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REACTIVITY OF IMINOPHOSPHORANES TOWARDS SOME SYMMETRICAL DICARBONYL DICHLORIDES : SYNTHESES AND MECHANISMS

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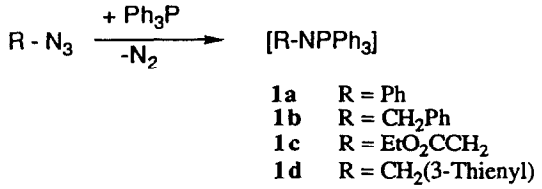
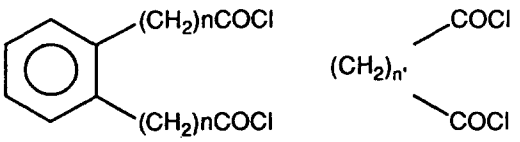
Abstract.

In situ generated iminophosphoranes **1** react with dicarbonyl dihalides **2a-b** and **3a-c** to give known or new nitrogen heterocycles. The proposed mechanisms involve elimination of either triphenyl-phosphine oxide or dichlorotriphenylphosphorane depending upon both the iminophosphorane and the dicarbonyl compound.

The reaction of iminophosphoranes with mono-carbonyl compounds has been extensively studied,[1] but very few authors report on the reactivity of iminophosphoranes towards dicarbonyl derivatives : the condensation of silyl iminophosphoranes with ß-dicarbonyl compounds has been shown by Kloek and al[2a] to lead to enamines. Also the synthesis of tetrahydropyridines by reaction of acyl iminophosphoranes and glyoxylates was achieved by Jung and al.[2b] However, in both cases the specificity of the starting materials is a severe limitation of the reaction. Moreover, one of the carbonyl groups of the dicarbonyl compounds does not react with the iminophosphorane. In contrast, orthophthalaldehyde[3] and phthalic anhydride[4] both undergo a straight one-step cyclisation reaction involving the two carbonyl groups with a large range of iminophosphoranes. These new expeditious pathways to various nitrogen heterocycles and the ease of the condensation of iminophosphoranes with mono-carbonyl halides[5] prompted us to undertake a general study of the reactivity of imino-phosphoranes towards dicarbonyl dichlorides. In a preliminary communication,[6] we reported the synthesis of seven-membered nitrogen heterocycles by condensation of the in situ generated iminophosphoranes **1**[7] with **2b** and **3c** (Scheme 1). We now describe and comment on the reaction of **1** with the dicarbonyl dichlorides **2a-b** and **3a-c** which were selected for their simplicity and high symmetry.



1a R = Ph
1b R = CH_2Ph
1c R = EtO_2CCH_2
1d R = CH_2(3-Thienyl)



2a n = 0
2b n = 1

3a n' = 2
3b n' = 3
3c n' = 4

Scheme 1.

The condensation of iminophosphoranes **1a-d** with phthaloyl dichloride **2a** at -20°C in dichloromethane followed by alkaline hydrolysis at the same temperature afforded acceptable yields of phthalimides **4** (Scheme 2), which can be considered as protected amines. Garcia[4] also described the synthesis of similarly protected amines via iminophosphoranes, but the present method offers the advantage of avoiding the use of cyanide derivatives.

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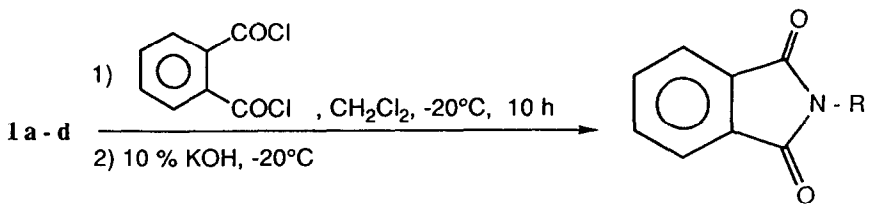
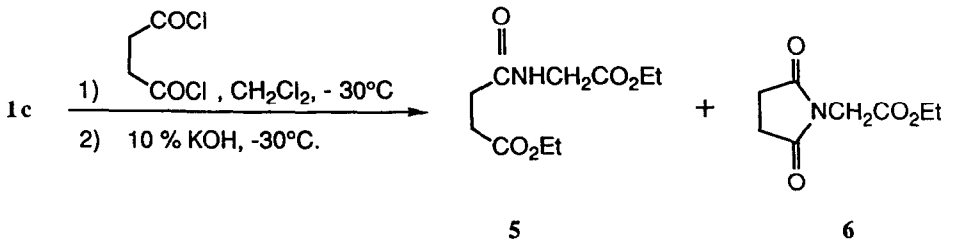


4a R = Ph (69 %)
4b R = CH_2Ph (54 %)
4c R = CH_2CO_2Et (62 %)
4d R = CH_2-(3-Thienyl) (58 %)

Scheme 2.

