Reaction of aromatic aldehydes with β-dicarbonyl compounds in a catalytic system: piperidinium acetate—1-butyl-3-methylimidazolium tetrafluoroborate ionic liquid*

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Condensation of aromatic (heteroaromatic) aldehydes with 1,3-dicarbonyl compounds under the 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim][BF_4]) ionic liquid—piperidinium acetate catalytic system (0.2 equiv. of each component) in the absence of a solvent affords, depending on the structures of the reagents, 2-arylidene derivatives of methyl acetoacetate and acetylacetone, diethyl 2,4-bis(trifluoroacetyl)-3-phenylpentanedioate, or dimethyl 2-aryl-4-hydroxy-6-oxocyclohexane-1,3-dicarboxylates. The reactions of the resulting 2-arylidene derivatives with *O*-methylisourea in the [Bmim][BF_4] ionic liquid produced methyl 2-methoxy-4-methyl-6-aryldihydropyrimidine-5-carboxylates and 1-(2-methoxy-4-methyl-6-phenyldihydropyrimidin-5-yl)ethanone (mixtures of 3,6- and 1,6-dihydro isomers), which were transformed into the corresponding 3,4-dihydropyrimidin-2(1*H*)-one derivatives.

Key words: Knoevenagel condensation, ionic liquids, catalysis, cyclohexanone-2,4-dicarboxylic acids, dihydropyrimidines, 3,4-dihydropyrimidin-2(1*H*)-ones.

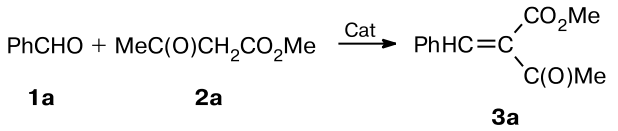
Base-catalyzed condensation of aldehydes with methylene-active compounds (Knoevenagel reaction) is widely used for the synthesis of polyfunctional organic compounds with different structures.[1,2] This reaction is generally performed in polar organic solvents (for example, in EtOH or THF), which provide good solvation of CH-acid anions and promote dehydration of aldols.[3—11] Recently, the results of investigation of Knoevenagel condensation in solutions of imidazolium salts with fluorine-containing anions have been reported.[12—19] The latter belong to moisture-resistant ionic liquids (IL) of the second generation.[20—23] The use of this class of solvents made it possible to decrease the reaction time and increase the yields of the products.[13,16—19] In some cases, the reaction occurs in the absence of a base catalyst, because IL acts as a catalyst by itself.[18,19] However, IL are of limited usefulness as solvents because of their relatively high cost.[24]

The published data suggest that catalytic amounts of IL are sufficient for the Knoevenagel reaction to occur. The reactions performed directly in a binary mixture of the starting compounds without a solvent are most promising from the viewpoint of green chemistry.[25,26]

To verify this hypothesis, we studied the effect of catalytic amounts of 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim][BF_4]), which has been used earlier as a solvent,[13,18] on the reaction of aromatic aldehydes with β-dicarbonyl compounds. The reaction was carried out in the absence of a solvent and a catalyst or in the presence of piperidinium acetate ([Pip][OAc]) as a base catalyst for Knoevenagel condensation.[5,10] The influence of IL on the Knoevenagel reaction in the absence of a solvent has been earlier unknown.

We studied condensation of benzaldehyde (**1a**) with methyl acetoacetate (**2a**) as the model reaction (Scheme 1, Table 1).

Scheme 1



Cat is a catalyst

We found that compounds **1a** and **2a**, which do not react with each other in the absence of a catalyst, give condensation product **3a** (a mixture of *Z* and *E* isomers) upon the addition of 0.2 equiv. of [Bmim][BF_4] and/or [Pip][OAc] to the reaction mixture. The [Bmim][BF_4] salt exhibits low catalytic activity. At 120 °C, the yield of product **3a** is at most 18%. As expected, acetate [Pip][OAc] proved to be a more active catalyst. In the

