SHORT PAPER

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Thermal reaction of cinnamic acid and of β-styrylphosphonic acid with urea†

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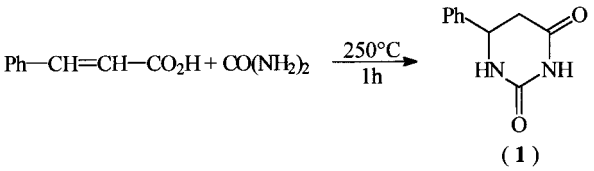
The thermal reaction of b-styrylphosphonic acid under experimental conditions similar to those applied to cinnamic acid and to methyl cinnamate to provide 6-phenyl-5,6-dihydrouracil, led to the formation of the novel 6-phenyl-5,6-dihydro-4-phosphorylamide-(1H,3H)-2-pyrimidinone.

In connection with our interests in the chemistry of the β-styrylphosphonic system,[1] we have examined the thermal reaction between β-styrylphosphonic acid and methyl styrylphosphonate with urea respectively, comparing the results with those corresponding to cinnamic acid and methyl cinnamate.

The thermal reaction of an equimolecular mixture of cinnamic acid and urea at 250 °C was first reported to furnish 6-phenyl-5,6-dihydrouracil (**1**) in 14 % yield.[2]

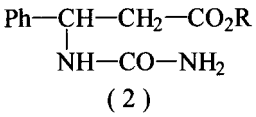


(**1**)

An improvement in the yield of **1** was obtained by introducing minor modifications which include a decrease of the temperature of reaction down to 190^{0}C and increasing the reaction time from one to six hours (34 %).[3]

We now report the application of a similar methodology to related compounds containing the PO_3R_2 group (R = H, Me) instead of CO_2R. Before attempting an examination of these reactions, we repeated the basic procedure described by Evans and Johnson[3] using cinnamic acid and methyl cinnamate under a variety of reaction conditions.

Experiments starting with different proportions of reactants at different temperatures and for different reaction times afforded the dihydrouracil **1** and the β-ureide of the β-phenylpropionic acid (**2**; R = H) as the main products. In the case of the cinnamic acid the product of condensation with urea PhCH=CHCONHCONH$_2$ (**3**) was also isolated.

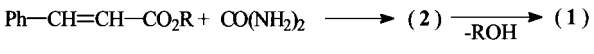


(**2**)

R = H , Me

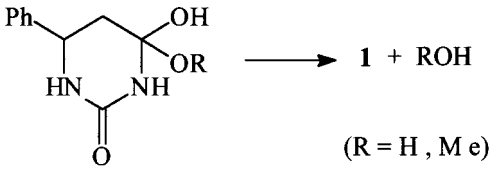
The product distributions are summarised in Tables 1 and 2. From comparison of the data presented in Table 1 with the results reported by Evans and Johnson,[3] it follows that the action of an excess of urea together with a reduction of the reaction time raises the yield of the dihydrouracil from 34 to more than 60%. It was also observed that the best yields of the dihydrouracil resulting from the acid and from the ester were obtained under identical conditions of substrate proportions, temperature and reaction time.

As regard the mechanism of the process, formation of **1** had been suggested to proceed through initial nucleophilic attack of one of the amino groups of the urea molecule at the β-position of the substrate, followed by intramolecular condensation of the resulting intermediate leading to cyclisation.

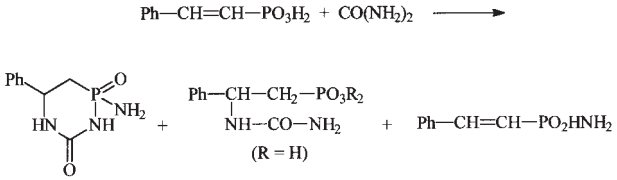


R = H , Me

However, we could not find evidence supporting this hypothesis since formation of the dihydrouracil by heating the ureide (**2**; R = H) or subjecting it to reaction with different amounts of urea under different conditions of temperature and reaction time could not be attained. Similarly, the fact that we were also unable to convert the product of condensation of cinnamic acid and urea (**3**) into **1** by subjecting it to the reaction conditions consigned in Table 2 seems to argue against a successive condensation/addition two step process. On the basis of the present results it seems reasonable to assume that, although the stepwise routes cannot be rigorously dismissed, the formation of the dihydrouracil by the described procedure involves the simultaneous occurrence of the addition and condensation components in a concerted pathway to furnish an intermediate which would lead to the dihydrouracil.



When the β-styrylphosphonic acid was subjected to reaction with urea under the optimal conditions leading to the best yields of **1** from the cinnamic compounds, a similar work-up of the product mixture led to the isolation of three main products identified as 6-phenyl-5,6-dihydro-4-phosphorylamide-(1H,3H)-2-pyrimidinone (**4**), and the β-ureide- (**5**; R = H) and the monoamide of β-styrylphosphonic acid (**6**). The results are summarised in Table 3.



