A One-Pot *Biginelli* Synthesis of 6-Unsubstituted 5-Aroylpyrimidin-2(1*H*)-ones and 6-Acetyl-1,2,4-triazin-3(2*H*)-ones

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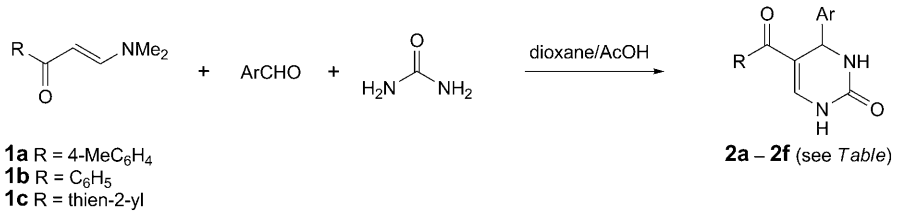
The three-component *Biginelli*-like cyclocondensation reaction of enamines **1**, urea, and aldehydes in dioxane/acetic acid efficiently afforded the corresponding 6-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones **2** in good yields (*Scheme 1*, *Table*). The corresponding reaction of azaenamine (= hydrazone) **7** with benzaldehyde and urea afforded 6-acetyl-1,2,4-triazin-3(2*H*)-ones in good yields (*Scheme 3*).

Introduction. – The *Biginelli* reaction is one of the most useful multicomponent reactions. It offers an efficient way to access multifunctionalized 3,4-dihydropyrimidin-2(1*H*)-ones and related heterocyclic compounds. Dihydropyrimidinones (DHPMs) have attracted considerable interest because of their wide spectrum of pharmacological and therapeutic activities [1–8]. Appropriately functionalized DHPMs have been used as antihypertensive agents [2–5] and potent calcium channel blockers [3][5]. Recently, DHPMs have also been shown to be useful for the development of anticancer drugs [6][7]. The established synthesis of DHPMs by the *Biginelli* reaction [1][9] involves the one-pot multicomponent condensation of β-keto esters, aldehydes, and urea in refluxing EtOH containing a catalytic amount of HCl.

Results and Discussion. – As a part of our continued interest in enamine and azaenamine chemistry [10–15], we report here our preliminary investigation dealing with the use of these compounds as substitutes to β-keto esters utilizing *Biginelli* reaction conditions. The utility of enamines gave us the opportunity to prepare corresponding new 6-unsubstituted 5-aroyl-3,4-dihydropyrimidin-2(1*H*)-one derivatives in moderate to good yields by means of a simple and efficient protocol for the *Biginelli*-like three-component cyclocondensation reactions of aldehydes, enamines, and urea. In the preliminary study, we found that heating enamine **1a** with benzaldehyde and urea in the presence of dioxane/AcOH resulted in the formation of condensation product **2a** *via* ammonia and water elimination (*Scheme 1*). The chemical structure of compound **2a** was established based on spectroscopic data. Thus, the mass spectra of **2a** revealed the molecular-ion peak at *m/z* 292 (19%). The ^{1}H-NMR spectrum of **2a** featured characteristic *d*s at δ(H) 5.43 assigned to H–C(4) and δ(H) 7.05 assigned to H–C(6). It also showed two broad *s*s at δ(H) 7.87 and 9.34 assigned to H–N(1) and H–N(3). The Me group and aromatic H-atoms appeared at

their expected positions. Furthermore, full assignment of the ^{13}C-NMR data confirmed the structure of **2a**, where the key signal at δ(C) 53.8 was assigned to C(4) (sp^3 C-atom), that at δ(C) 112.9 to C(5), and that at δ(C) 191.8 to the CO group. All other C-atoms appeared as expected. To investigate the scope of this reaction, several other enamines and aldehydes were studied, as summarized in the *Table*. In all cases, the three-component reaction proceeded smoothly and yielded 5-aroyl-3,4-dihydropyrimidin-2(1*H*)-ones **2b**–**2f** (*Table*). The structures of the prepared products were elucidated based on spectroscopic data.