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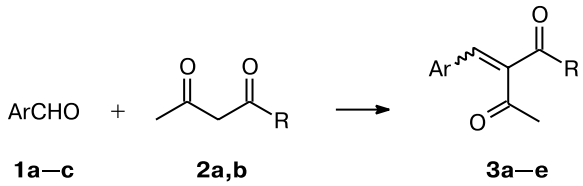
Table 1. Influence of the additives of [Bmim][BF_4] (0.2 equiv.) and [Pip][OAc] (0.2 equiv.) and the reaction conditions on the yield of methyl 2-acetyl-3-phenylacrylate (**3a**) produced by condensation of benzaldehyde (**1a**) with methyl acetoacetate (**2a**) in a binary solution of the starting compounds

Additive	τ/h	*T*/°C	Yield of **3a** (%)
—	6	120	0
[Bmim][BF_4]	4	120	18
[Pip][OAc]	20	20	70
[Bmim][BF_4]—[Pip][OAc]	4	20	85

presence of the latter, product **3a** was prepared in 70% yield already at 20 °C. The best results were obtained with the use of the combined [Bmim][BF_4]—[Pip][OAc] salt system (0.2 equiv. of each component). In this case, the yield of ketoester **3a** was as high as 85%, the reaction time being substantially shorter. Apparently, the [Bmim][BF_4] and [Pip][OAc] salts complement each other under the reaction conditions: [Pip][OAc] acts as a base, whereas [Bmim][BF_4] stabilizes the carbanion of the CH-acid (presumably, through hydrogen bonding with the involvement of the proton at position 2 of the imidazole ring[27]).

Scheme 2



1a—c **2a,b** **3a—e**

1: Ar = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 2-ClC_6H_4 (**c**)
2: R = OMe (**a**), Me (**b**)

3	Ar	R
a	Ph	OMe
b	Ph	Me
c	4-$MeOC_6H_4$	OMe
d	4-$MeOC_6H_4$	Me
e	2-ClC_6H_4	OMe

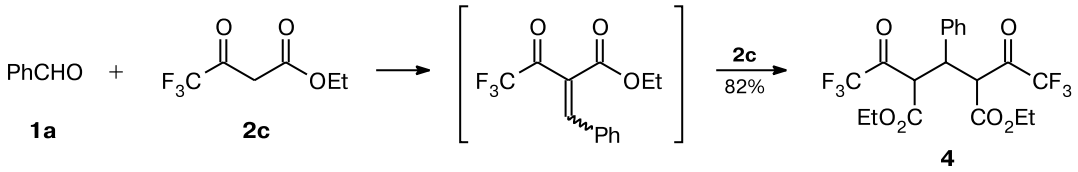
The use of the [Bmim][BF_4]—[Pip][OAc] catalytic system in condensation of various aldehydes and CH-acids demonstrated that, depending on the structures of the reagents, the reaction can afford different products (Table 2). For example, benzaldehyde (**1a**), 4-methoxybenzaldehyde (**1b**), and 2-chlorobenzaldehyde (**1c**) containing either an inactivated or sterically hindered aldehyde group react with methyl acetoacetate (**2a**)

Table 2. Comparative estimates of the yields of the condensation products of aldehydes **1a—i** with methyl acetoacetate (**2a**), acetylacetone (**2b**) and ethyl trifluoroacetylacetate (**2c**) under different conditions

