PYRIMIDINE-RING FORMATION BY THE REACTION OF CONJUGATED CARBODIIMIDES WITH AN AMIDINE (1)

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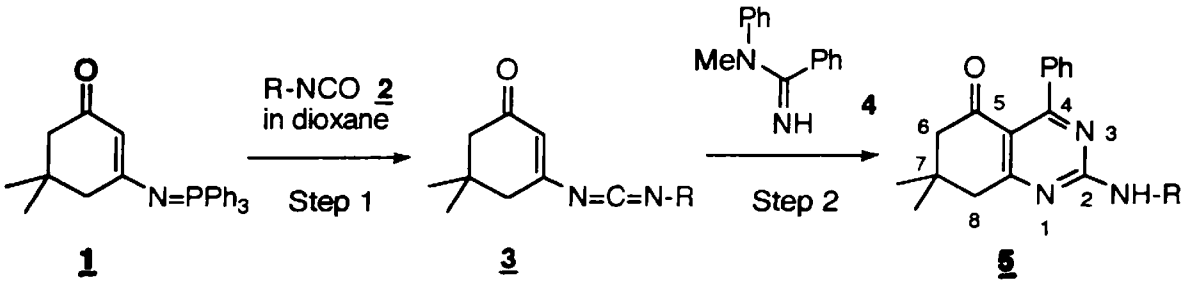
Abstract: The reaction of conjugated carbodiimides, *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl)-**3** and *N*-[6-methyl-2-oxo-4-(2*H*)-pyranyl]-*N'*-(substituted) carbodiimides **8**, with amidine **4** in refluxing dioxane gave fused pyrimidine derivatives **5** and **9** in moderate yields. The nucleophilic addition of **4** to the carbodiimides leading to guanidine intermediates and their 6π-cyclization are key steps for this pyrimidine-ring formation.

Since a facile and versatile route to conjugated carbodiimides *via* aza-Wittig reaction of iminophosphoranes with isocyanates was reported (2), conjugated carbodiimides have been recognized as a useful synthetic tool for heterocyclic systems; their intermolecular cycloaddition as well as intramolecular cyclizations provided nitrogen heterocycles such as pyridines (3) and 1,3-diazepines (4). However, the pyrimidine-ring formation *via* conjugated carbodiimides has received limited attention and only a few examples were found (5); *e.g.*, pyrido[1,2-*f*]-pyrimido[4,5-*d*]pyrimidines were prepared by the reaction of 6-(triphenylphosphoranylideneamino)uracil with isocyanates and pyridine (5b). In the continuation of our investigation on the heterocycle synthesis using functionalized carbodiimides (1), we report here a preparation of fused pyrimidine derivatives by the reaction of conjugated carbodiimides with an amidine.

N-(5,5-Dimethyl-3-oxo-1-cyclohexenyl)-*N'*-substituted carbodiimides **3**, generated *in situ* by the aza-Wittig reaction of iminophosphorane **1** with the corresponding isocyanates **2** in dioxane, were allowed to react with N^1-methyl-N^1-phenylbenzamidine **4** giving 2-(substituted amino)-quinazoline derivatives **5** as single products. The structures of **5** were established on the basis of their spectral data and elemental analyses. In the reaction of carbodiimide **3d** with amidine **4**

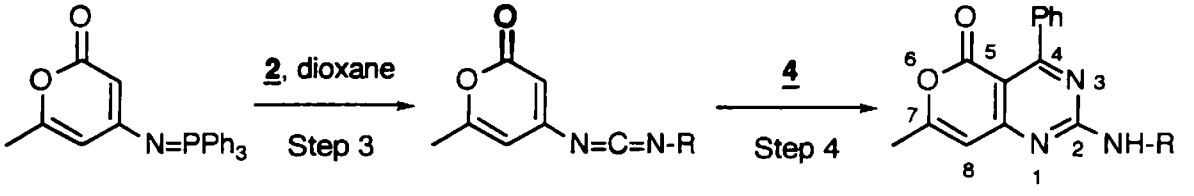


1 3 5

Reaction Conditions

Run	R	(Temp.[a]/ Time; h) Step 1	Step 2			Product (Yield;%)
1	Ph	reflux/1	r.t./12	-	reflux/12	5a (42)
2	Bu	reflux/2	r.t./12	-	reflux/18	5b (51)
3	1-Naphthyl	reflux/2	r.t./ 8	-	reflux/12	5c (48)
4[b]	CH_2Ph	reflux/2	r.t./12	-	reflux/ 8	5d (14)

a r.t.: room temperature. b Another product 6 was also obtained.



