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2-ACYLMETHYL-1H-BENZIMIDAZOLES IN THE BIGINELLI REACTION

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By cyclocondensation of 2-acylmethyl-1H-benzimidazoles with aromatic aldehydes and urea according to the Biginelli reaction, we have obtained previously unknown 6-substituted 4-aryl-5-(2-benzimidazolyl)-2-oxo-1,2,3,4-tetrahydropyrimidines. We have developed an efficient procedure for conducting the three-component reaction at fairly low temperatures. We have analyzed the structural features of the synthesized compounds based on ^{1}H NMR spectra and IR spectroscopy.

Keywords: aldehydes, benzimidazoles, pyrimidines, ureas, Biginelli reaction, cyclocondensation.

1,2,3,4-Tetrahydropyrimidines have a broad spectrum of useful practical properties and can be synthesized by the Biginelli reaction by three-component cyclocondensation of acetoacetic ester with aldehydes and urea; and by varying all three components, they can be synthesized with various substituents [1]. Thus recently we reported about development of conditions for obtaining pyrimidine compounds that are 2-benzothiazolyl-substituted in the 6 position when using 2-phenacylbenzothiazole as the methylenecarbonyl component of the reaction [2].

In this work, for the first time we have studied the conditions and effectiveness of using a number of 2-acylmethyl-substituted benzimidazoles **1a-c** in the Biginelli reaction. As the aldehyde component, we tested benzaldehydes **2a-i** containing electron-acceptor or electron-donor substituents in *p*-, *m*-, or *o*-positions, and also heteroaromatic aldehydes **2j,k** including π-electron deficient and π-electron rich heterocycles.

The conditions for the studied three-component cyclocondensation were optimized. We note that when the experiments were conducted under standard conditions for the Biginelli reaction (boiling in ethanol with catalysis by hydrochloric acid [1]), the compounds obtained proved to be impure; according to TLC, the impurities were mainly condensation products of the starting methylenecarbonyl and aldehyde components obtained *via* the Knoevenagel reaction, which as we established earlier [3] are poorly soluble compounds. We were unable to remove these impurities by crystallization. At the same time, carrying out the target cyclocondensation using the procedure we developed for 2-phenacylbenzothiazole (ratio of reagents 1:1.1:3; solvent, acetic acid; temperature, 40-50°C [2]) also did not yield satisfactory results. The reaction proceeded sluggishly, probably due to the low solubility and low reactivity of the starting methylenecarbonyl components. Nevertheless, when the latter procedure is slightly modified, specifically by adding concentrated hydrochloric acid (2.5 equivalents), the process becomes rather selective and efficient. In our opinion, using mild synthesis conditions and a three-fold excess of urea, in order to compensate for losses of the latter due to its hydrolysis, significantly eliminates the complications of the basic process caused by side reactions, since completeness of the intended consumption of reagents is ensured and the final operation of isolating the reaction products in pure form is simplified.