Reagents	Catalytic system*	Condensation product	Yield (%)	B.p./°C (*p*/Torr) [m.p./°C]
1a + **2a**	[Bmim][BF_4]—[Pip][OAc]	**3a**	73	122—123.5 (3)
	EtOH (30)—[Pip][OAc] (1)		85[5]	
1a + **2b**	[Bmim][BF_4]—[Pip][OAc]	**3b**	75	140—142 (3)
	THF (25)—$CuCl_2$ (cat.)		98 [7]	
1a + **2c**	[Bmim][BF_4]—[Pip][OAc]	**4**	82	[183—186]
1b + **2a**	[Bmim][BF_4]—[Pip][OAc]	**3c**	90	135.5—137 (3)
	C_6H_6 (25)—Piperidine (1)		53 [8]	
1b + **2b**	[Bmim][BF_4]—[Pip][OAc]	**3d**	85	156—157 (3) [62—64]
	C_6H_6 (25)—Piperidine (1)		64 [8]	[49—51][8]
1c + **2a**	[Bmim][BF_4]—[Pip][OAc]	**3e**	80	153—155 (3)
	C_6H_6 (25)—[Pip][OAc] (1)		84 [10]	195—196 (10)
1d + **2a**	[Bmim][BF_4]—[Pip][OAc]	**5a**	87	[174—176]
	MeOH (25)—Piperidine (1)		78 [11]	[183—185]
1e + **2a**	[Bmim][BF_4]—[Pip][OAc]	**5b**	85	[168—169]
	MeOH (25)—Piperidine (1)		80 [11]	[175—177]
1f + **2a**	[Bmim][BF_4]—[Pip][OAc]	**5c**	89	[162—164]
1g + **2a**	[Bmim][BF_4]—[Pip][OAc]	**5d**	84	[193—195]
	EtOH (30)—Piperidine (1)		75 [5]	[193.5—194.5]
1h + **2a**	[Bmim][BF_4]—[Pip][OAc]	**5e**	80	[191—192]
	EtOH (30)—Piperidine (1)		73 [5]	[191—192]
1i + **2a**	[Bmim][BF_4]—[Pip][OAc]	**5f**	92	[167—168]

* The composition of the catalytic system is given in parentheses in molar equivalents with respect to the starting aldehyde or CH-acid; in all cases, 0.2 equiv. of each reagent was used in the reactions involving the [bmim][BF_4]—[Pip][OAc] system.

Scheme 3

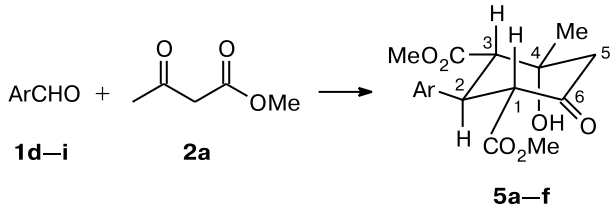


and acetylacetone (**2b**) in the presence of the [Bmim][BF_4]—[Pip][OAc] catalytic system to form arylidene derivatives **3a—e** (Scheme 2). The ^{1}H NMR spectra (signals for the protons of C(O)C<u>H</u>$_3$ and ArC<u>H</u>=) demonstrate that products **3a,c,e** exist as 3 : 2 mixtures of the *E* and *Z* isomers.

The reaction of benzaldehyde **1a** with the stronger CH-acid, *viz.*, ethyl trifluoroacetylacetate (**2c**), proceeds with the involvement of two molecules of the CH-acid to give diethyl 2,4-bis(trifluoroacetyl)-3-phenylpentanedioate (**4**) (Scheme 3) regardless of the component ratio.

Under the conditions used, condensation of aromatic aldehydes containing electron-withdrawing substituents in the *meta* and *para* positions of the aromatic ring (**1d—h**) and 2-thiophene aldehyde (**2i**) with methyl acetoacetate (**2a**) affords exclusively 2-aryl-4-hydroxy-6-oxocyclohexane-1,3-dicarboxylic acid derivatives (**5a—f**) (Scheme 4). Apparently, the formation of compounds **5a—f** occurs through intramolecular aldol cyclization of analogs of compound **4**, which are generated *in situ* under the reaction conditions. The yields of products **3** and **5** are, as a rule, close to (and, in some cases, are higher than) the yields of the same products prepared under standard conditions (see Table 2).

Scheme 4



1	5	Ar
d	a	4-ClC_6H_4
e	b	4-FC_6H_4
f	c	4-$MeO_2CC_6H_4$
g	d	4-$NO_2C_6H_4$
h	e	3-$NO_2C_6H_4$
i	f	2-Thienyl

The reaction is stereoselective. In spite of the presence of four asymmetric centers, compounds **5a—f** (^{1}H NMR spectroscopic data) were synthesized as individual diastereoisomers. The spin-spin coupling constants $^3J_{1,2}$ and $^3J_{2,3}$ (8.7—12.3 Hz) correspond to the diaxial arrangement of the protons at positions 1—3 of the cyclohexane ring.[28] The axial arrangement was assigned to the hydroxy group in products **5a—f** by analogy with compound **5** (Ar = Ph) synthesized earlier.[28]

It should be emphasized that, although 3-hydroxycyclohexan-1-one derivatives (**5**) have been prepared earlier in the reactions of aldehydes with β-dicarbonyl compounds in organic solvents,[5,11,28] the reactions in solutions of IL always produced exclusively compounds **3**.[13—18] Only one example of the addition of two CH-acid molecules to one aldehyde molecule (to give an analog of compound **4**) in the presence of IL as a solvent has been documented (the reaction of salicylaldehyde with cyanoacetic ester)[12].