Under the same conditions or at lower temperature, the condensation of **1a** and **1b** with

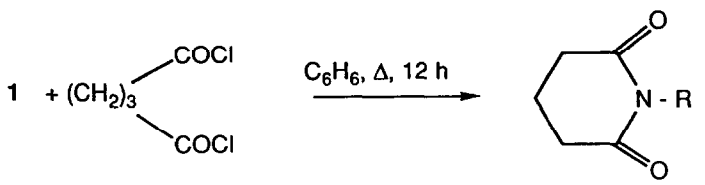
the aliphatic analog **3a** of phthaloyl dichloride gave only darkened mixtures from which no products could be isolated in significant amounts. However, starting from **1c** and carrying out the reaction at -30°C, the open-chain amide **5** and the 1-ethoxycarbonylmethylpyrrolidine-2,5-dione **6** have been obtained in 20 and 15 % yields respectively after chromatographic separation (Scheme 3).



5 **6**

Scheme 3.

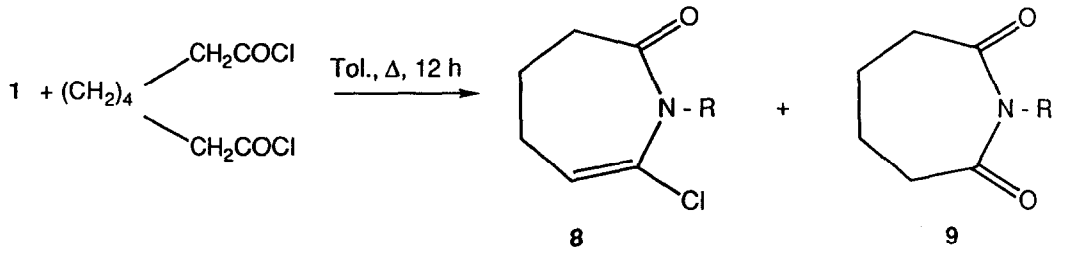
In contrast to the above experiments, the condensation of iminophosphoranes **1a-c** with glutaryl dichloride **3b** at room temperature did not produce an exothermic reaction, and no product could be isolated without refluxing conditions. Indeed, the piperidine-2,6-diones **7** have been obtained in good yields after refluxing in benzene for 12 h (Scheme 4).



7 a R = Ph (68 %)
7 b R = CH_2Ph (62 %)
7 c R = CH_2CO_2Et (55 %)

Scheme 4.

As we have previously reported,[6] the condensation of iminophosphoranes with adipoyl chloride required the conditions used with glutaryl dichloride. Nevertheless, the major products of the reaction were not imides but the new chlorolactames **8** (Scheme 5). No imide derivatives could be isolated starting from 0.1 mole of iminophosphorane. However, in one case ($PhCH_2$-$NPPh_3$), we carried out the experiment on a larger scale (0.6 mole) and isolated the azepine **9** in 2 % yield besides the azepine **8b** (30 %).



8 **9**

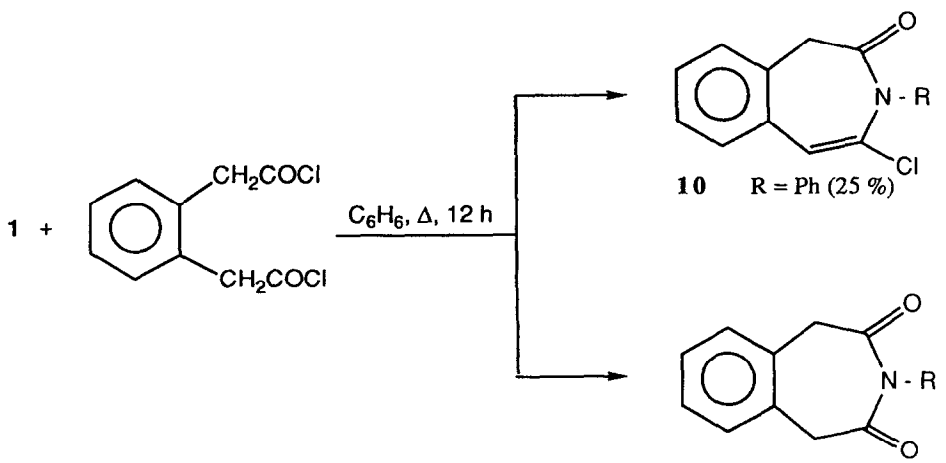
8a R = Ph (45 %)
8b R = CH_2Ph (31 %)
R = CH_2Ph (30 %)*
8c R = CH_2CO_2Et (50 %)

R = CH_2Ph (2 %)*

*large scale reaction.

