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New Catalysts of Biginelli Reaction

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Abstract—A synthesis was developed of new imidazole derivatives catalyzing three-component condensation of ethyl acetoacetate, aromatic aldehydes, and urea(or thiourea) by Biginelli reaction.

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3,4-Dihydropyrimidin-2(1*H*)-ones(thiones), among them also those with biological action [1] are conveniently prepared by a one-pot synthesis catalyzed with mineral, organic, or Lewis acids involving ureas (thioureas), aldehydes, and β-dicarbonyl compounds under standard conditions or under microwave irradiation [2, 3]. Two examples of synthesis of the said compounds were described performed by Biginelli reaction involving ionic fluids [4, 5]. No published data exist on application of monochloroacetic acid and N-substituted imidazoles to the synthesis of imidazolium salts, catalysts for organic reactions [6–8].

The synthesis of new imidazole derivatives involved mixing in MeCN solution equimolar quantities of *N*-methylimidazole (**Ia**) and monochloroacetic acid (**II**) (Scheme 1). The reaction product obtained at room temperature is an oily fluid whose composition and structure are confirmed by elemental analysis, IR and ^{1}H NMR spectra. The specific feature of the ^{1}H NMR spectrum of the product is a double set of signals (1:1) due to the presence of salts **IIIa** and **IVa** mixture. For instance. in the downfield region appear three-proton singlets of the methyl groups (3.84, 3.88 ppm), singlet of the methylene group (5.07 ppm), two-proton multiplet of protons H^4, H^5 of imidazole (7.50–7.80 ppm), and one-proton singlet belonging to H^3 of imidazole at 9.06, 9.26 ppm.

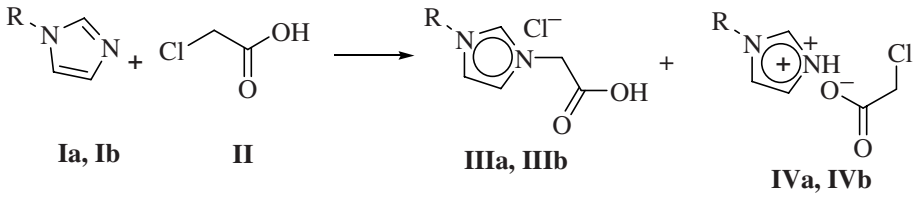
Analogously an oily mixture of compounds **IIIb** and **IVb** was synthesized using acid **II** and nitrile **Ib**.

In the IR spectrum of the mixture of compounds **IIIb** and **IVb** appear bands characteristic of carboxylates (1610–1550 and 1400 cm^{-1}), ammonium (2700–2250 cm^{-1}), cyano (2245 cm^{-1}), and chloromethyl (775 cm^{-1}), groups. In the ^{1}H NMR spectrum a multiplet set of signals from three methylene groups is observed in the region 3.13–4.71 ppm, and the signals from imidazole structural fragment are present in the region 7.44–9.42 ppm.

It was established that 0.6 mol% of the mixture of compounds **IIIb** and **IIIb** catalyzed the condensation of ethyl acetoacetate, aromatic aldehydes, and urea (or thiourea) (Scheme 2).

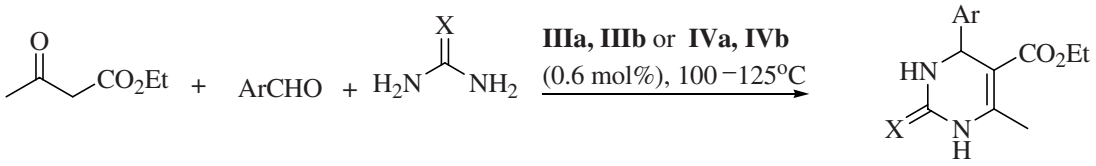
Syntheses of target products **Va, Vb–IXa, IXb** was performed at elevated temperature without solvent like described in [4, 5]. The replacement of catalyst **IIIa, IIIb** by **IVa, IVb** increased the yield of reaction products by 10%, in particular, compared to method [5]. It should be noted that in most cases the yield of 3,4-dihydropyrimidine-2(1*H*)-thiones is higher than that of their oxygen-containing analogs.

Scheme 1.



Ia, Ib **II** **IIIa, IIIb** **IVa, IVb**

Scheme 2.



Va, Vb–Xa, Xb

The catalytic action of the melts of the synthesized imidazole salts is apparently due to the activity of the free carboxy group of acetic acid [9] together with probable generation of trace amounts of HCl that also initiate the reaction [4].