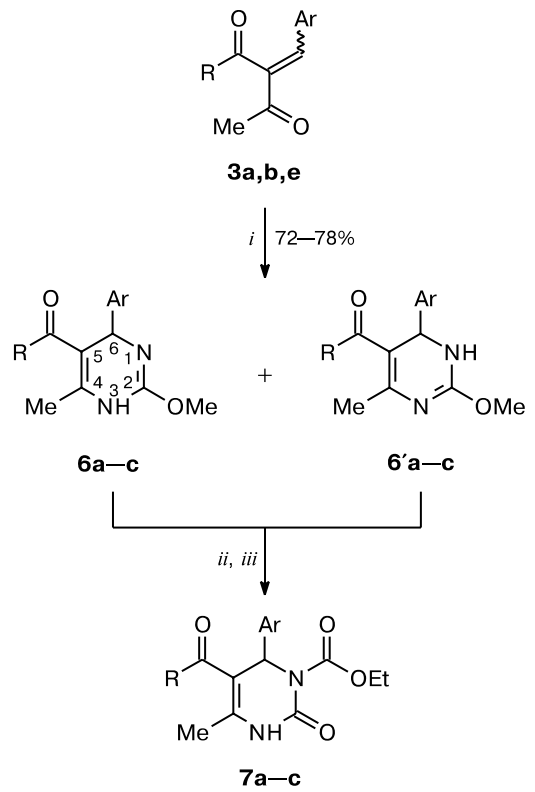
Therefore, the [Bmim][BF_4]—[Pip][OAc] system is an efficient catalyst for condensation of aromatic aldehydes with β-dicarbonyl compounds, which allows one to synthesize linear and cyclic products with different structures in the absence of an organic solvent using a catalytic amount of an ionic liquid.

The [Bmim][BF_4]—[Pip][OAc] catalytic system enables one to perform one-pot multistep syntheses of heterocycles involving Knoevenagel condensation as the first step. For example, the reactions of compounds **3a,b,e**, which were prepared (without additional purification) under the above-described conditions, with *O*-methylisourea in the [Bmim][BF_4] ionic liquid (4 equiv.) produced dihydropyrimidine derivatives **6a—c** (Scheme 5) in high yields as mixtures of isomeric 3,6- (**6**) and 1,6-dihydropyrimidines (**6´**) (^{1}H NMR data). The **6** : **6´** isomer ratio is 2 : 1 in products **6a,b** and 3 : 1 in product **6c**.

The results of our study demonstrated that the condensation process is substantially affected by IL. The reactions of benzaldehyde and 2-chlorobenzaldehyde with ethyl acetoacetate in DMF afforded exclusively 3,6-dihydropyrimidines.[29] Apparently, under the reaction conditions (in the presence of $NaHCO_3$), compounds **6** in an IL medium, which is more polar than DMF,[27] undergo partial isomerization to give **6´**.

We failed to isolate condensation products **6a—c**, which are oils, in analytically pure form. These compounds were identified by ^{1}H NMR spectroscopy and their structures were confirmed by the transformations into the corresponding 3,4-dihydropyrimidin-2(1*H*)-one derivatives (**7a—c**) by *N*-alkoxycarbonylation and *O*-demethylation (*cf.* lit. data[11]) (see Scheme 5).

Scheme 5



6, 6′, 7	Ar	R	6 : 6′
a	Ph	OMe	2 : 1
b	Ph	Me	2 : 1
c	2-ClC_6H_4	OMe	3 : 1

Reagents and conditions: *i*. $H_2N^+{=}C(OMe)NH_2 \cdot [0.5\ SO_4]^-$ (1 equiv.), $NaHCO_3$ (4 equiv.), [Bmim][BF_4] (4 equiv.), 50 °C, 24 h; *ii*. $ClCO_2Et$, Py, CH_2Cl_2, 20 °C, 30 min; *iii*. HCl (0.1 equiv.), MeOH, 20 °C, 40 min.