Scheme 5.

Unexpectedly, the condensation of iminophosphoranes **1a-c** with the related 1,2-phenylenediacetic acid dichloride **2b** afforded the latter two types of azepine derivatives (chlorolactame **10** or imide **11**) as the major product of the reaction, depending upon the nature of **1** (Scheme 6).



10 R = Ph (25 %)

11a R = CH_2Ph (30 %)
11b R = CH_2CO_2Et (42 %)

Scheme 6.

Our results can be explained by the mechanisms described in Scheme 7 : in the case of phthaloyl and succinyl dichloride, we assume that the key intermediate is the highly reactive

immonium halide **12**. Such a species is known to react easily with a-methylene ketones[8] and amides[9]. That probably explains the failure of the condensation reactions with succinyl dichloride. For the condensation with glutaryl and 1,2-phenylenediacetic acid dichloride, we propose a mechanism via the acyliminoether **13** which undergoes a Mumm rearrangment[10], as Zbiral[5] proposed for the condensation of acyclic analogues under similar experimental conditions. At last, a third mechanism[11] involving a Chapman rearrangment **12** is responsible for the formation of the azepines **8a-c** and the 3-benzazepine **10**.

Thus the mechanism of the reaction of iminophosphoranes with dicarbonyl dichloride is very substrate-dependent. However, the usefulness of such a reaction has been clearly shown since various nitrogen heterocycles including seven-membered heterocycles of potential biological interest have been isolated in a one-step procedure and in acceptable yields (except when the dicarbonyl compound is succinyl dichloride). Moreover, a very large number of dicarbonyl dichlorides are commercially or readily available. Finally, it has to be pointed out that the new azepine derivatives **11** are good precursors for the efficient synthesis (2 steps from **11**) of new tricyclic systems of biological interest[13] (Scheme 7).

EXPERIMENTAL

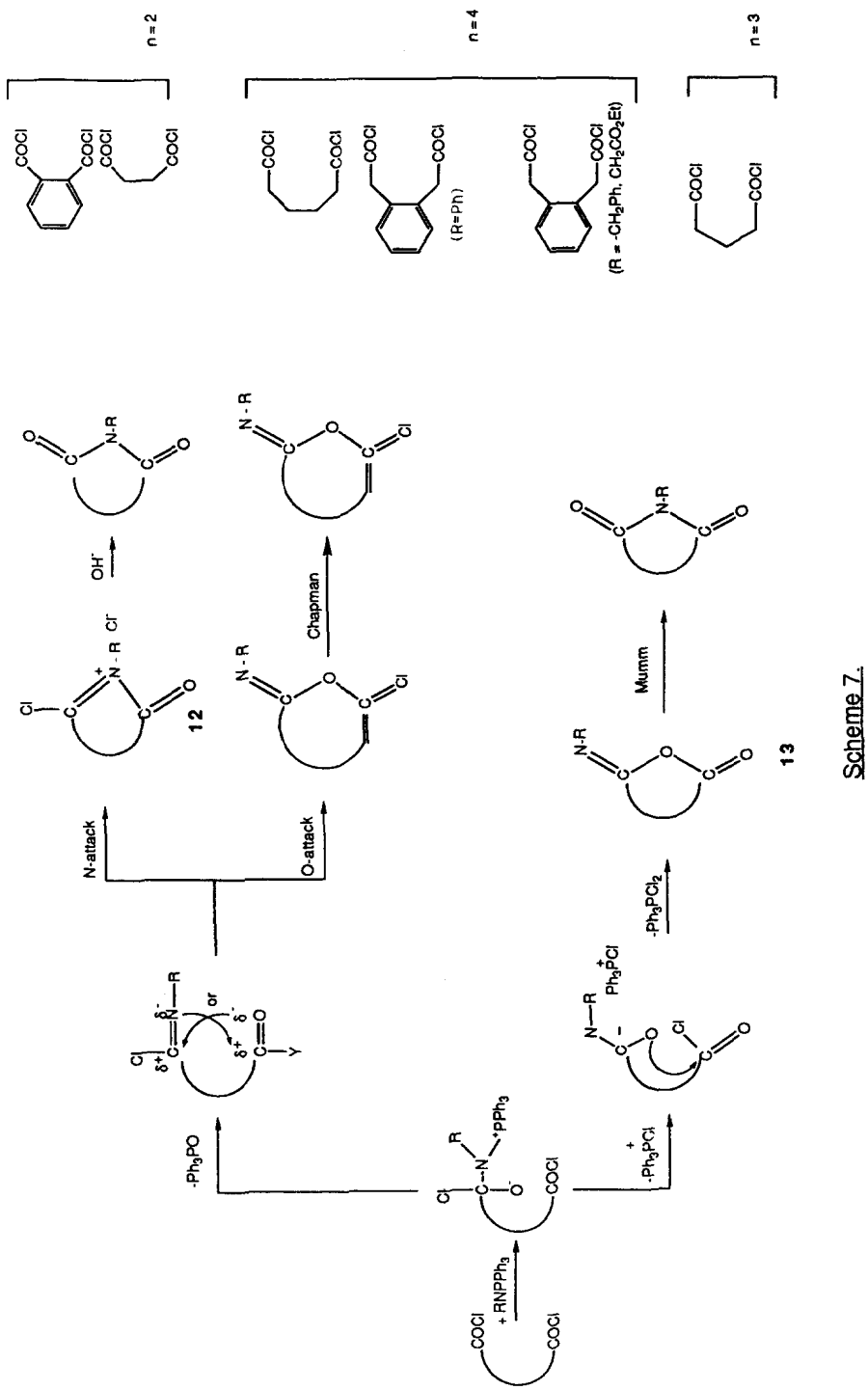
Melting points were determined on a Kofler heated stage, and are uncorrected. IR spectra were recorded on a Perkin Elmer 580 B spectrophotometer. ^{1}H NMR spectra were obtained on a Bruker WM 400 (400 MHz) spectrometer of the CEREMA ("Centre de Résonance Magnétique of the University of Burgundy). Mass spectra were recorded on a Finnigan 3300 mass spectrometer, using electron-impact ionization (70 eV). Synthesis and characteristics of azepines **8** and benzazepines **10** and **11** are described in reference 6.