7 8 9

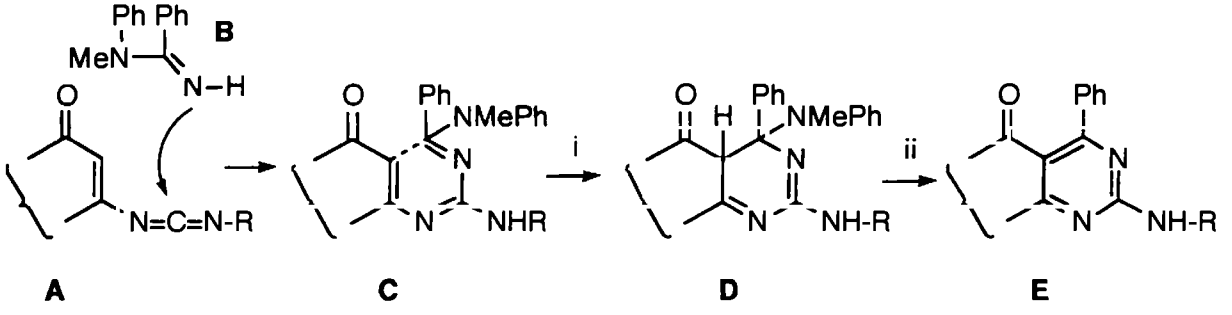
Reaction Conditions

Run	R	(Temp.[a]/Time; h) Step 3	Step 4			Product (Yield;%)
5	Ph	reflux/ 1	r.t./ 8	-	reflux/12	9a (64)
6	Bu	r.t./18	r.t./12	-	reflux/15	9b (50)
7	1-Naphthyl	reflux/ 4	r.t./ 8	-	reflux/ 8	9c (55)
8	CH_2Ph	reflux/ 4	r.t./15	-	reflux/12	9d (38)

a r.t.: room temperature.

(Run 4), another product 6. 2-(*N,N'*-dibenzylureido)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinazoline, was also obtained in 15% yield. Similarly, the reaction of *N*-[6-methyl-2-oxo-4-(2*H*)-pyranyl]-*N'*-substituted carbodiimides 8 with amidine 4 afforded also pyrimidine derivatives 9 in moderate yields.

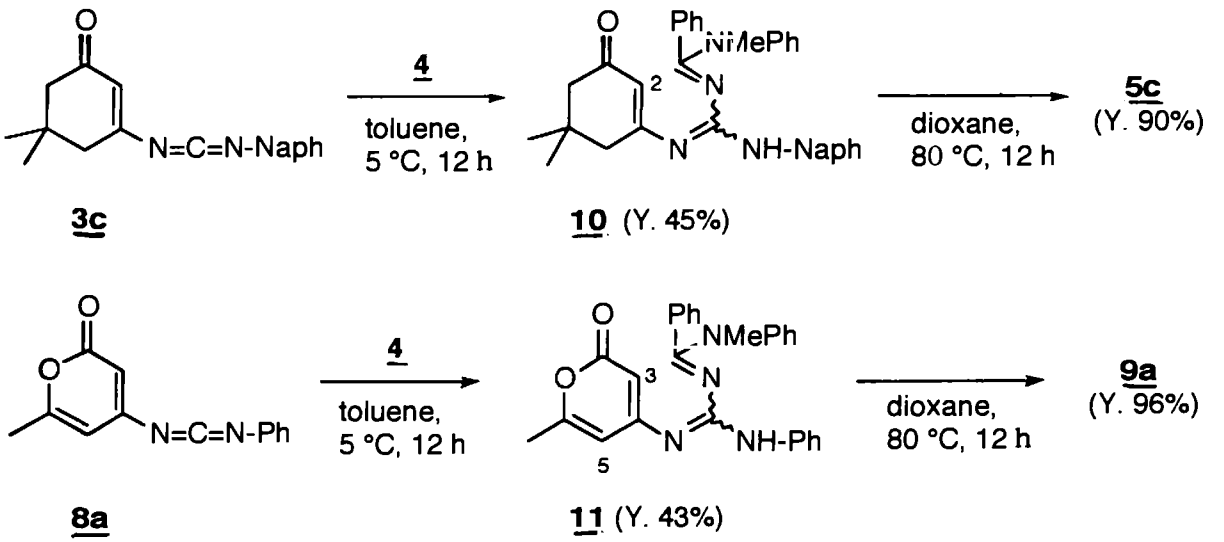
As speculated from the results of the pyridine-ring formation by the reaction of 3 with enamines (1b), the pyrimidine-ring formation would proceed as follows: the nucleophilic attack of the imine nitrogen atom in amidine B to the center carbon atom in carbodiimide A takes place giving guanidine C. The 6π-electrocyclic ring closure of C gives dihydropyrimidine D, which is aromatized to pyrimidine E with the elimination of *N*-methylaniline (Scheme 1).