Scheme 1



1a R = 4-MeC_6H_4
1b R = C_6H_5
1c R = thien-2-yl

2a – **2f** (see *Table*)

Table. *Yields of Compounds* **2a**–**2f**[a])

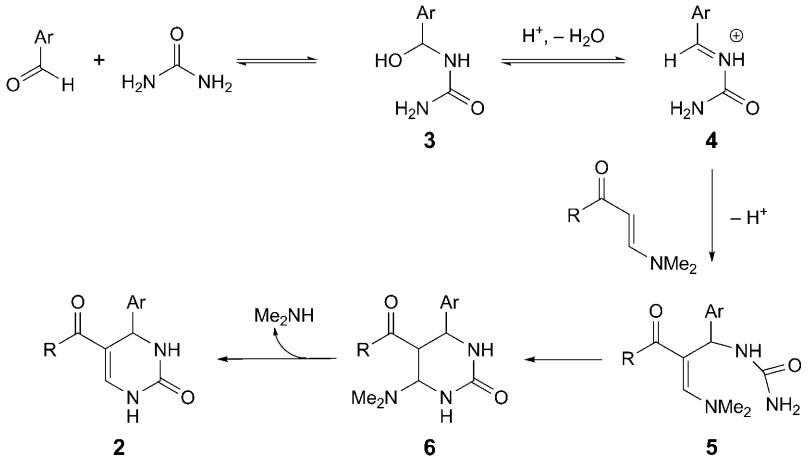
	R	Ar	Yield [%]		R	Ar	Yield [%]
2a	4-Me–C_6H_4	Ph	66	**2d**	thien-2-yl	Ph	68
2b	4-Me–C_6H_4	4-MeO–C_6H_4	63	**2e**	thien-2-yl	4-Cl–C_6H_4	70
2c	Ph	Ph	65	**2f**	thien-2-yl	4-MeO–C_6H_4	67

[a]) *Cf. Scheme 1.*

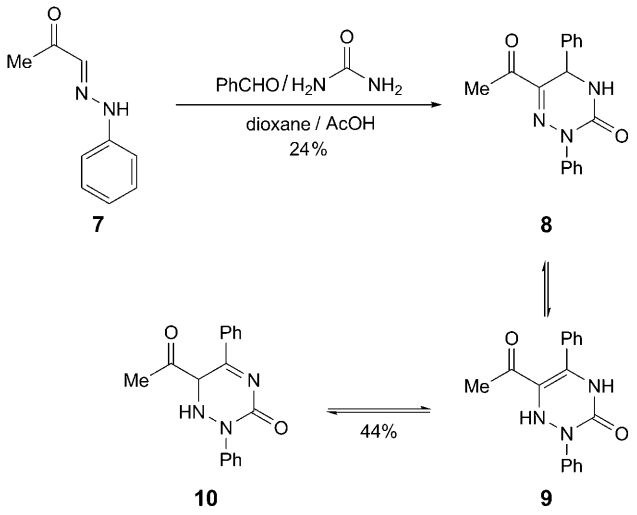
Following the recently published literature [16], the mechanism of this reaction involves the acid-catalyzed formation of an *N*-acyliminium ion intermediate of type **4** from the aldehyde and urea precursors (*via* **3**). Interception of the iminium ion **4** by enamine **1** produces an open-chain ureidoenone **5**, which subsequently cyclizes to hexahydropyrimidine **6**. Acid-catalyzed elimination of the Me_2N group from **6** ultimately leads to the final DHPM product **2** (*Scheme 2*). The reaction mechanism can, therefore, be classified as an α-amidoalkylation, or more specifically as an α-ureidoalkylation.

In an extension of the program to discover versatile routes to the *Biginelli*-like reaction, the possible utility of azaenamines was also investigated. It was discovered that azaenamine (= hydrazone) **7** with a sufficiently acidic CH=N moiety reacted with benzaldehyde and urea following the reaction conditions described for compounds **2a**–**2f**, resulting in the formation of 6-acetyl-1,2,4-triazin-3(2*H*)-ones. The formed products can be in theory formulated as **8**–**10**. The ^{1}H-NMR spectrum indicated the presence of a 1:2 mixture of **8** and **10**, as it showed two signals at δ(H) 2.54 and 2.35 for two Me groups. It also indicated the presence of a *d*s at δ(H) 4.38 and a broad *s* at δ(H) 5.99 for **10**. In addition, it featured a *d* at δ(H) 4.90 and a broad *s* at δ(H) 6.15 for **8**.

Scheme 2



Scheme 3



Conclusions. – We could establish a new and efficient synthesis of 6-unsubstituted 5-aroylpyrimidin-2(1*H*)-ones using simple starting materials. We could also extend this technique to the synthesis of 6-acetyl-1,2,4-triazin-3(2*H*)-one.