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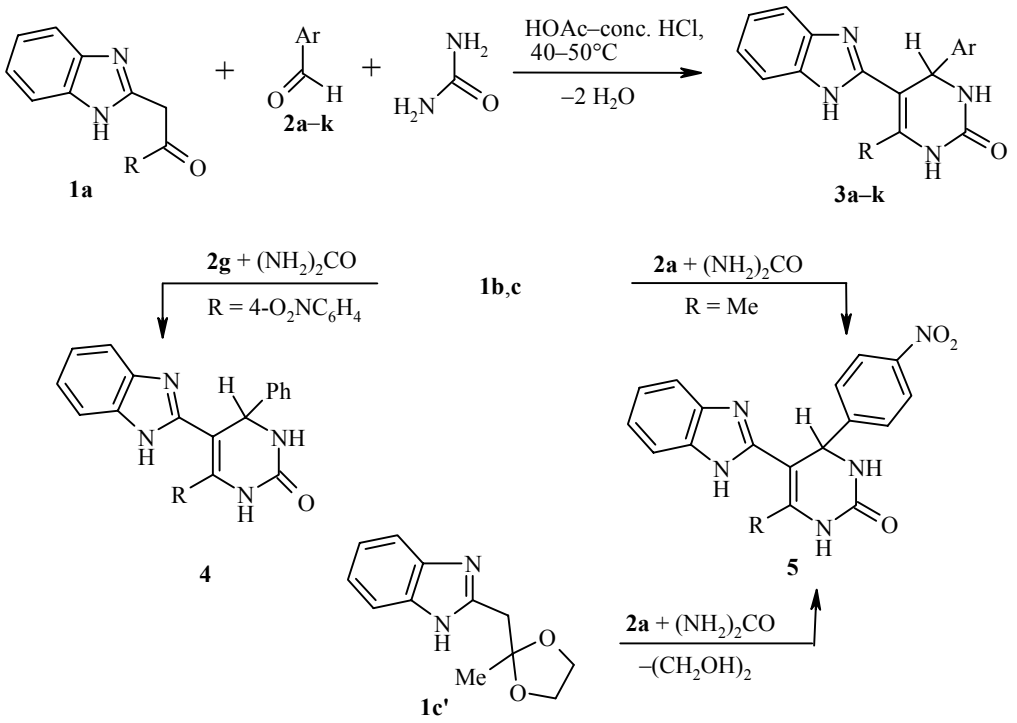
Cyclocondensation of 2-phenacylbenzimidazole **1a** with aldehydes **2a-k** and urea leads to formation of previously unknown 4-aryl-5-(2-benzimidazolyl)-2-oxo-1,2,3,4-tetrahydro-6-phenylpyrimidines **3a-k**. 2-(*p*-Nitrophenacyl)benzimidazole **1b** reacted with benzaldehyde **2g** and urea yields the pyrimidine compound **4**, isomeric to compound **3g**; this suggests that, under the conditions used, no migration of the multiple bond occurs in the tetrahydropyrimidine ring. 2-Acetonylbenzimidazole **1c** reacts with *p*-nitrobenzaldehyde and urea to form the corresponding 6-methylpyrimidine compound **5**, and may be successfully replaced (with no loss of yield and with no change in the reaction time) by its ethylene ketal **1c'**, which is more accessible and more stable during prolonged storage.



1 a R = Ph, **b** R = 4-$O_2NC_6H_4$, **c** R = Me; **2**, **3 a** Ar = 4-$O_2NC_6H_4$, **b** Ar = 3-$O_2NC_6H_4$, **c** Ar =2-$CF_3C_6H_4$, **d** Ar =4-ClC_6H_4, **e** Ar =2-ClC_6H_4, **f** Ar =2-IC_6H_4, **g** Ar =Ph, **h** Ar =4-$MeOC_6H_4$, **i** Ar = 4-$Me_2NC_6H_4$, **j** Ar = 4-pyridyl, **k** Ar = 2-thienyl; **3a-k** R = Ph, **4** R = 4-$O_2NC_6H_4$, **5** R = Me

With a decrease in the electrophilicity of the methylenecarbonyl and aldehyde components used, the time required to obtain compounds **3a-k, 4,** and **5** increases to 2-14 days while the yields are somewhat decreased to 72-97%.

The synthesized pyrimidines are stable high-melting crystalline materials. The nitro derivatives **3a,b**, and **4** are pale yellow; the rest of the compounds are colorless. Some physical and chemical characteristics of these compounds are presented in Table 1; the IR and proton spectral parameters are given in Table 2.

In the IR spectra of the compounds obtained, an absorption band from the carbonyl group appears in the 1690-1705 cm^{-1} region, while the N–H bonds give two absorption bands in the 3210-3260 cm^{-1} and 3320-3470 cm^{-1} ranges.

More meaningful information about the structure of the compounds is given by the ^1H NMR spectra. The doublet in the range 5.44-6.97 ppm corresponds to the vicinal proton on the C(4) atom of the tetrahydropyrimidine ring, and allows us to assign the signals for the NH protons. The proton signal for N(1) appears as a normal singlet in the range 8.85-9.23 ppm, while the signal for the proton on N(3) appears as a

