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N-Alkenyl-3,5-Pyrazolidinediones from Ketone Hydrazones, PCl_3 and Malonic acid.

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Abstract: The title compounds **3**, a new series of 3,5-pyrazolidinediones, have been synthesized at room temperature by a one-pot reaction between ketone hydrazone **1**, PCl_3 and malonic acid. Changing the order of addition of reagents, or their simultaneous addition, gave identical results. In all the procedures the yields are good and in the cases **a**,**b**,**c** and **g** the *E*-alkenyl isomer was obtained as the exclusive isomer. A dual mechanism which depends on the order of addition of the reactants is hypothesised.

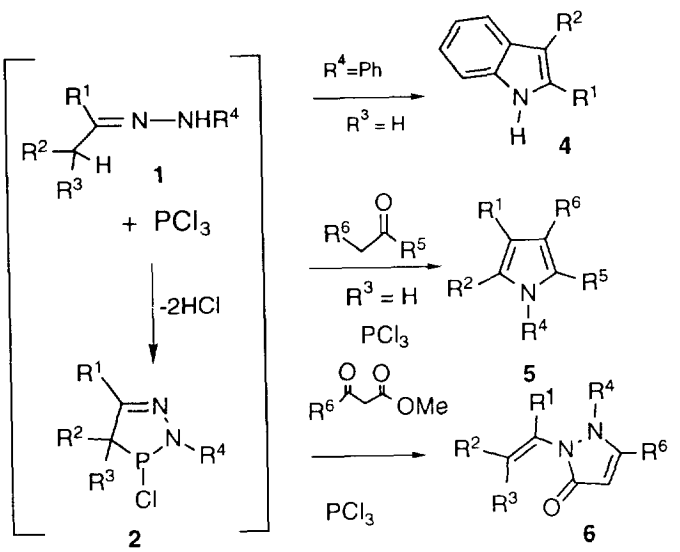
3,5-Pyrazolidinediones[1] have become of increasing importance in the last years owing to the application as medical substances, colour agents, photographic light-sensitive and thermal printing materials of a large number of derivatives of these compounds.They are generally prepared by condensation of malonic acid derivatives with hydrazines in several reaction conditions (100-150°C) depending on the nature of the substituents on the starting products. We now describe a convenient one-pot synthesis at room temperature of the title compounds **3** which are to date an unknown series of 3,5-pyrazolidinediones bearing a *N*-alkenyl group. In recent years organophosphorus reagents have received much attention for their great utility for the facilitation of several organic transformations as documented by the variety and number of examples listed in the literature. Our reaction is one of these in which the adduct PCl_3-hydrazone is used to obtain azaheterocycles under mild conditions.

Some years ago we devised[2] that the reaction between an arylhydrazone **1** (R^4=Ph) and PCl_3 gives indoles **4** in goods yields after few minutes at room temperature. Successively we discovered that chlorodiazaphospholine such as **2** or its ionic forms[3], are intermediates for a one-pot two steps synthesis of unsymmetrically substituted pyrroles[4] **5**. The first step is the generation of intermediate such as **2** by reaction of ketone methylhydrazone **1** (R^4=Me) with PCl_3. The second step is an addition of enolizable ketone and PCl_3 to the previous reaction mixture to give the corresponding pyrroles. Subsequently we found[5] that when in the second step we used methyl acetoacetate 1,2-dihydro-2-alkenyl-3*H*-pyrazol-3-ones **6** were obtained (See Scheme 1).

In order to explain the formation of azaheterocycles such as pyrroles **5** or 1,2-diazaheterocycles such as pyrazolones **6** we have recently reported[6] a plausible interpretation which can be summarised by this statement. When chlorodiazaphospholine such as **2** or its ring-opened forms after reaction with a reagent gives an intermediate, which can give a [3,3]sigmatropic rearrangement, azaheterocycles such as pyrroles **5** are formed;

on the contrary, when this type of rearrangement cannot occur but another type of spontaneous intramolecular cyclization is possible, diazaheterocycles such as pyrazolones **6** are obtained.

