters **3a-e** by reaction with diazomethane and characterized as such except for **3c**, an oily product, which was transformed into its hydrazide (see Experimental).

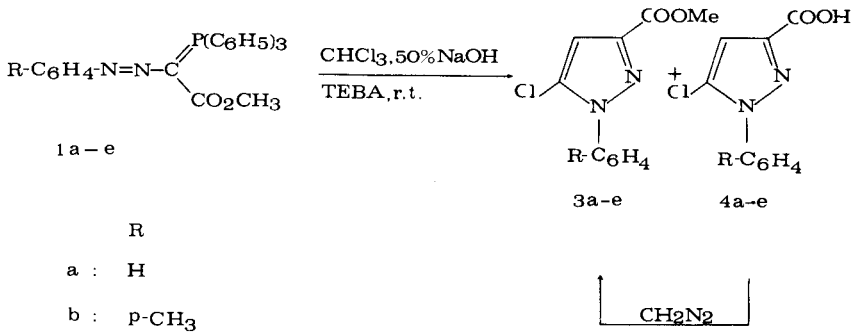
Table 1

Yields, Physical and Spectroscopic Data of Pyrazoles **3a-e**

Products	Yield [a] (%)	mp °C solvent	IR (nujol)	^{1}H NMR (ppm)
3a	46	61 [b]	1750	3.8 (3H, s, OCH_3), 6.8 (1H, s, C_4-H), 7.3-7.6 (5H, m, C_6H_5)
3b	58	90 [b]	1725	2.4 (3H, s, CH_3-Ar), 3.8 (3H, s, OCH_3), 6.8 (1H, s, C_4-H), 7.1-7.5 (4H, dd, C_6H_4)
3c	59	oil		3.8-3.9 (6H, d, OCH_3), 6.8 (1H, s, C_4-H), 6.9-7.5 (4H, m, C_6H_4)
3d	57	98 [b]	1740	3.9-4 (6H, d, OCH_3), 6.8 (1H, s, C_4-H), 6.8-7.4 (4H, dd, C_6H_4)
3e	33	94 [b]	1750	3.9 (3H, s, OCH_3), 6.8 (1H, s, C_4-H), 7.2-7.5 (4H, dd, C_6H_4)

[a]: Overall yields of 5-chloropyrazoles **3**. [b]: Diisopropyl ether.

Scheme I



1a-e

R

a : H

b : p-CH_3

c : o-OCH_3

d : p-OCH_3

e : p-Cl

Yields, analytical and spectroscopic data of pyrazoles **3** are listed in Table 1, while elemental analysis are reported in Table 2.

Table 2

Analytical Characterization of Compounds **3**

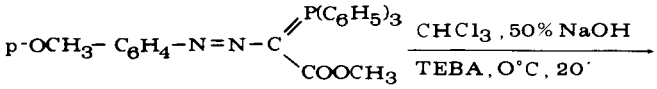
Product [a]	Formula (Molecular weight)	Analysis (%) Calcd./Found C	H	N
3a	$C_{11}H_9ClN_2O_2$ (236.65)	55.82 / 55.68	3.83 / 3.78	11.84 / 11.69
3b	$C_{12}H_{11}ClN_2O_2$ (250.67)	57.49 / 57.12	4.42 / 4.38	11.17 / 11.07
3d	$C_{12}H_{11}ClN_2O_3$ (266.67)	54.04 / 54.48	4.16 / 4.13	10.50 / 10.54
3e	$C_{11}H_8Cl_2N_2O_2$ (271.09)	48.73 / 48.32	2.97 / 2.93	10.33 / 10.29

[a] Compound **3d**; ms: m/e 266, 268 (M^+).

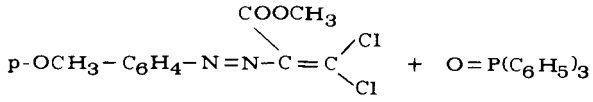
Monitoring the reactions reported in Scheme I by tlc (eluant: light petroleum/ethyl acetate 7:3) we observed the intermediate formation of a product, visible as an orange spot, which disappeared as the reaction was completed.