Scheme 1 ***Reactions***. i, 6π-cyclization; ii, elimination of *N*-methylaniline

In two cases the guanidine intermediates 10 and 11 were isolated by the reaction at 5 °C in toluene followed by a short column chromatography on silica gel. The ^{1}H-NMR spectra of 10 and 11 show characteristic proton signals at δ 6.48 (singlet) and 5.58 (singlet), assigned to the vinyl protons 2-H and 3-H, respectively. ^{13}C-NMR spectral data of 10 and 11 are also consisted with the proposed structures. Guanidines 10 and 11 were not so stable under both acidic and basic conditions giving intractable mixtures of products. On gently heating 10 and 11 in dioxane gave the final products 5c and 9a in nearly quantitative yields (Scheme 2).

In this paper we have reported that the conjugated carbodiimides 3 and 8 undergo an intermolecular cyclization reaction with amidine 4 giving pyrimidine derivatives 5 and 9, respectively. We believe that this type of cyclization reaction could provide a convenient route to other fused pyrimidine derivatives.



Scheme 2

Experimental (6)

Iminophosphorane 7 was prepared from 4-hydroxy-6-methyl-2(2*H*)-pyrone similarly to the reported method for iminophosphorane 1 (1b). 7: Colorless prisms from ethanol-hexane; yield 52% (based on the starting material); mp 157-158 °C (Found: C, 74.56; H, 5.57; N, 3.37. $C_{24}H_{20}NO_2P$ requires C, 74.80; H, 5.23; N, 3.63%).

One-pot Procedure for the Preparation of Fused Pyrimidine Derivatives: Phenyl isocyanate (2a; 0.058 ml, 0.50 mmol) was added to a solution of iminophosphorane (7; 0.20 g, 0.50 mmol) in dioxane (5 ml). The reaction mixture was heated under reflux for 1 h. To the mixture cooled to room temperature amidine [4 (7); 0.126 g, 0.50 mmol] in dioxane (1 ml) was added, the resulting mixture was stirred at the same temperature for 12 h, and heated under reflux for additional 12 h. The solvent was distilled out and the residue was subjected to column chromatography on silica gel to afford 9a (0.105 g, 64%) with hexane-ethyl acetate= 4/1.

9a: Colorless prisms from EtOH; mp 163-165 °C (Found: C, 72.33; H, 4.91; N, 12.98. $C_{20}H_{15}N_3O_2$ requires C, 72.93; H, 4.59; N, 12.76%); νmax/cm^{-1} 3360 (NH) and 1760 (CO); δ_H ($CDCl_3$, 270 MHz) 2.16 (3H, s, 7-Me), 6.10 (1H, br s, 8-H), and 6.80-7.62 (11H, phenyl-H and NH); δ_C ($CDCl_3$, 68 MHz) 20.2 (7-Me), 103.6 (4a-C), 105.0 (8-C), 120.1, 123.9, 127.9, 128.8, 129.0, 130.1, 138.0, and 138.2 (phenyl-C), 159.8 (4-C), 160.2 (7-C), 164.0 and 164.6 (2- and 5-C), and 172.5 (8a-C); *m/z* 329 (M^+).

Selected data for fused pyrimidines 5, 6, and 9 are summarized as belows. All new compounds except for 10 and 11 gave satisfactory analytical (C, ± 0.40; H, ± 0.32; N, ± 0.27) and mass spectral data.