Alkoxycarbonylation occurs regioselectively. The 1*N* position of the ester group in products **7a—c** was confirmed by the presence of a cross-peak (Overhauser effect) of the closely-spaced protons of the 3-NH and 4-Me groups in compound **7a**. The identity of alkoxycarbonylation products of both isomers **6** and **6′** is, apparently, attributed to the identity of the anions formed by deprotonation of these NH-acids under the action of a base.

Experimental

The NMR spectra were recorded on a Bruker AM-300 instrument (300.13 MHz). Elemental analysis was carried out on a Perkin—Elmer 2400 instrument. Commercial (Acros) aldehydes **1a—i** and β-dicarbonyl compounds **2a—c** were used without additional purification. Acetate [Pip][OAc] was prepared immediately before the reactions by mixing equimolar amounts of piperidine and AcOH, and [Bmim][BF_4] was synthesized according to a procedure described earlier.[30] The solvents were dried according to standard procedures.[31]

Condensation of aldehydes 1a—i with β-dicarbonyl compounds 2a—c (general procedure). A mixture of aldehyde (3 mmol), a β-dicarbonyl compound (3 mmol), freshly prepared [Pip][OAc] (0.05 g, 0.6 mmol), and [Bmim][BF_4] (0.14 g, 0.6 mmol) was stirred at 20 °C for 5 h. Then the reaction mixture was diluted with benzene (10 mL), successively washed with water (2×5 mL), concentrated $NaHCO_3$ (2×5 mL) and NaCl (2×5 mL) solutions, 2 *N* H_2SO_4 (5 mL), and water (2×5 mL), and dried over $MgSO_4$. The solvent was removed and the residue was distilled *in vacuo* or crystallized from 75% Pr^iOH. The boiling (melting) points of products **3a—e**, **4a**, and **5a—f** are given in Table 2.

Methyl *E*- and *Z*-2-acetyl-3-phenylacrylates (3a). ^{1}H NMR (DMSO-d_6), δ: 2.32 (s, 1.2 H, CMe, *Z*-**3a**); 2.43 (s, 1.8 H, CMe, *E*-**3a**); 3.78 (s, 3 H, OMe); 7.38—7.50 (m, 5 H, Ph); 7.61 (s, 0.4 H, CH, *Z*-**3a**); 7.71 (s, 0.6 H, CH, *E*-**3a**).

3-(Benzylidene)pentane-2,4-dione (3b). ^{1}H NMR (DMSO-d_6), δ: 2.26 and 2.30 (both s, 3 H each, Me); 7.14—7.30 (m, 5 H, Ph); 7.68 (s, 1 H, CH).

Methyl *E*- and *Z*-2-acetyl-3-(4-methoxyphenyl)acrylates (3c). ^{1}H NMR ($CDCl_3$), δ: 2.32 (s, 1.2 H, CMe, *Z*-**3c**); 2.34 (s, 1.8 H, CMe, *E*-**3c**); 3.73—3.82 (m, 6 H, OMe); 6.80—6.88 and 7.25—7.38 (both m, 2 H each, H_{Ar}); 7.46 (s, 0.6 H, CH, *E*-**3c**); 7.56 (s, 0.4 H, CH, *Z*-**3c**).

3-(4-Methoxybenzylidene)pentane-2,4-dione (3d). ^{1}H NMR ($CDCl_3$), δ: 2.31 and 2.39 (both s, 3 H each, CMe); 3.83 (s, 3 H, OMe); 6.89 and 7.34 (both d, 2 H each, H_{Ar}, J = 8.0 Hz); 7.41 (s, 1 H, CH).

Methyl *E*- and *Z*-2-acetyl-3-(2-chlorophenyl)acrylates (3e). ^{1}H NMR ($CDCl_3$), δ: 2.26 (s, 1.8 H, CMe, *E*-**3e**); 2.45 (s, 1.2 H, CMe, *Z*-**3e**); 3.70 (s, 1.8 H, OMe, *E*-**3e**); 3.83 (s, 1.2 H, OMe, *Z*-**3e**); 7.28—7.56 (m, 4 H, C_6H_4); 7.81 (s, 0.4 H, CH, *Z*-**3e**); 7.86 (s, 0.6 H, CH, *E*-**3e**).