In order to give a deeper insight into the reaction mechanism we performed this reaction under controlled conditions, with the aim to isolate the intermediate product. After reacting **1d** with chloroform, 50% sodium hydroxide and TEBA as catalyst at 0° for 20 minutes, we were able to isolate in good yield the product corresponding to the orange spot, which was the methyl-3,3-dichloro-2-arylazoacrylate **2** (Scheme II).

Scheme II



1d

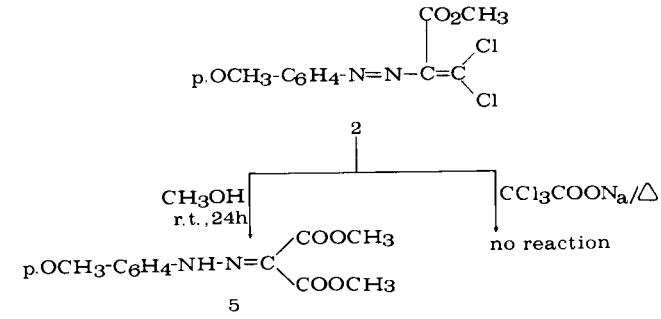


2

Compound **2** arises from a coupling reaction between the "*in situ*" generated dichlorocarbene and the phosphorane moiety of compound **1d** [6,7] and its formation represents the first example of attack, by an electrophile, to the ylidic carbon atom in azophosphoranes **1**.

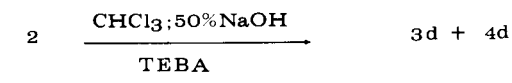
Compound **2** proved to be unreactive towards the dichlorocarbene "*in situ*" generated by thermal decomposition of sodium trichloroacetate, while it easily added a weak nucleophile like methanol, leading to the hydrazone of the diester of oxomalonic acid **5** (Scheme III) [8].

Scheme III



Moreover compound **2** reacted with chloroform and 50% sodium hydroxide under phase transfer conditions at room temperature, leading to the same mixture of pyrazoles **3d** and **4d** directly obtained from compound **1d** (Scheme IV), thus indicating that **2** is actually an intermediate in the reaction of Scheme I.

Scheme IV



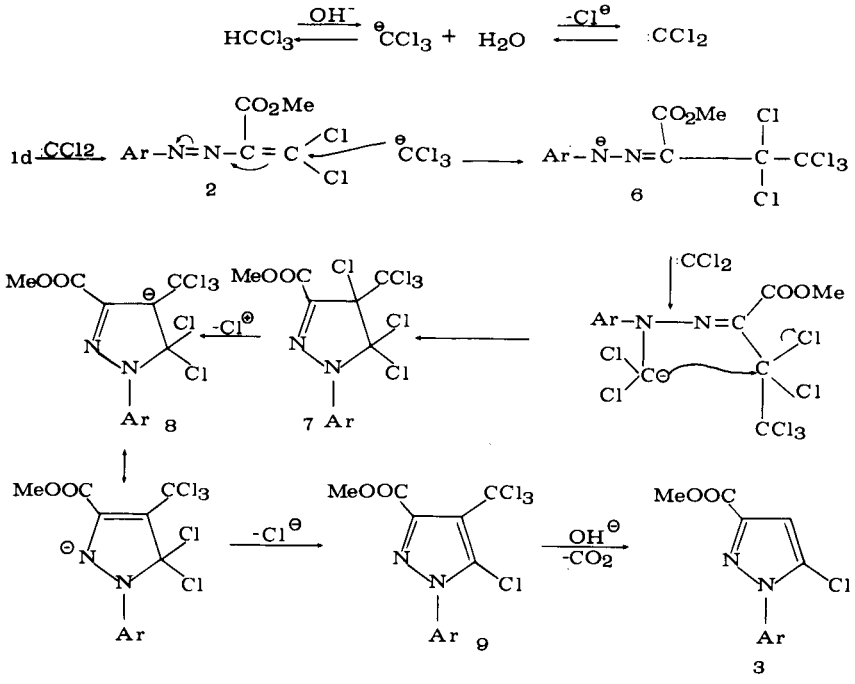
In addition, a careful separation made by flash chromatography (eluant: light petroleum/diethyl ether 8:2) on the crude reaction mixture arising from **2** (Scheme IV) allowed us to isolate a small amount of the 5-chloro-4-trichloromethyl-3-methoxycarbonyl-1-*p*-methoxyphenylpyrazole **9**. This compound is the precursor of pyrazole **3d**; in fact it could be transformed into compound **4d** by treatment with sodium hydroxide in phase transfer conditions. Compound **4d** was then esterified to give compound **3d**.