Phthalimides 4 - General Procedure : To a solution of azide (5 mmol) in anhydrous dichloromethane (10 ml) was added dropwise at room temperature a solution of triphenylphosphine (1.31 g, 5 mmol) in the same solvent (15 ml). The solution was stirred at room temperature for 2-4 h and then cooled to -20°C. After dropwise addition of a solution of phthaloyl dichloride (1.02 g, 5 mmol) at -20°C followed by stirring overnight at the same temperature, the reaction mixture was hydrolysed by 10 % KOH (10 ml) at -20°C and then allowed to warm to room temperature. The aqueous layer was extracted with dichloromethane and the combined organic layers were washed with water, dried, and evaporated under reduced pressure. Chromatography of the residue over silica gel eluting with dichloromethane-hexane (3/1) followed by recrystallization gave the phthalimides **4** as white needles.

2-Phenyl-isoindoline-1,3-dione, **4a** : m.p. 208°C (from dichloromethane). Litt.[14] 210°C. Yield 69 %.

2-Phenylmethyl-isoindoline-1,3-dione, **4b** : m.p. 117-118°C (from diethyl ether-hexane). Litt.[14] 116°C. Yield 54 %.

2-Ethoxycarbonylmethyl-isoindoline-1,3-dione, **4c** : m.p. 114-115°C (from diethyl ether-hexane). Litt.[14] 112-113°C. Yield 62 %.


n = 2
n = 4
n = 3
(R=Ph)
(R = -CH2Ph, CH2CO2Et)
+ RNPPh3
-Ph3PO
-Ph3PCl2
N-attack
O-attack
Chapman
Mumm
OH-
12
13

Scheme 7.

2-(3-Thienylmethyl)-isoindoline-1,3-dione, **4d** : m.p. 130-132°C (from diethyl ether-hexane). Yield 58 % ; n_{max} (KBr) : 1775 (CO, sym.), 1701 (CO, antisym.), 1391, 1107, 950 cm^{-1} ; ^1H NMR : d($CDCl_3$), 4.85 (s, 2H, CH_2), 7.15 (dd, J = 1.23 and 4.97 Hz, 1H, 4'-H), 7.24 (dd, J = 2.97 and 4.97 Hz, 1 H, 5'-H), 7.33 (m, 1H, 2'-H), 7.70 (m, 2H, 5-H and 6-H), 7.84 (m, 2H, 4-H and 7-H) ; m/z 243 (M^+, 100 %), 214, (22), 130 (55), 104 (54), 76 (57) ; Anal. Calcd. for $C_{13}H_9NO_2S$: C, 64.18 ; H, 3.73 ; N, 5.76 ; S, 13.18. Found : C, 64.11; H, 3.61 ; N, 5.64 ; S, 13.28.