Diethyl 2,4-bis(trifluoroacetyl)-3-phenylpentanedioate (4). Found (%): C, 47.55; H, 3.40. $C_{14}H_{14}F_6O_6$. Calculated (%): C, 47.67; H, 3.29. ^{1}H NMR (DMSO-d_6), δ: 0.81 (t, 6 H, Me, J = 7.1 Hz); 2.82 (t, 1 H, CH, J = 11.9 Hz); 3.30 (d, 2 H, CH, J = 11.9 Hz); 3.74 (m, 4 H, CH_2, $J_{H,H}$ = 7.1 Hz, $J_{H,F}$ = 3.7 Hz); 4.07 (t, 1 H, CH, J = 11.9 Hz); 7.20—7.35 (m, 5 H, Ph).

Dimethyl 2-(4-chlorophenyl)-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (5a). ^{1}H NMR ($CDCl_3$), δ: 1.27 (s, 3 H, Me); 2.40 and 2.88 (both d, 1 H each, H(5), J = 13.7 Hz); 3.30 (d, 1 H, H(3), J = 9.9 Hz); 3.40 and 3.49 (both s, 3 H each, OMe); 3.85—3.96 (m, 2 H, H(1), H(2)); 4.66 (s, 1 H, OH); 7.24—7.33 (m, 4 H, C_6H_4, J = 8.3 Hz).

Dimethyl 2-(4-fluorophenyl)-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (5b). ^{1}H NMR (DMSO-d_6), δ: 1.27 (s, 3 H, CMe); 2.38 and 2.90 (both d, 1 H each, H(5), J = 13.4 Hz); 3.28 (d, 1 H, H(3), J = 8.9 Hz); 3.38 and 3.49 (both s, 3 H each, OMe); 3.83—3.97 (m, 2 H, H(1), H(2)); 4.70 (s, 1 H, OH); 6.98 and 7.32 (both dd, 2 H each, H_{Ar}, $J_{H,H}$ = $J_{H,F}$ = 8.5 Hz).

Dimethyl 4-hydroxy-4-methyl-2-[(4-methoxycarbonyl)phenyl]-6-oxocyclohexane-1,3-dicarboxylate (5c). Found (%): C, 60.34; H, 5.88. $C_{19}H_{22}O_8$. Calculated (%): C, 60.31; H, 5.86. ^{1}H NMR (DMSO-d_6), δ: 1.28 (s, 3 H, CMe); 2.38 and 2.92 (both d, 1 H each, H(5), J = 13.7 Hz); 3.36 (d, 1 H, H(3), J = 8.7 Hz); 3.37, 3.47, and 3.85 (all s, 3 H each, OMe); 3.90—4.02 (m, 2 H, H(1), H(2)); 4.77 (s, 1 H, OH); 7.43 and 7.88 (both d, 2 H each, H_{Ar}, J = 8.3 Hz).

Dimethyl 4-hydroxy-4-methyl-2-(4-nitrophenyl)-6-oxocyclohexane-1,3-dicarboxylate (5d). ^{1}H NMR ($CDCl_3$), δ: 1.37 (s, 3 H, CMe); 2.57 and 2.78 (both d, 1 H each, H(5), J = 14.2 Hz); 3.11 (d, 1 H, H(3), J = 11.9 Hz); 3.43 (s, 3 H, OMe); 3.45 (s, 1 H, OH); 3.60 (s, 3 H, OMe); 3.70 (d, 1 H, H(1), J = 10.1 Hz); 4.19 (dd, 1 H, H(2), J_1 = 11.9 Hz, J_2 = 10.1 Hz); 7.46 and 8.21 (both d, 2 H each, H_{Ar}, J = 8.7 Hz).