			δH ($CDCl_3$, 270 MHz)			
	mp (°C)	νNH	7-Me	8-H	6-H	others
5a	180-181	3250	1.12	2.49	2.29	7.78-8.04 (phenyl-H and NH)
5b	132-133	3250	1.11	2.46	2.84	0.82-1.70, 3.44 (CH_3 and $-CH_2-$) 6.03 (NH), 7.40 (phenyl-H)
5c	237-239	3250	1.10	2.50	2.90	6.88-8.13 (aromatic-H and NH)
5d	133-134	3230	1.10	2.50	2.82	4.30, 4.52 ($-CH_2-$), 6.57-8.02 (phenyl-H and NH)

6: Colorless prisms from EtOH; mp 122-124 °C (Found: C, 76.08; H, 6.00; N, 11.21. $C_{31}H_{30}N_4O_2$ requires C, 75.89; H, 6.16; N, 11.42%); νmax/cm^{-1} 3440 (NH) and 1680 (CO); δ_H ($CDCl_3$, 270 MHz) 1.08 (6H, s, 7-Me), 2.48 (2H, 2, 8-H), 2.88 (2H, s, 6-H), 4.36 and 4.62 (each 1H, 2d, *J*= 16.2 Hz, $-CH_2-$), 5.54 (2H, s, $-CH_2-$), 7.0-7.8 (15H, phenyl-H), and 10.7 (1H, br s, NH); *m/z* 490 (M^+).

			δ_H ($CDCl_3$, 270 MHz)		
	mp (°C)	νNH	7-Me	8-H	others
9b	69-70	3240	2.27	6.03	0.92 (CH_3), 1.12-1.78, 3.11-3.58 ($-CH_2-$), 7.02-7.58 (phenyl-H and NH)
9c	215-216	3240	2.16	6.13	7.20-8.18 (aromatic-H and NH)
9d	131-132	3240	2.19	6.08	4.32, 4.60 ($-CH_2-$), 6.45 (NH), 6.78-7.52 (phenyl-H)

Characterization and Conversion of Reaction Intermediates 10 and 11: 1-Naphthyl isocyanate (2c; 0.072 ml, 0.5 mmol) was added to a solution of iminophosphorane (1; 0.20 g, 0.50 mmol) in toluene (5 ml). The mixture was heated under reflux for 20 h and cooled to 5 °C with ice bath. Amidine (4; 0.126 g, 0.60 mmol) in toluene (5 ml) was added to the mixture and the resulting mixture was stirred at the same temperature for 12 h. The solvent was evaporated to dryness, which was subjected to chromatography through a short silica gel column to give 10 (0.111 g, 45%) with hexane-ethyl acetate= 1/4.

10: Pale yellow crystals; νmax/cm^{-1} 3290 (NH) and 1620 (CO); δ_H ($CDCl_3$, 270 MHz) 0.78 (6H, s, 5-Me), 1.92 (2H, s, 4-H), 2.12 (2H, s, 6-H), 3.40 (3H, s, N-Me), 6.48 (1H, s, 2-H), and 6.06-7.72 (aromatic-H and NH); δ_C ($CDCl_3$, 68 MHz) 27.8 (5-Me), 32.0 (5-C), 40.5 (N-Me), 43.4 (4-C), 50.4 (6-C), 106.4 (2-C), 119.0-122.0 (aromatic-C), 153.9 (-C=N-), 156.8 (3-C), 160.6 (-C=N-), and 199.3 (1-C).

11: Yellow crystals; νmax/cm^{-1} 3280 (NH) and 1720 (NH), δ_H ($CDCl_3$, 270 MHz) 2.12 (3H, s, 6-Me), 3.58 (3H, s, N-Me), 5.58 (1H, s, 3-H), 5.73 (1H, s, 5-H), and 7.03-7.62 (phenyl-H and NH); δ_C ($CDCl_3$, 68 MHz) 19.7 (6-Me), 40.6 (N-Me), 95.3 (3-C), 104.3 (5-C), 121.0-144.5 (phenyl-C), 154.8, 160.3, 161.2, and 161.8 (2- and 4-C and -C=N-), and 165.7 (6-C).

A solution of 10 (0.15 g, 0.30 mmol) in dioxane (3 ml) was heated at 80 °C for 12 h. The reaction mixture was passed through a florisil pad and the solvent was evaporated to dryness. Crystallization of the residue with hexane-ether gave 5c (0.106 g, 90%).

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(6) The general experimental procedures were the same as in Part 2 [1b]

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