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Experimental Part

General. M.p.: *Stuart* melting-point apparatus; uncorrected. IR Spectra: *Bruker-Vector-22* FT-IR spectrophotometer; KBr pellets; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Varian-Gemini* NMR spectrometer; at 300 or 400 MHz (^1H) and 75 or 100 Mz (^{13}C); in (D_6)DMSO with Me_4Si as internal standard; δ in ppm, coupling constants J in Hz. MS: *Shimadzu-GMMS-QP-1000-EX* mass spectrometer; at 70 eV; in m/z (rel. %).

Biginelli-*Like Reaction: General Procedure.* Urea (1.0 mmol) was added to a soln. of aldehyde (1.0 mmol) and enamine **1** (**a**, **b**, or **c**) or azaenamine **7** in dioxane (20 ml) and a few drops of AcOH or HCl, and the mixture was refluxed until the reaction reached completion (TLC monitoring). After completion of the reaction, the mixture was triturated with H_2O, and the crude products were directly filtrated and purified by recrystallization to afford the products **2a**–**2f** (see *Table*) or **8**/**10** (see below).

*3,4-Dihydro-5-(4-methylbenzoyl)-4-phenylpyrimidin-2(1*H*)-one* (**2a**): White solid. R_f (AcOEt/petroleum ether 1:1) 0.5. M.p. 306–308° (EtOH/dioxane). IR: 3240, 3110, 1718, 1641. ^1H-NMR (400 MHz): 2.36 (*s*, Me); 5.43 (*d*, J = 2.8, H–C(4)); 7.05 (*d*, J = 5.9, H–C(6)); 7.26–7.87(*m*, 9 arom. H); 7.87 (br. *s*, 1 NH); 9.34 (br. *s*, 1 NH). ^{13}C-NMR (100 MHz): 21.2; 53.8; 112.9; 126.9; 127.8; 128.6; 128.9; 129.4; 136.2; 141.4; 141.7; 144.6; 151.7; 191.8. MS: 292 (19). Anal. calc. for $C_{18}H_{16}N_2O_2$ (292.33): C 73.95, H 5.52, N 9.58; found: C 73.93, H 5.49, N 9.46.

*3,4-Dihydro-4-(4-methoxyphenyl)-5-(4-methylbenzoyl)pyrimidin-2(1*H*)-one* (**2b**): White solid. R_f (AcOEt/petroleum ether 1:1) 0.52. M.p. 242–244° (EtOH/dioxane). IR: 3239, 3109, 1716, 1638. ^1H-NMR (300 MHz): 2.34 (*s*, Me); 3.72 (*s*, MeO); 5.37 (*d*, J = 2.4, H–C(4)); 6.88 (*d*, J = 8.1, 2 arom. H); 6.99 (*d*, J = 5.7, H–C(6)); 7.23–7.37 (*m*, 4 arom. H); 7.40 (*d*, J = 8.1, 2 arom. H); 7.75 (br. *s*, 1 NH); 9.23 (br. *s*, 1 NH). MS: 322 (M^+). Anal. calc. for $C_{19}H_{18}N_2O_3$ (322.36): C 70.79, H 5.63, N 8.69; found: C 70.69, H 5.57, N 8.68.

*5-Benzoyl-3,4-dihydro-4-phenylpyrimidin-2(1*H*)-one* (**2c**): White solid. R_f (AcOEt/petroleum ether 1:1) 0.69. M.p. 298–300° (EtOH/dioxane). IR: 3240, 3110, 1718, 1641. ^1H-NMR (300 MHz): 5.43 (*d*, J = 3.3, H–C(4)); 7.05 (*d*, J = 5.4, H–C(6)); 7.26–7.53 (*m*, 10 arom. H); 7.85 (br. *s*, 1 NH); 9.30 (br. *s*, 1 NH). MS: 278 (37.4). Anal. calc. for $C_{17}H_{14}N_2O_2$ (278.31): C 73.37, H 5.07, N 10.07; found: C 73.24, H 4.98, N 9.79.