2-Phenacyl-isoindoline-1,3-dione, **4e** : m.p. 168-169°C (from diethyl ether). Litt.[15] 165-167°C. Yield 3 %.

Amide 5 and Pyrrolidine 6 : The condensation reaction of the iminophosphorane **1c** with succinyl dichloride **3a** was carried out as above, except that the temperature of condensation and hydrolysis was -30°C. This reaction led to a mixture of **5** and **6** which were separated by chromatography over silica gel eluting with dichloromethane-acetone (10/1) and recrystallized from diethyl ether-hexane.

Ethyl N-ethoxycarbonylmethyl-4-amino-4-oxobutanoate, **5** : m.p. 73-74°C. Yield 20 % ; n_{max} (KBr) : 3319 (NH), 1748 and 1731 (2 x COOEt), 1651 (CONH) cm^{-1} ; ^1H NMR : d (DMSO-d_6), 1.20 and 1.22 (2xt, J = 7.11 Hz, 2x3H, 2xCH_2CH_3), 2.46 and 2.52 (2xm, 2x2H, CH_2-CH_2), 3.84 (d, J = 5.92 Hz, collapses to a singlet upon deuteriation, 2H, $NHCH_2$), 4.07 and 4.11 (2xq, J = 7.11 Hz, 2x2H, 2xCH_2CH_3), 8.37 (t, J = 5.92 Hz, disappears on D_2O shake, 1H, NH); m/z 231 (M^+, 1 %), 186 (10), 158 (20), 129 (100), 112 (30), 101 (98) ; Anal. Calcd. for $C_{10}H_{17}NO_5$: C, 51.94 ; H, 7.41 ; N, 6.06. Found : C, 52.01; H, 7.38 ; N, 6.04.

1-Ethoxycarbonylmethyl-pyrrolidine-2,5-dione, **6** : m.p. 68°C. Litt.[16] = 67°C. Yield 15 %.

Piperidines 7 - General Procedure : To a solution of azide (10 mmol) in anhydrous benzene (50 ml) was added dropwise at room temperature a solution of triphenylphosphine (2.62 g, 10 mmol) in the same solvent (75 ml). The reaction mixture was stirred at room temperature for 2-4 h and then added dropwise at the same temperature to a solution of glutaryl dichloride (1.69 g, 10 mmol) in anhydrous benzene (70 ml). After refluxing the reaction mixture for 12 h, the solvent was evaporated and the resulting residue was chromatographied over silica gel eluting with dichloromethane-hexane (3/1), dichloromethane, or dichloromethane-acetone (40/1) to give respectively the piperidines **7a**, **7b** and **7c**. The oily material **7c**, only reported in a patent[17], as well as **7b**[18] were identified by N.M.R. spectroscopy.

1-Phenyl-piperidine-2,6-dione, **7a** : m.p. 147-148°C (from diethyl ether). Litt.[19] = 145°C, [20] = 151°C. Yield 68 %.

1-Phenylmethyl-piperidine-2,6-dione, **7b** : (oil) Yield 62 %; ^1H NMR : d(CCl_4) 1.90 (quint., J = 6.07 Hz, 2H, 4-H_2), 2.56 (t, J = 6.07 Hz, 4H, 3-H_2 and 5-H_2), 4.82 (s, 2H, N-CH_2-Ph), 7.12 to 7.31 (m, 5H, ArH). Litt.[18] : 1.9 (m, 2H, 4-H_2), 2.44 (t, J = 6 Hz, 4H, 3-H_2 and 5-H_2), 4.74 (s, 2H, N-CH_2-Ph), 7.02 to 7.27 (m, 5H, ArH).

1-Ethoxycarbonylmethyl-piperidine-2,6-dione, **7c** : (oil) Yield 55 %; ^1H NMR : d($CDCl_3$) 1.26 (t, J = 7.19 Hz, 3H, CH_2CH_3), 2.00 (quint., J = 6.76 Hz, 2H, 4-H_2); 2.71 (t, J = 6.76 Hz, 4H, 3-H_2 and 5-H_2), ,4.17 (q, J = 7.19 Hz, 2H, CH_2CH_3), 4.51 (s, 2H, N-CH_2).

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