Thus we demonstrated that the melts of the N-substituted imidazoles monochloroacetates catalyzed the Biginelly reaction.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Specord 75IR from mulls in mineral oil. Melting points were measured on a Boëtius heating block and were not corrected. ^{1}H NMR spectra were registered from solutions in DMSO-d_6 on spectrometers Bruker AC-E 200 and Bruker AC-80, chemical shifts are reported with respect to TMS (internal reference). TLC was carried out on Silufol plates (Czechia), spots were visualized by 5% solution of phosphomolybdic acid in EtOH followed by heating, or with acidified 2% water solution of $KMnO_4$.

Synthesis of IIIa and IIIb mixture. To a vigorously stirred solution of 4.53 g (0.048 mol) of monochloroacetic acid in 2 ml of anhydrous MeCN at 20°C was added dropwise a solution of 4 g (0.048 mol) of *N*-methylimidazole in 2 ml of anhydrous MeCN. The reaction mixture was stirred for 6 h at 20°C, left overnight. After distilling off the solvent we obtained 8.4 g (99%) of oily mixture. IR spectrum, ν, cm^{-1}: 3390, 3150, 1730, 1630, 1575, 1550, 1400, 1275, 1165, 1080, 825, 775, 700, 625. ^{1}H NMR spectrum, δ, ppm: 3.84 s, 3.88 s (6H, 2CH_3), 5.07 s (4H, 2CH_2), 7.50–7.80 m (4H, 2H^4, 2H^5), 9.06 s, 9.26 s (2H, 2H^3).

Mixture IVa and IVb was similarly obtained from 3.12 g (0.033 mol) of monochloroacetic acid and 4 g (0.033 mol) of cyanide **Ib**. Yield 7 g (99%). Oily light-yellow substance. IR spectrum, ν, cm^{-1}: 3400, 3150, 2700–2250, 2245, 1730, 1630, 1560, 1400, 1275, 1165, 1075, 980, 825, 750, 700, 630. ^{1}H NMR spectrum, δ, ppm: 3.21 t (2H, CH_2CN, *J* 6.4 Hz), 3.28 t (2H, CH_2CN, *J* 5.98 Hz), 4.24-4.71 m (4H, N–CH_2CH_2), 5.14 s (4H, 2CH_2CO_2), 7.44–8.01 m (4H, 2H^4, 2H^5), 8.82 s, 9.43 s (2H, 2H^3).

3,4-Dihydropyrimidin-2(1*H*)-ones(thiones). **General procedure.** To a mixture of 1.3 g (0.01 mol) of ethyl acetoacetate, 0.76 g (0.01 mol) of thiourea and (0.01 mol) of an appropriate aldehyde was added 0.6 mol% of a mixture of compounds **IIIa** and **IIIb** (method *a*) or **IVa** and **IVb** (method *b*). The reaction mixture was heated for 2–5 h at 100–125°C. On completion of the reaction (TLC monitoring) the mixture was dispersed in ethanol, the residue was filtered off and washed with H_2O. A sample was recrystallized for analysis from EtOH.

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Va). Yield 56 (*a*), 61% (*b*), mp 213–214°C. IR spectrum, ν, cm^{-1}: 3250, 2940, 2900, 1720, 1690, 1630, 1210, 750. ^{1}H NMR spectrum, δ, ppm: 1.14 t (3H, MeCH_2, *J* 7.0 Hz), 2.26 s (3H, Me), 3.91 q (2H, MeCH_2, *J* 7.0 Hz), 5.12 d (1H, H^4, *J* 4.5 Hz), 7.30 s (5H, Ph), 7.67 d (1H, NH, *J* 4.5 Hz), 9.09 s (1H, NH). Found, %: C 64.60; H 6.20; N 10.76. $C_{14}H_{16}N_2O_3$. Calculated, %: C 64.55; H 6.10; N 10.52.

Ethyl 6-methyl-2-thioxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Vb). Yield 55 (*a*), 67% (*b*), mp 212–213°C. IR spectrum, ν, cm^{-1}: 2940, 1980, 1940, 1810, 1650, 1240, 1050, 790. ^{1}H NMR spectrum, δ, ppm: 1.18 t (3H, MeCH_2, *J* 7.0 Hz), 2.30 s (3H, Me), 4.00 q (2H, MeCH_2, *J* 7.0 Hz), 5.19 d (1H, H^4, *J* 3.6 Hz), 7.25–7.56 m (5H, Ph), 7.67 d (1H, NH, *J* 3.6 Hz), 10.15 C (1H, NH). Found, %: C 60.88; H 5.78; N 10.35. $C_{14}H_{16}N_2O_2S$. Calculated, %: C 60.85; H 5.84; N 10.40.

Ethyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (VIa). Yield 41 (*a*), 50% (*b*), mp 195–198°C. IR spectrum, ν, cm^{-1}: 3260, 2960, 2920, 1710–1550, 1550, 780. ^{1}H NMR

spectrum, δ, ppm: 1.11 t (3H, MeCH$_2$, *J* 7.2 Hz), 2.24 s (3H, Me), 3.36 s, 3.71 s (6H, 2 MeO), 3.99 q (2H, MeCH$_2$, *J* 7.1 Hz), 5.10 d (1H, H^4, CH, *J* 3.7 Hz), 6.64–6.95 m (3H$_{arom}$), 7.66 d (1H, NH, *J* 3.6 Hz), 9.14 c (1H, NH). Found, %: C 60.06; H 6.22; N 8.59. $C_{16}H_{20}N_2O_5$. Calculated, %: C 59.99; H 6.29; N 8.74.

Ethyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (VIb). Yield 63 (*a*), 69% (*b*), mp 177–178°C. IR spectrum, ν, cm^{-1}: 3320, 2960–2900, 1680, 1580, 1190, 750. ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, MeCH$_2$, *J* 7.1 Hz), 2.28 s (3H, Me), 3.36 s, 3.71 s (6H, 2MeO), 4.02 q (2H, MeCH$_2$, *J* 7.03 Hz), 5.12 d (1H, H^4, CH, *J* 3.67 Hz), 6.72–6.97 m (3H$_{arom}$), 9.58 d (1H, NH, *J* 3.5 Hz), 10.29 s (1H, NH). Found, %: C 57.22; H 5.78; N 8.39. $C_{16}H_{20}N_2O_4S$. Calculated, %: C 57.12; H 5.99; N 8.33.

Ethyl 4-(2,4-dimethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (VIIa). Yield 80 (*a*), 77% (*b*), mp 221–222°C. IR spectrum, ν, cm^{-1}: 3240, 2920, 1710, 1680, 1500, 1210, 1090, 740. ^{1}H NMR spectrum, δ, ppm: 1.04 t (3H, MeCH$_2$, *J* 7.1 Hz), 2.27 s (3H, Me), 3.72 s, 3.77 s (6H, 2 MeO), 3.91 q (2H, MeCH$_2$, *J* 7.1 Hz), 5.4 d (1H, H^4, CH, *J* 2.98 Hz), 6.36–6.99 m (3H$_{arom}$), 7.20 d (1H, NH, *J* 3.3 Hz), 9.07 s (1H, NH). Found, %: C 59.77; H 6.12; N 8.71. $C_{16}H_{20}N_2O_5$. Calculated, %: C 59.99; H 6.29; N 8.74.

Ethyl 4-(2,4-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (VIIb). Yield 67 (*a*), 68% (*b*), mp 155–157°C. IR spectrum, ν, cm^{-1}: 3320, 2980, 1700, 1560, 1180, 1125, 750. ^{1}H NMR spectrum, δ, ppm: 1.05 t (3H, MeCH$_2$, *J* 7.08 Hz), 2.27 s (3H, Me), 3.73 s, 3.77 s (6H, 2OMe), 3.94 q (2H, MeCH$_2$, *J* 7.01 Hz), 5.39 d (1H, H^4, CH, *J* 3.5 Hz), 6.38–6.98 m (3H$_{arom}$), 9.16 d (1H, NH, *J* 3.4 Hz), 10.54 s (1H, NH). Found, %: C 57.31; H 5.82; N 8.24. $C_{16}H_{20}N_2O_4S$. Calculated, %: C 57.12; H 5.99; N 8.33.

Ethyl 4-(2,4-dichlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (VIIIa). Yield 50 (*a*), 44% (*b*), mp 247–249°C. IR spectrum, ν, cm^{-1}: 3350, 1690, 1160, 1090, 645. ^{1}H NMR spectrum, δ, ppm: 1.00 t (3H, MeCH$_2$, *J* 7.14 Hz), 2.30 s (3H, Me), 3.90 q (2H, MeCH$_2$, *J* 7.04 Hz), 5.60 d (1H, H^4, CH, *J* 2.15 Hz), 7.25–7.75 m (3H$_{arom}$), 7.75 d (1H, NH, *J* 2.8 Hz), 9.31 s (1H, NH). Found, %: C 51.32; H 4.11; N 8.64. $C_{14}H_{14}Cl_2N_2O_3$. Calculated, %: C 51.08; H 4.29; N 8.51.