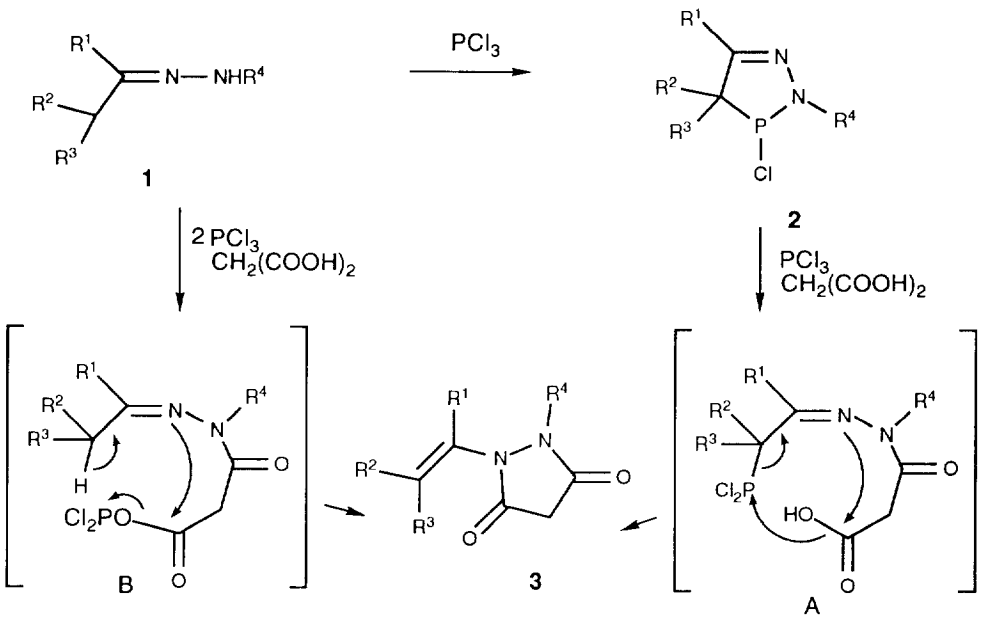
To explore the further applicability of this statement and to test the possibility of synthesizing new *N*-alkenyl 1,2-diazaheterocycles we have carried out some experiments using another bifunctional reagent such as malonic acid or its derivatives.



Scheme 1

RESULTS and DISCUSSION

When we used malonic acid, the *N*-alkenylpyrazolidine-3,5-dione derivatives **3a-f** are formed (75-85 % yields) (Scheme 2) with the exclusive formation of one isomer with the *E*-configuration of the *N*-alkenyl group in the cases **3a,b,c** . In contrast , when we used malonic esters pyrazolidinediones **3** are obtained only in very small amounts even with longer reaction time. Compounds **3** are a new series of pyrazolidinediones , which bearing a *N*-alkenyl group, are likely to be difficult to prepare by conventional methods and were identified essentially by ^{1}H-NMR and mass spectrometry (See Table) . The structures were established from their spectroscopic properties . The presence of two carbonyl groups was easily detected through the IR absorption at about 1700 and 1745 cm^{-1} . The *E*-configuration was deduced from NOE experiments carried out on a *E,Z* mixture (9:1). This mixture was obtained by isomerization of *E*-isomer in acidic medium[7]. A characteristic feature of ^{1}H-NMR spectra of *E*-**3a,b,c,g** and **3f** is the singlet for the two protons of 4-CH_2 .The chemical equivalences of these protons might be due to the coplanarity of the *N*-alkenyl group and the pyrazole ring, which is reinforced by the presence of an hydrogen bond between alkenyl hydrogen and the close carbonyl group. In contrast in compounds **3d,e** and *Z*-**3a** an AB signal for 4-CH_2 is observed as a consequence of the loss of this coplanarity produced by the absence of the above H bond and by a restricted rotation around the C-N bond.