*3,4-Dihydro-4-phenyl-5-(thien-2-ylcarbonyl)pyrimidin-2(1*H*)-one* (**2d**): White solid. R_f (AcOEt/petroleum ether 1:1) 0.6. M.p. 276–278° (EtOH/dioxane). IR: 3249, 3123, 1712, 1646. ^1H-NMR (300 MHz): 5.41 (*d*, J = 2.4, H–C(4)); 7.14–7.32 (*m*, 6 arom. H, 1 NH); 7.47 (*d*, J = 5.7, H–C(6)); 7.65 (*d*, J = 3.3, 1 H, thienyl); 7.66–7.87 (*m*, 2 H, thienyl); 9.36 (br. *s*, 1 NH). ^{13}C-NMR (75 MHz): 21.2; 53.8; 112.9; 126.9; 127.8; 128.9; 129.4; 136.2; 141.4; 141.7; 144.6; 151.7; 191.8. MS: 286 (43.63). Anal. calc. for $C_{15}H_{12}N_2O_2S$ (284.33): C 63.36, H 4.25, N 9.85, S 11.28; found: C 63.19, H 4.81, N 9.69, S 11.12.

*4-(4-Chlorophenyl)-3,4-dihydro-5-(thien-2-ylcarbonyl)pyrimidin-2(1*H*)-one* (**2e**): White solid. R_f (AcOEt/petroleum ether 1:1) 0.56. M.p. 242–244° (EtOH/dioxane). IR: 3256, 3139, 1726, 1661. ^1H-NMR (300 MHz): 5.40 (*d*, J = 3, H–C(4)); 6.95 (*d*, J = 8.7, 2 arom. H); 7.16 (*d*, J = 8.7, 2 arom. H); 7.26 (*d*, J = 5.9, H–C(6)); 7.48 (br. *s*, 1 NH); 7.67 (*d*, J = 4.5, 1 H, thienyl); 7.85–7.91 (*m*, 2 H, thienyl); 9.43 (br. *s*, 1 NH). MS: 320 (23.8). Anal. calc. for $C_{15}H_{11}ClN_2O_2S$ (318.78): C 56.52, H 3.48, Cl 11.12, N 8.79, S 10.06; found: C 56.98 H 3.82, Cl 11.38, S 9.91.

*3,4-Dihydro-4-(4-methoxyphenyl)-5-(thien-2-ylcarbonyl)pyrimidin-2(1*H*)-one* (**2f**): White solid. R_f (AcOEt/petroleum ether 1:1) 0.47. M.p. 276–278° (EtOH/dioxane). IR: 3234, 3109, 1710, 1639. ^1H-NMR (300 MHz): 3.71 (*s*, MeO); 5.35 (*d*, J = 2.7, H–C(4)); 6.86 (*d*, J = 8.7, 2 arom. H); 7.14 (br. *s*, 1 NH); 7.17(*d*, J = 8.7, 2 arom. H); 7.43 (*d*, J = 6, H–C(6)); 7.64–7.75 (*m*, 2 H, thienyl); 7.86 (*d*, J = 5.1, 1 H, thienyl); 9.32 (br. *s*, 1 NH). ^{13}C-NMR (75 MHz): 52.9; 55.0; 112.4; 113.7; 120.6; 127.8; 131.3; 132.2; 136.1; 139.4; 142.5; 151.2; 158.5; 182.3. MS: 316 (32.17). Anal. calc. for $C_{16}H_{14}N_2O_3S$ (314.36): C 61.13, H 4.49, N 8.91, S 10.20; found: C 60.59, H 4.94, N 8.73, S 9.88.

*6-Acetyl-4,5- and 1,6-dihydro-2,5-diphenyl-1,2,4-triazin-3(2*H*)-one* (**8** and **10**; ratio 1:2). White solid. M.p. 188–190 (EtOH/dioxane). IR: 3233, 1690, 1653. ^1H-NMR (400 MHz; italic signals for the predominant isomer **10**) *2.35* (*s*, Me); 2.54 (*s*, Me); *4.38* (*d*, J = 4.26, H–C(6)); 4.90 (*d*, J = 3.1, H–C(5)); *5.99* (br. *s*, 1 NH); 6.15 (br. *s*, 1 NH); 6.71–7.27 (*m*, 20 arom. H). ^{13}C-NMR (100 MHz; italic signals for the predominant isomer **10**): 24.2; *24.5*; 50.1; *68.2*; 115.1; *116.1*; *122.7*; 125.8; *127.5*; 127.6; 127.7;

127.8; *128.4*; 128.5; *128.8*; *129.2*; *129.5*; 129.7; 137.7; *138.3*; *141*; 141.8; *143.1*; 144.8; *194.7*; 195.8. MS: 293 (M^+).

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