The isolation of intermediate **9** together with the transformation of compounds **2** and **9** into pyrazoles **3d** and **4d** are in agreement with the reaction mechanism we propose in Scheme V.

Because of the unreactivity of dichloroazoalkene **2** towards :CCl_2 (see Scheme III), a nucleophilic addition of $^-CCl_3$ to dichloroazoalkene **2** occurs to give the aza anion **6** which, by reaction with :CCl_2, affords the pyrazolidine derivative **7**. The Cl^+ elimination, operated by the OH^-, from position 4 of compound **7** to give the stabilized azaallyl-anion **8** and the subsequent expulsion of a chloride ion from the adjacent position 5 leads to the trichloromethyl-pyrazole **9** which, in turn, by the decaboxylative hydrolysis of the CCl_3 group give the compound **3**.

In conclusion, the reaction of azophosphoranes **1** with chloroform and sodium hydroxide under phase transfer conditions affords in a "one pot reaction", the 5-chloro-pyrazole derivatives **3a-e**; few examples of this class of compounds are known and often are difficult to prepare and are obtained in low yields [9].

Scheme V



Moreover intermediates in such reactions are the methyl-3,3-dichloro-2-arylazoacrylates. Although we isolated only the dichloroazaalkene **2**, in all the other reactions of Scheme I an analogous compound could be detected by tlc analysis.

We wish to point out that compound **2** represents the first example of an unknown class of azoalkenes, whose reactivity could be an interesting subject of study in the future.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded on a Perkin-Elmer X98 Spectrophotometer. The ^{1}H nmr spectra were recorded on a A90 Varian spectrometer, using deuteriochloroform as the solvent and tetramethylsilane as the internal standard; chemical shifts are given in δ units. The azophosphoranes **2a-e** have been prepared as previously reported [1].

5-Chloro-1-arylpyrazoles **3a-e** and **4a-e**: General Procedure.

To a solution of compound **1** (1 mmole) in dichloromethane (10 ml), chloroform (1 ml), 50% sodium hydroxide (3 ml) and TEBA (50 mg) were added. After standing under vigorous stirring at room temperature for 12 hours, the mixture was diluted with water, the organic layer separated and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude residue was chromatographed on a silica gel column (eluant, ethyl acetate:light petroleum 1/1). Compounds **3a,b,d,e** were crystallized by the solvents indicated in the Table 1, while compound **3c** was reacted with hydrazine in methanol solution to give the hydrazide derivative, mp 165° (from methanol); ir (nujol): 1670 cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}ClN_4O_2$: C, 48.81; H, 4.10; N, 20.70. Found: C, 49.29; H, 4.14; N, 20.55.

From the aqueous layer, the 5-chloro-3-carboxy-1-arylpyrazoles **4a-e** could be recovered by acidification with 5% hydrochloric acid solution and extraction with dichloromethane. After evaporation of the solvent the crude acids **4a-e** were suspended in anhydrous diethyl ether and treated with diazomethane to give compounds **3a-e**.