(**4**) (**5**) (**6**)

Again, attempts to convert **5** into **4** by a similar procedure to that applied to the ureide (**2**; R = H) afforded by the reaction with cinnamic acid were unsuccessful. However, partial conversion of the β-styrylphosphonamide **6** into **4** by heating the former in the presence of an equimolecular amount of urea

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

Table 1 Products of the reaction of cinnamic acid with urea

Reactant proportions[a]	Temperature (°C)	Reaction time (h)	Product distribution (%)[b] 1	2(R = H)	3
A	160	1[c]	–	–	–
B	160	1[c]	–	–	–
C	160	1	25	23	6
C	180	0.5	23	20	3
C	180	1	36	25	9
C	180	3	52	26	6
C	190	1	63	21	2
C	190	2	65	12	2
C	190	4	15	8	3

[a]A: [cinnamic acid] / [urea] = 1:1; B: [cinnamic acid] / [urea] = 1:2; C: [cinnamic acid] / [urea] = 1:5; [b]Yields of crude isolated products;. [c]Reactants recovered unchanged.

Table 2 Products of the reaction of methyl cinnamate with urea

Reactant proportions[a]	Temperature (°C)	Reaction time (h)	Product distribution (%)[b] 1	2(R = H)	3
A	160	1[c]	-	-	
B	160	1[c]	-	-	
C	160	1	20	8	
C	180	0.5	18	15	
C	190	1	34	16	
C	190	2	36	12	
C	190	4	6	9	

[a]A: [methyl cinnamate]/[urea] = 1:1; B: [methyl cinnamate]/[urea] = 1:2; C: [methyl cinnamate]/[urea] = 1:5; [b]of crude isolated products;. [c]reactants recovered unchanged.

for four hours could be achieved. This may be taken as indication that the monoamide is an intermediate in the formation of **4**.

In the case of the reaction with methy β-styrylphosphonate, only the α-ureide $PhCH(NHCONH_2)CH_2PO_3Me_2$ (**5**; R = Me) could be detected and isolated from the product mixture whereas the remaining products could not be identified. The apparent absence of formation of the corresponding uracil might perhaps be attributed to the fact that intramolecular condensation could not be achieved with a totally esterified phosphonic group.

Evidence for the structures assigned to the phosphonic derivatives came from elemental analysis and spectral data. The IR spectrum of compound **4** showed absorption bands at 3340 and 3310 cm^{-1} in agreement with the presence of the amino group, and bands at 1635 ($\gamma_{C=O}$) and 1240 cm^{-1} ($\gamma_{P=O}$). The ^1H NMR spectrum contained an AMX system with two doublets between 2.78 and 3,60 ppm and two doublets at 4.58 ppm, a multiplet in the aromatic region, and three broad signals at 7.84 (NH_2), 8.20 (NH) and 8.82 ppm (NH). For the IR, compound **5** (R = H) exhibited bands at 3600–2200, 1250–1000 and 1650 cm^{-1} showing the presence of P–OH, P=O and P-O, and C=O respectively. Its ^1H NMR showed an ABX pattern (a doublet at 2.38 and a triplet at 4.40 ppm due to CH_2-CH), two broad signals at 5.82 (NH) and 7.92 ppm (NH_2), and a multiplet corresponding to the aromatic protons. The ^1H NMR of compound **6** contains a pair of doublets at 5.90 and 6.25 ppm arising from the olefinic protons, an aromatic multiplet between 6.62 and 7.24 ppm, and a broad signal at 7.78 ppm due to the NH_2 group.

Table 3 Products of the reaction of $PhCH{=}CHPO_3R_2$ with urea[a]

R	Temperature (°C)	Reaction time (h)	Product distribution (%)[b] 4	5	6
			4	5	6
	170	1	5	4	13
	170	3	11	9	12
H	180	1	16	10	4
	180	3	15	11	3
	190	1	18	9	15
	170	1	-	16c	-
Me	170	3	-	12c	-
	190	4	-	9c	-

[a][$PhCHCHPO_3R_2$] / [urea] = 1:5; [b]yields of crude isolated products; [c]together with unidentified products.

Experimental

Melting points were determined with a koffer apparatus and are uncorrected. ^1H NMR were recorded on a Bruker AC 200 Spectrometer with TMS as internal standard. IR were obtained with a Perkin Elmer 599B spectrometer.

Reactions with the cinnamic compounds: A mixture of the appropriate proportions of cinnamic acid and urea was heated using an oil bath at a specified temperature for a given length of time. The product mixture was then taken up with hot water, boiled for half an hour, and the hot solution filtered off. After cooling the aqueous extract to room temperature a precipitate separated which was collected by filtration and recrystallised from ethanol to provide cinnamoylurea (**3**), m.p. 219–220°C (lit,[4] 219 °C). The mother-liquors of **3** were extracted with ether and the organic solvent evaporated to give a solid which was recrystallised from ethanol/ether (2:1) to afford 6-phenyl-5,6-dihydro-2,4-(1H,3H)-pyrimidindione (**1**), m.p. 216–218 °C (lit,[3] 217°C) as white crystals. The aqueous filtrate was warmed up and the pH adjusted with hydrochloric acid to 2. After cooling the solution to room temperature a solid separated which was recrystallised from ethanol/DMSO (3:1) to provide the β-ureide of the β-phenylpropionic acid (**2**; R = H), m.p. 189–190 °C (lit,[5] 191 °C).