TABLE 1. Characteristics of Synthesized Compounds **3a-k,4,5**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Reaction time, days	Yield
		C	H	N			
3a	$C_{23}H_{17}N_5O_3$	67.15 / 66.97	4.16 / 4.21	17.02 / 17.15	263-64	3	91
3b	$C_{23}H_{17}N_5O_3$	67.15 / 67.30	4.16 / 4.25	17.02 / 17.13	319-21	4	91
3c	$C_{24}H_{17}F_3N_4O$	66.36 / 66.21	3.94 / 3.78	12.90 / 13.07	267-68	13	83
3d	$C_{23}H_{17}ClN_4O$	68.91 / 68.75	4.27 / 4.35	13.98 / 13.85	253-56	4	98
3e	$C_{23}H_{17}ClN_4O$	68.91 / 68.80	4.27 / 4.20	13.98 / 13.88	256-58	13	87
3f	$C_{23}H_{17}JN_4O$	56.11 / 56.03	3.48 / 3.55	11.38 / 11.45	238-40	14	76
3g	$C_{23}H_{18}N_4O$	75.39 / 75.22	4.95 / 5.07	15.29 / 15.17	265.5-67	9	91
3h	$C_{24}H_{20}N_4O_2$	72.71 / 72.55	5.08 / 5.17	14.13 / 14.21	316-17.5	11	90
3i	$C_{25}H_{23}N_5O$	73.33 / 73.27	5.66 / 5.78	17.10 / 17.19	315-17	8	95
3j	$C_{22}H_{17}N_5O$	71.92 / 72.14	4.66 / 4.73	19.06 / 19.21	304.5-06	3	80
3k	$C_{21}H_{16}N_4OS$	67.72 / 67.83	4.33 / 4.21	15.04 / 14.91	189-91	12	93
4	$C_{23}H_{17}N_5O_3$	67.15 / 67.22	4.16 / 4.21	17.02 / 16.86	284-85	2	99
5	$C_{18}H_{15}N_5O_3$	61.89 / 62.05	4.33 / 4.15	20.05 / 20.22	293-94	2	99

* Crystallized from the following mixtures: water–DMF, 1:2 (**5**), 1:4 (**3a**), water–Py, 1:1 (**3h,i**), 1:2 (**4**), 1:3 (**3b-f,j**), and water–acetone 1:1 (**3g,k**).

broadened singlet (distortion of the doublet with small spin–spin coupling constant) in the range 7.46-8.03 ppm. After addition of D_2O, the signals from the protons bonded to the nitrogen atoms disappear, while the doublet from the proton on the $C_{(4)}$ atom of the pyrimidine ring changes to a singlet. In the series of *m*- and *p*-phenyl-substituted compounds **3a,b,d,g-i**, we can see a trend toward a certain regularity in the appearance of signals from protons on the N(1), N(3), and C(4) atoms: as we go from electron-acceptor substituents on the aromatic ring of the starting aldehyde (Ar) to electron-donor substituents, the chemical shifts for these protons successively decrease. The protons for the N(1)–H bonds in this case appear 1.12-1.65 ppm downfield compared with those in the N(3)–H bonds. This is probably evidence for transfer of electron density from the N(1) atoms on the vinyl moiety C(5)=C(6) to the benzimidazole ring, with formation of an energetically more favorable conjugation system. The latter is probably so favorable that it holds the pyrimidine and benzimidazole moieties of the molecule in the same plane, although the C(6)-phenyl moiety of compounds **3a-k** deviates from this plane due to steric hindrances. In this case, there is disruption of the overlap between the π orbitals of the electron-deficient C(6) atom of the pyrimidine ring and the adjacent phenyl moiety, and consequently the protons of the latter appear as a very narrow multiplet in the range 7.30-7.36 ppm, which is more typical [4] for alkylbenzenes. Such structural features, implied by the ^{1}H NMR spectra and confirmed by X-ray diffraction, were observed earlier [2] in benzothiazole analogs of compounds **3a-k**.

Let us separately consider how protons from the benzimidazole moiety appear in the ^{1}H NMR spectra. We recall that usually in solutions of benzimidazoles, rapid intermolecular migration of the proton from one

TABLE 2. Spectral Characteristics of Synthesized Compounds **3a-k, 4,** and **5**

Compound	IK spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm. (*J*, Hz)								
	C=O	NH	NH(1), s	NH(3), br. s	CH(4), d	C(6)–R, m (s)	C(5)-benzimidazolyl				Aromatic protons of Ar substituent, m
							NH(1'), s	CH(4')*, m	CH(7'), m	CH(5', 6'), m	
3a	1690	3210, 3440	9.16	7.98	5.65 (3.3)	7.36	11.02	7.44	7.16	7.01	7.74-8.24
3b	1690	3205, 3460	9.22	8.03	5.65 (3.3)	7.37	11.07	7.45	7.16	7.03	7.65-8.40
3c	1690	3210, 3470	9.11	7.46	5.88 (2.7)	7.32	11.36		7.13	6.97	7.43-7.98
3d	1700	3220, 3450	9.08	7.87	5.53 (3.0)	7.32	11.08		7.15	7.02	7.39-7.49
3e	1700	3220, 3430	9.09	7.67	5.97 (3.2)	7.34	11.21		7.14	6.99	7.23-7.64
3f	1690	3210, 3440	9.08	7.57	5.81 (3.2)	7.31	11.23		7.13	6.99	7.36-7.79
3g	1700	3220, 3430	8.97	7.79	5.56, (2.9)	7.32	11.07		7.14	7.01	7.20-7.45
3h	1695	3220, 3320	8.90	7.69	5.51, (3.0)	7.32	11.04	7.42	7.13	7.02	6.85-7.36*[2]
3i	1690	3215, 3430	8.85	7.61	5.44 (2.9)	7.30	11.08	7.40	7.13	7.01	6.62-7.23*[2]
3j	1700	3220, 3320	9.14	7.96	5.54 (3.5)	7.35	11.03		7.18	7.04	7.46-8.55
3k	1705	3230, 3420	9.11	7.93	5.80 (3.1)	7.36	10.96		7.18	7.03	6.93-7.34
4	1700	3235, 3450	9.23	7.92	5.65 (2.9)	7.58-8.20	11.45		7.19	7.03	7.23-7.45
5	1700	3260, 3360	9.02	7.90	5.76 (2.9)	2.31	12.03	7.49	7.38	7.09	7.53-8.18