Ethyl 4-(2,4-dichlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (VIIIb). Yield 68 (*a*), 82% (*b*), mp 92–93°C. IR spectrum, ν, cm^{-1}: 3200, 1710, 1575, 1090, 1030, 740, 620. ^{1}H NMR spectrum, δ, ppm: 1.02 t (3H, MeCH$_2$, *J* 7.02 Hz), 2.32 s (3H, Me), 3.93 q (2H, MeCH$_2$), *J* 6.99 Hz), 5.62 d (1H, H^4, CH, *J* 2.9 Hz), 7.24–7.59 m (3H$_{arom}$), 9.62 d (1H, NH, *J* 3.1 Hz), 10.40 s (1H, NH). Found, %: C 48.52; H 4.07; N 8.22. $C_{14}H_{14}Cl_2N_2O_2S$. Calculated, %: C 48.70; H 4.09; N 8.11.

Ethyl 6-methyl-4-(4-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IXa). Yield 72 (*a*), 69% (*b*), mp 209–211°C. IR spectrum, ν, cm^{-1}: 3250, 2900, 1690, 1640, 1605, 1500, 1270, 1160, 1070, 775. ^{1}H NMR spectrum, δ, ppm: 1.09 t (3H, MeCH$_2$, *J* 7.04 Hz), 2.23 s (3H, Me), 3.71 s (3H, MeO), 4.00 q (2H, MeCH$_2$, *J* 6.54 Hz), 5.09 d (1H, H^4, CH, *J* 3.39 Hz), 6.85 d, 6.94 d (4H$_{arom}$, *J* 6.45, *J* 19.74 Hz), 7.65 d (1H, NH, *J* 3.7 Hz), 9.13 s (1H, NH). Found, %: C 62.22; H 6.22; N 9.56. $C_{15}H_{18}N_2O_4$. Calculated, %: C 62.06; H 6.25; N 9.65.

Ethyl 6-methyl-4-(4-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IXb). Yield 69 (*a*), 68% (*b*), mp 156–157°C. IR spectrum, ν, cm^{-1}: 3310, 2900, 1660, 1615, 1500, 1165, 760. ^{1}H NMR spectrum, δ, ppm: 1.1 t (3H, MeCH$_2$, *J* 6.96 Hz), 2.28 s (3H, Me), 3.72 s (3H, MeO), 4.00 q (2H, MeCH$_2$, *J* 7.12 Hz), 5.10 d (1H, H^4, CH, *J* 3.4 Hz), 7.30–6.80 d, 6.97 d (4H$_{arom}$, *J* 6.3, *J* 12.4 Hz), 9.59 d (1H, NH, *J* 3.81 Hz), 10.28 s (1H, NH). Found, %: C 58.67; H 5.85; N 9.10. $C_{15}H_{18}N_2O_3S$. Calculated, %: C 58.80; H 5.92; N 9.14.

Ethyl 4-(4-dimethylaminophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Xa). Yield 68 (*a*), 63% (*b*), mp 257–258°C. IR spectrum, ν, cm^{-1}: 3250, 1725, 1700, 1360, 1220, 1160, 1085, 780. ^{1}H NMR spectrum, δ, ppm: 1.11 t (3H, MeCH$_2$, *J* 7.02 Hz), 2.23 s (3H, Me), 2.84 c (6H, NMe$_2$), 3.97 q (2H, MeCH$_2$, *J* 7.05 Hz), 5.03 d (1H, H^4, CH, *J* 3.26 Hz), 6.63 d, 6.78 d (4H$_{arom}$, *J* 8.76, *J* 32 Hz), 7.58 d (1H, NH, *J* 3.66 Hz), 9.08 s (1H, NH). Found, %: C 63.04; H 7.03; N 13.81. $C_{16}H_{21}N_3O_3$. Calculated, %: C 63.35; H 6.98; N 13.85.

Ethyl 4-(4-dimethylaminophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Xb). Yield 53 (*a*), 64% (*b*), mp 211–213°C. IR spectrum, ν, cm^{-1}: 3300, 1370, 1170, 1660, 1100, 750. ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, MeCH$_2$, *J* 6.94 Hz), 2.27 s (3H, Me), 2.86 s (6H, NMe$_2$), 3.97 q (2H, MeCH$_2$, *J* 7.24 Hz), 5.03 d (1H, H^4, CH, *J* 3.65 Hz), 6.65 d,

6.78 d (4H_{arom}, *J* 8.08, *J* 29.3 Hz), 9.53 d (1H, NH, *J* 3.89 Hz), 10.51 s (1H, NH). Found, %: C 60.44; H 6.57; N 13.11. $C_{16}H_{21}N_3O_2S$. Calculated, %: C 60.16; H 6.63; N 13.16.

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