The reactions of methyl cinnamate with urea were carried out according to a procedure similar to that described above except that in this case no precipitate was formed by cooling the hot water extract from the product mixture of the thermal reaction. Extraction of this solution with ether provided uracil **1**. The aqueous filtrate was concentrated under vacuum and left to cool. Addition of cold ethanol provided a solid which was recrystallised from ethanol to give methyl β-phenyl-β-ureide-propionate (**2**; R = Me) m.p. 142–143 °C. Characterisation data are as follows: δ_H(DMSO-d_6) 2.45 (2H, d, J = 11.8 Hz), 4.52 (1H, t, J = 11.8 Hz), 5.68 (1H, broad s), 6.76–7.18 (5H, m), 8.15 (2H, broad s) (Found C, 59.01; H, 6.29; N, 12.98. $C_{11}H_{14}N_2O_3$ requires C, 59.48; H, 6.30; N, 12.60 %).

Reaction of the styrylphosphonic compounds with urea: For these substrates the reactions were initiated by an experimental procedure and a work up sequence similar to that used for the cinnamic compounds. When the hot water extract of the reaction with the styrylphosphonic acid separated by filtration was cooled to room temperature, a yellowish solid formed which was filtrated off and recrystallised from ethanol/ether (2:1) to provide compound **6** as pale yellow needles, m.p. 235–238 °C, identified as the monoamide of the β-styrylphosphonic acid; δ_H(DMSO-d_6) 5.90 (1H, d, J = 15.5 Hz), 6.25 (1H, d, J = 15.5 Hz), 6.62–7.24 (5H, m), 7.78 (2H, broad s); ν/cm^{-1}(Nujol) 3300-2200, 1250–1040, 940 (Found C, 52.62; H, 5.36; N, 7.84; P, 16.61. $C_8H_{10}NO_2P$ requires C, 52.49; H, 5.46; N, 7.64; P, 16.92 %). The mother-liquors of **6** were extracted with ether and the extract evaporated to afford pale yellow crystals, mp 227–229°C, identified as 6-phenyl-5,6-dihydro-4-phosphorylamide-(1H,3H)-2-pyrimidone (**4**); δ_H(DMSO-d_6) 2.78–3.60 (2H, ddd, J = 15.8, 8.2, and 5.0 Hz), 4.58 (1H, dd, 8.2, and 5.0 Hz), 6.70–7.32 (5H, m), 7.84 (2H, broad s), 8.20 (1H, broad s), 8.82 (1H, broad s); ν/cm^{-1}(Nujol) 3340, 3310, 1635, 1240 (Found C, 47.94; H, 5.26; N, 18.90; P, 13.44. $C_9H_{12}N_3O_2P$ requires C, 48.03; H, 5.33; N, 18.66; P, 13,76 %). After acidification of the aqueous layer resulting from the ethereal extraction to pH 2, a solid was obtained which was filtered off and recrystallised from ethanol/acetone (1:1) to give the α-ureide of the β-styrylphosphonic (**5**; R = H) as white crystals, m.p. 202–205 °C.

Characterisation data are as follows: $\delta_H(CD_3CO_2D)$ 2.38 (2H, d, *J* = 12 Hz), 4.40 (1H, t, *J* = 12 Hz), 5.82 (1H, broad s), 6.60–7.18 (5H, m), 7.92 (2H, broad s); ν/cm^{-1}(Nujol) 3600–2200, 1250–1000, 1650 (Found C, 44.33; H, 5.15; N, 11.48; P, 12.30. $C_9H_{13}N_2O_4P$ requires C, 44.29; H, 5.32; N, 11.47; P, 12,69 %). An experimental procedure similar to that applied to methyl β-styrylphosphonate led to the isolation of pale yellow crystals from the acidified aqueous layer resulting from the ethereal extraction, characterised as the α-ureide of the methyl β-styrylphosphonate (5: R = Me), m.p. 176–179 °C; δ_H(DMSO-d_6) 2.36 (2H, d, *J* = 11.6 Hz), 3.06 (3H, d, *J*=10.8 Hz), 4.12 (3H, d, *J*=10.8 Hz), 4.38 (1H, t, J = 11.6 Hz), 5.80 (1H, broad s), 6.65–7.22 (5H, m), 7.38 (2H, broad s); ν/cm^{-1}(Nujol) 3350, 3320, 3285, 1630, 1220 (Found C, 48.25; H, 6.33; N, 10.48; P, 10.98. $C_{11}H_{17}N_2O_4P$ requires C, 48.56; H, 6.24; N, 10.29; P, 11,38 %). The remaining products could not be identified.

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Paper 00/262

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