Dimethyl 4-hydroxy-4-methyl-2-(3-nitrophenyl)-6-oxocyclohexane-1,3-dicarboxylate (5e). ^{1}H NMR (DMSO-d_6), δ: 1.31 (s, 3 H, CMe); 2.42 and 2.97 (both d, 1 H each, H(5), J = 13.7 Hz); 3.40 (s, 3 H, OMe); 3.48 (d, 1 H, H(3), J = 8.8 Hz); 3.51 (s, 3 H, OMe); 4.00—4.17 (m, 2 H, H(1), H(2)); 4.78 (br.s, 1 H, OH); 7.54 (t, 1 H, *m*-H_{Ar}, J = 7.9 Hz); 7.73 (d, 1 H, *o*-H_{Ar}, J = 7.9 Hz); 8.08 (d, 1 H, *p*-H_{Ar}, J = 7.9 Hz); 8.33 (s, 1 H, *o*-H_{Ar}).

Dimethyl 4-hydroxy-4-methyl-6-oxo-2-thiophen-2-ylcyclohexane-1,3-dicarboxylate (5f). Found (%): C, 55.47; H, 5.45; S, 9.68. $C_{15}H_{18}O_6S$. Calculated (%): C, 55.20; H, 5.56; S, 9.83. ^{1}H NMR (DMSO-d_6), δ: 1.26 (s, 3 H, CMe); 2.35 and 2.88 (both d, 1 H each, H(5), J = 13.3 Hz); 3.25 (d, 1 H, H(3), J = 12.0 Hz); 3.47 and 3.55 (both s, 3 H each, OMe); 3.85 (d, 1 H, H(1), J = 12.3 Hz); 4.20 (t, 1 H, H(2), J = 12.3 Hz); 4.78 (s, 1 H, OH); 6.86—6.95 (m, 2 H, H_{Het}); 7.19 (d, 1 H, H_{Het}, J = 4.7 Hz).

Synthesis of 3,6- and 1,6-dihydropyrimidine derivatives (6a—c) (general procedure). A mixture of compounds **3a**, **3b**, or **3e** (3 mmol), *O*-methylisourea sulfate (0.37 g, 3 mmol), $NaHCO_3$ (1.0 g, 12 mmol), and [Bmim][BF_4] (2.72 g, 12 mmol) was vigorously stirred at 55—65 °C for 24 h, cooled to room temperature, and extracted with a 3 : 1 benzene—diethyl ether mixture (2×5 mL). The organic solution was successively washed with water (2×5 mL), concentrated aqueous $NaHCO_3$ (2×5 mL) and NaCl (2×5 mL) solutions, and water (2×5 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and compounds **6a—c** were obtained as a mixture of isomers, which were used in reactions without additional purification.

A mixture of methyl 2-methoxy-4-methyl-6-phenyl-3,6-dihydropyrimidine-5-carboxylate (6a) and methyl 2-methoxy-4-methyl-6-phenyl-1,6-dihydropyrimidine-5-carboxylate (6´a). The yield was 73%, oil. ^{1}H NMR (DMSO-d_6), δ: 2.26 (s, 2 H, CMe, **6a**); 2.30 (s, 1 H, CMe, **6´a**); 3.55 (s, 3 H, OMe, **6a** and **6´a**); 3.64 (s, 2 H, OMe, **6a**); 3.75 (s, 1 H, OMe, **6´a**); 5.30 (d, 0.33 H, CH, **6´a**, J = 4.5 Hz); 5.45 (s, 0.66 H, CH, **6a**); 7.10—7.31 (m, 5 H, Ph, **6a** and **6´a**); 8.33 (d, 0.33 H, NH, **6´a**, J = 4.5 Hz); 9.18 (s, 0.66 H, NH, **6a**).

A mixture of 1-(2-methoxy-4-methyl-6-phenyl-3,6-dihydropyrimidin-5-yl)- (6b) and 1-(2-methoxy-4-methyl-6-phenyl-1,6-dihydropyrimidin-5-yl)ethanones (6´b). The yield was 72%, oil. ^{1}H NMR (DMSO-d_6), δ: 1.95 (s, 1 H, CMe, **6´b**); 2.10 (s, 2 H, CMe, **6b**); 2.25 (s, 1 H, CMe, **6´b**); 2.30 (s, 2 H, CMe, **6b**); 3.53 (s, 3 H, OMe, **6b** и **6´b**); 5.10 (d, 0.33 H, CH, **6´b**, J = 4.5 Hz); 5.23 (s, 0.66 H, CH, **6b**); 7.10—7.26 (m, 5 H, Ph, **6b** и **6´b**); 8.29 (d, 0.33 H, NH, **6´b**, J = 4.5 Hz); 9.10 (s, 0.66 H, NH, **6b**).