a; R^1= Ph, R^2= Me, R^3=H, R^4= Me
b; R^1= Me, R^2= Ph, R^3=H, R^4 = Me
c; R^1= R^2= Ph, R^3=H, R^4 = Me
d; R^1=i-Pr, R^2= R^3=Me, R^4 = Me
e; R^1= Me, R^2= R^3= Ph, R^4 = Me
f; R^1= Ph, R^2= R^3=H, R^4 = Me
g; R^1= Ph, R^2= Ph, R^3= H, R^4 = Ph

Scheme 2

It should be noted that changing the order of addition of reagents gave practically identical results.Then different procedures can be used. A first typical procedure is as follows. A dichloromethane solution of methylhydrazone **1** (R^4=Me) is treated, at room temperature, with equimolar amounts of PCl3. The mixture was allowed to react at room temperature, and after few minutes a THF solution of malonic acid and further PCl3 were added to the mixture, which was allowed at room temperature. Depending on the structure of the reactants, the length of the time required for completion of the reaction is in a range of 30 min. to 2 h. Compounds **3** were purified by simple crystallization or by silica gel column chromatography. It should be noted that is not necessary to expect the complete formation of **2** to have the best results[8].

A second and more simple procedure consists in an addition of a THF solution of hydrazone **1**to a THF solution of malonic acid and two equiv. of PCl3 to give **3** with the same high yields.

Although the conversion of carboxylic acids into the corresponding chlorides by PCl3 is a general applied synthetic method[9], this reaction does not occur at room temperature but it needs 50°-90°C for almost 1h and particular proportion of the reagents[10]. In fact in our reaction conditions we did not observe the formation of any acid chloride.

It should be noted that with this second procedure it was possible to obtain from hydrazone **1** with R^4=Ph the compound **3g** but in a mixture (1:1) with the corresponding indole **4** (R^1=R^2=Ph). In contrast when the first procedure was used only the indole was obtained in accord with Scheme 1. This result and the fact that different procedures can be used reveals that when a dicarboxylic acid is involved in this type of

reaction, the mechanism is more complex than previous studies in the case of related synthesis of indoles, pyrrole or pyrazolones suggest[2,6]. In the first procedure the second addition of PCl_3 presumably acts as an activator to favour the reaction of one carboxylic group of the malonic acid[10] with the nitrogen atom of the *N*-Me group of **2**, giving the hypothetical intermediate A. In the second procedure one equiv. of PCl_3 acts in similar manner to form the same amidic bond giving the hypothetical intermediate B which is now activated to undergo a second nucleophilic attack as depicted in Scheme 2. In the procedure , where PCl_3 is added last to a mixture of **1** and malonic acid, the formation of both intermediates is likely . The observed low reactivity of malonic ester can be in accord with the formation of the above intermediates. It should be noted that an excess of the total used PCl_3 gives a decrease in the yields. In fact the excess of PCl_3 might to react with the two carboxylic groups and the amino group preventing the final cyclization.

Table : HRMS and ^1H NMR[a] Data of Pyrazolidinediones **3**.