Methyl 2-*p*-Methoxyphenylazo-3,3-dichloroacrylate **2**.

To a solution of **1d** (26 mmoles) in chloroform (200 ml), 50% sodium hydroxide (50 ml) and TEBA (2 g) were added. After 20 minutes under vigorous stirring at 0°, the mixture was diluted with water and the organic layer separated and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude residue was chromatographed on silica gel column (eluant light petroleum: ethylacetate 7/3). Compound **2d** thus recovered was washed with *n*-hexane at room temperature, yield 68%, mp 69°, bp 185°/0.4 mm Hg; ir (Nujol): 1740 cm^{-1}; ^{1}H nmr: 3.9 (6H, d, OCH_3), 6.8-7.9 (4H, dd, aromatic).

Anal. Calcd. for $C_{11}H_{10}Cl_2N_2O_3$: C, 45.70; H, 3.46; N, 9.69. Found: C, 46.03; H, 3.51; N, 9.47.

5-Chloro-4-Trichloromethyl-3-methoxycarbonyl-1-*p*-methoxyphenylpyrazole **9** from **2**.

To a solution of **2** (10 mmoles) in dichloromethane (70 ml), chloroform (12 ml), 50% sodium hydroxide (15 ml) and TEBA (0.3 g) were added. After 12 hours under vigorous stirring at room temperature, the mixture was diluted with water, the organic layer separated and dried over sodium sulfate. The crude residue was chromatographed on silica gel column (eluant light petroleum:diethyl ether 8/2). Compound **9** thus recovered (70 mg) was crystallized from *n*-hexane, mp 87-88°; ^{1}H nmr: 3.9 (6H, d, OCH_3), 6.9-7.4 (4H, dd, aromatic); ms: m/e 384, 386, 388 (M^+).

Anal. Calcd. for $C_{13}H_{10}Cl_4N_2O_3$: C, 40.64; H, 2.62; N, 7.29. Found: C, 40.35; H, 2.65; N, 6.97.

Hydrolysis of Compound **9** to Compound **4d**.

To a solution of compound **9** (10 mg) in dichloromethane (2 ml), 50% sodium hydroxide (0.5 ml) and a catalytic amount of TEBA were added at room temperature with magnetic stirring. After the starting compound disappeared, the mixture was diluted with water, the aqueous phase was separated, acidified with 10% hydrogen chloride and extracted with dichloromethane. The organic layer was separated, dried over sodium

sulfate and evaporated. The residue (4 mg) was refluxed with methanol saturated with gaseous hydrogen chloride. Compound **4d** was identified by comparison of the ^1H nmr of the crude reaction mixture with those of the pure compound.

REFERENCES AND NOTES

[1] A. Alemagna, P. Del Buttero, E. Licandro, S. Maiorana and R. Trave, *Tetrahedron*, **40**, 971 (1984).

[2] A. Alemagna, P. Del Buttero, E. Licandro, A. Papagni and M. Ballabio, *Tetrahedron*, **41**, 2503 (1985).

[3] A. Alemagna, P. Del Buttero, E. Licandro, S. Maiorana and A. Papagni, *Tetrahedron*, **41**, 3321 (1985).

[4] A. Alemagna, C. Baldoli, E. Licandro, S. Maiorana and A. Papagni, *Tetrahedron*, **42**, 5397 (1986).

[5] A. Alemagna, P. Del Buttero, E. Licandro and A. Papagni, *Gazz. Chim. Ital.*, **118**, 249 (1988).

[6] R. Oda, Y. Ito and M. Okano, *Tetrahedron Letters*, 7 (1964).

[7] Y. Ito, M. Okano and R. Oda, *Tetrahedron*, **22**, 2615 (1966).

[8] Compound **5** was identical to an authentic sample prepared according to the literature method; *Beilstein*, **15**, 601.

[9] Michaelis, *Ann. Chem.*, **358**, 44 (1911).