A mixture of methyl 6-(2-chlorophenyl)-2-methoxy-4-methyl-3,6-dihydropyrimidine-5-carboxylate (6c) and methyl 6-(2-chlorophenyl)-2-methoxy-4-methyl-1,6-dihydropyrimidine-5-carboxylate (6´c). The yield was 78%, oil. ^{1}H NMR (DMSO-d_6), δ: 2.30 (s, 2.25 H, CMe, **6c**); 2.33 (s, 0.75 H, CMe, **6´c**); 3.46 (s, 3 H, OMe, **6c** and **6´c**); 3,58 (s, 2.25 H, OMe, **6c**); 3.77 (s, 0.75 H, OMe, **6´c**); 5.78 (d, 0.25 H, CH, **6´c**, J = 4.5 Hz); 5.82 (s, 0.75 H, CH, **6c**); 7.12—7.36 (m, 4 H, C_6H_4 **6c** and **6´c**); 8.27 (d, 0.25 H, NH, **6´c**, J = 4.5 Hz); 9.22 (s, 0.75 H, NH, **6c**).

Synthesis of 3,4-dihydropyrimidin-2(1*H*)-one derivatives 7a—c (general procedure). Ethyl chloroformate (0.32 g, 3 mmol) and pyridine (0.23 g, 3 mmol) were successively added to a solution of a mixture of isomers **6a—c** (3 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was kept at 20 °C for 30 min. The solvent was removed *in vacuo*, the residue was dissolved in methanol (5 mL), and 3—5 drops of 2 *M* HCl were added to the resulting solution until the mixture became turbid. Then the reaction mixture was kept at 20 °C for 40 min. The solvent was removed and the residue was crystallized from diethyl ether and dried in air.

Methyl 3-ethoxycarbonyl-6-methyl-2-oxo-4-phenyl-3,4-dihydropyrimidine-(1*H*)-5-carboxylate (7a). Found (%): C, 64.71; H, 6.49; N, 8.62. $C_{17}H_{20}N_2O_4$. Calculated (%): C, 64.54; H, 6.37; N, 8.86. ^{1}H NMR (DMSO-d_6), δ: 1.31 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.0 Hz); 2.30 (s, 3 H, CMe); 3.68 (s, 3 H, OMe); 4.25 (q, 2 H, CH_2, J = 7.0 Hz); 6.16 (s, 1 H, CH); 7.18—7.35 (m, 5 H, Ph); 10.05 (s, 1 H, NH).

5-Acetyl-3-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-(1*H*)-2-one (7b). Found (%): C, 68.21; H, 6.80; N, 9.17. $C_{17}H_{20}N_2O_3$. Calculated (%): C, 67.98; H, 6.71; N, 9.33. ^{1}H NMR (DMSO-d_6), δ: 1.32 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.1 Hz); 2.27 (s, 3 H, CMe); 2.33 (s, 3 H, C(O)Me); 4.26 (q, 2 H, CH_2, J = 7.0 Hz); 6.25 (s, 1 H, CH); 7.20—7.61 (m, 6 H, NH, Ph).

Methyl 4-(4-chlorophenyl)-3-ethoxycarbonyl-6-methyl-2-oxo-3,4-dihydropyrimidine-(1*H*)-5-carboxylate (7c). Found (%): C, 58.45; H, 5.30; Cl, 9.97; N, 8.11. $C_{17}H_{20}ClN_2O_4$. Calculated (%): C, 58.21; H, 5.46; Cl, 10.11; N, 7.99. ^{1}H NMR (DMSO-d_6), δ: 1.28 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.1 Hz); 2.31 (s, 3 H, CMe); 3.60 (s, 3 H, OMe); 4.20 (q, 2 H, CH_2, J = 7.1 Hz); 6.40 (s, 1 H, CH); 7.21—7.35 (m, 4 H, C_6H_4Cl); 10.20 (s, 1 H, NH).

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