Comp.	Exact Mass (calc.)	δ_H(CDCl3)
E-**3a**	230.1051	1.97 (d,J 7.4,3H,MeCH=) 2.90(s,3H,1-Me)
	(230.1055)	3.29 (s,2H,4-CH_2) 6.11(q,J 7.4,1H,MeCH=) 7.2-7.4 (m,5H,ArH)
Z-**3a**[b]		1.95 (d,J 7.4,3H,MeCH=) 2.85(s,3H,1-Me)
		3.40 (qAB,J 23,δA 3.45,δB 3.35,2H,4-CH_2) 6.37(q,J 7.4,1H,MeCH=)
		7.18-7.45 (m,5H,ArH)
E-**3b**	230.1054	2.10 (s,3H,MeC=) 3.13(s,3H,1-Me)
	(230.1055)	3.27 (s,2H,4-CH_2) 6.64(s,1H,Ph-CH=) 7.3-7.4(m,5H,ArH)
E-**3c**	292.1211	2.97 (s,3H,1-Me) 3.37 (s,2H,4-CH_2)
	(292.1212)	6.86 (s,1H,Ph-CH=) 7.1-7.37 (m,10H,ArH)
3d	210.1369	1.05 (d,J 6.9,3H,Me-CHMe)1.08 (d,J 6.9,3H,Me-CHMe)
	(210.1368)	1.74(s,3H,Me-CMe=)1.89(s,3H,Me-CMe=)3.02(ept,J 6.9,1H,MeCHMe)
		3.03 (s,3H,1-Me) 3.27 (qAB,J 22,δA 3.34,δB 3.21,2H,4-CH_2)
3e	306.1369	2.02 (s,3H,Me-C=)3.01 (s,3H,1-Me)
	(306.1368)	3.11 (qAB,J 24,δA 3.16,δB 3.06,2H,4-CH_2) 7.17-7.40 (m,10H,ArH)
3f	216.0898	2.94 (s,1H,1-Me) 3.39 (s,2H,4-CH2)
	(216.0895)	5.47 (s,1H,CH=CPh cis) 5.82 (s,1H,CH=CPh trans)
		7.20-7.40 (m,5H,ArH)
E- **3g**	354.1360	3.57 (s,2H,CH_2) 6.80-730(m,16H, -CH= and ArH)
	(354.1368)	

[a] ^1H-NMR spectra were obtained from $CDCl_3$ solution. δ with respect to $SiMe_4$ as internal standard (J values are in Hz). [b] Spectrum obtained from a *E,Z* mixture (9:1)

As a conclusion, we think that the results outlined here reveal a new cyclocondensation and rearrangement which have made easily available several *N*-alkenyl pyrazolidinediones **3** hitherto unknown and demonstrate that this type of reaction can have further synthetic possibility to produce a large number of new *N*-alkenyl 1,2-diazaheterocycles.

Acknowledgements.

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EXPERIMENTAL SECTION

General

All chemicals and solvents were of reagent grade. ^{1}H-NMR spectra were recorded at 200 MHz with a Gemini 200 instrument. Chemical shifts are given in ppm from Me_4Si. Mass spectra were recorded with a VG 7070 spectrometer or with an HP-5890 gaschromatograph equipped with a methyl silicone capillary column and by an HP-5970 mass detector. IR spectra were obtained in CH_2Cl_2 in a Perkin Elmer 1600 spectrophotometer. Mps were determined with a Buchi apparatus. The purity of all the products was cheched by TLC, GC-MS and ^{1}H-NMR spectra . Commercial PCl_3 was used without further purification. Yields are based on starting quantities of malonic acid. Flash chromatography was performed in a Gilson apparatus.

Hydrazones- These were obtained by heating the respective hydrazine and ketone together in equivalent amounts in benzene solution at reflux for *ca.* 2 h. under Dean-Stark conditions. After removal of the solvent the crude products were used immediately.

First Typical Procedure for the Synthesis of Pyrazolidinediones 3

Phosphorus trichloride (10 mmol) was added at room temperature to a stirred dichloromethane solution (50 ml) of a hydrazone (10 mmol). The mixture was allowed to react at room temperature for few minutes. After about 10-15 min a THF solution (15 ml) of malonic acid (10 mmol) and further PCl_3 (10 mmol) were added to the mixture which was kept at room temperature for about 2 h. The course of this stage of the reaction was followed by GC-MS analysis and TLC. Evaporation under reduced pressure at 60°- 70°C using a Rotavapor was carried out to remove the solvent and the excess of PCl_3. The crude oil or solid was dissolved in dichloromethane and washed with water and then with saturated sodium carbonate and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give crude product **3** which was purified by crystallization or by silica gel column chromatography. Pyrazolidinediones **3** were charactherized essentially by ^{1}H NMR, mass spectrometry (see Table 1) and mycroanalysis.