* Compounds **3c-g,j,k,** and **4**: the signal is overlapped by the multiplet from the protons of the Ar substituent.

*[2] Other signals for the compounds: **3h**, 3.69 (3H, s, OCH_3); **3i**, 2.82 (6H, s, $N(CH_3)_2$).

ring atom of the benzimidazole ring to another occurs, and consequently the molecule acquires a high degree of symmetry in the π-electron density distribution, while the 4, 7 positions, like the 5,6 positions, become chemically equivalent [5]. For example, in the ^{1}H NMR spectrum of unsubstituted benzimidazole, the aromatic protons resonate at 7.70 ppm and 7.26 ppm (2H(4,7) and 2H(5,6) [5]). In the compounds we synthesized, multiplet signals from the benzimidazole protons in the 4 and 7 positions appear separately in the ranges 7.40-7.49 ppm and 7.13-7.38 ppm, while signals from protons at the 5 and 6 positions overlap each other in the range 6.97-7.09 ppm. In this case, we see a downfield shift of the signals and asymmetry in the electron density distribution on the ring. This probably is due to the above-noted electron-donor effect of the pyrimidine moiety, the shielding effect of its aryl substituents, and steric hindrances to free migration of the amino group proton. Also note the resonance of the proton in the N–H bond of the benzimidazole ring. For the 6-arylpyrimidine compounds **3a-k** and **4**, the signal from this proton appears in the range 10.96-11.36 ppm (as we know, in its structural analogs, the 2-(4-pyrazolyl)benzimidazoles, the signal is at ~12 ppm [7]). The clear downfield shift of the signal by about 1 ppm is probably due to the above-noted distinctive orientation of the C(6)-phenyl ring, and the range over which it has a shielding effect encompasses the 1 position of the benzimidazole ring. Such shielding is impossible in the 6-methyl-substituted compound **5**, and the signal for the corresponding proton is observed in the usual region at 12.03 ppm.

Thus in our work we have shown that 2-acylmethyl-substituted benzimidazoles are a convenient component of the Biginelli reaction for obtaining previously unknown 5-(2-benzimidazolyl)-2-oxo-1,2,3,4-tetrahydropyrimidines, which contain various substituents in the 4 and 6 positions (including functional groups).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian VXR-300 (300 MHz), solvent DMSO-d_6, internal standard TMS. Compounds **1a-c,c'** were obtained by the procedures described in [8-10]. The IR spectra were taken on a UR-40 spectrometer in KBr disks. The course of the reactions and the purity of the synthesized compounds were monitored by TLC (Silufol UV-254, 9:1 chloroform–methanol).

6-Substituted 4-Aryl-5-(2-benzimidazolyl)-2-oxo-1,2,3,4-tetrahydropyrimidines (3a-k, 4, 5). A mixture of compound **1a-c,c'** (1 mmol), aldehyde **2a-k** (1.1 mmol), urea (3 mmol), glacial acetic acid (1 ml), and conc. HCl (0.25 ml, 2.5 mmol) was stirred at 40-50°C until homogenized, and then held for a long period without outside interference (the process times are indicated in Table 1). Water (2 ml), acetone (2 ml), and 25% NH_4OH (0.75 ml) were added to the reaction mixture formed. The mixture was boiled with stirring until crystallization began. After cooling down to 20-25°C, the precipitate was filtered out, washed with water, 2-propanol, and ether, and then dried for 5 h under a vacuum created with a water-jet pump at 150°C.

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