Second Typical Procedure for the Synthesis of Pyrazolidinediones 3

To a THF solution (15 ml) of malonic acid (10 mmol) was added PCl_3 (20 mmol) and the mixture was allowed at room temperature; after few minutes a THF solution (50 ml) of hydrazone **1** was added to the reaction mixture and stired for about 1-2 h. Pyrazolidinediones **3** were isolated by the same procedure used above. It should be noted that adding PCl_3 at last gave identical results.

1-Methyl-2-(1-phenylprop-1-enyl)-3,5-pyrazolidinedione (*E*-3a);

as white solid , m.p. 137-138°C (76 %yield) R_f 0.32 (diethyl ether -dichloromethane 2:1 as eluent) IR,ν(CO) 1702, 1743 cm^{-1}. (Found: C, 67.7; H, 6.2; N,12.1.$C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N,12.2.)

1-Methyl-2-(1-methyl-2-phenylvinyl)-3,5-pyrazolidinedione (*E*-3b)

as white solid , m.p. 139-140°C (80 % yield) R_f 0.36 (diethyl ether -dichloromethane 2:1 as eluent) IR:ν(CO) 1694, 1739 cm^{-1}.(Found: C, 67.7; H, 6.2; N,12.1.$C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N,12.2.)

1-Methyl-2-(1,2-diphenylvinyl)-3,5-pyrazolidinedione (*E*-3c)

as white solid , m.p. 125-126°C (83 %yield) R_f 0.41 (diethyl ether -dichloromethane 2:1 as eluent) IR:ν(CO) 1707, 1736 cm^{-1} (Found: C, 73.8; H, 5.6; N, 9.6.$C_{18}H_{16}N_2O_2$ requires C, 73.9; H, 5.5; N, 9.6.)

1-Methyl-2-(1-isopropyl-2-methylprop-1-enyl)-3,5-pyrazolidinedione (3d)

as white needles , m.p. 69-70°C (85 %yield) R_f 0.71 (diethyl ether-dichloromethane-methanol 4:1:1 as eluent) IR : ν(CO) 1692, 1736 cm^{-1} (Found: C, 62.6; H, 8.7; N, 13.1.$C_{11}H_{18}N_2O_2$ requires C, 62.8; H, 8.6; N, 13.3.)

1-Methyl-2-(1-methyl-2,2-diphenylvinyl)-3,5-pyrazolidinedione (3e)

as white solid, m.p. 112-114°C (73 %yield) R_f 0.43 (diethyl ether -dichloromethane 2:1 as eluent) IR : ν(CO) 1698, 1741 cm^{-1}.(Found: C, 74.6;H, 5.8;N, 9.0.$C_{19}H_{18}N_2O_2$ requires C, 74.5; H, 5.9;N, 9.1).

1-Methyl-2-(1-phenylvinyl)-3,5-pyrazolidinedione (3f)

as white solid, m.p. 117-118°C (70 %yield) R_f 0.43 (acetone as eluent); IR : ν(CO) 1710, 1748 cm^{-1}. (Found: C, 66.6;H, 5.5;N, 12.8.$C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6;N, 13.0.)

1-Phenyl-2-(1,2-diphenylvinyl)-3,5-pyrazolidinedione (*E*-3g)

as white solid, m.p. 135-136°C (41 %yield) R_f 0.43 (diethyl ether -dichloromethane 3:1 as eluent) IR : ν(CO) 1717, 1750 cm^{-1}.(Found: C, 77.7;H, 5.2;N, 7.8.$C_{23}H_{18}N_2O_2$ requires C, 77.9; H, 5.1; N, 7.9.) In this case the corresponding indole **4** (R^1=R^2=Ph) was obtained in 40% yield and its structure was assigned by comparison with authentic sample obtained with the procedure[11] depicted in Scheme 1.

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