Sonochemical synthesis of Biginelli compounds

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The ultrasound effect accelerates the Biginelli reaction 40 and more times. A sonochemical method for the synthesis of ethyl 4-R-6-methyl-2-oxo- and 4-R-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates was developed. The target products were obtained within 2 to 5 min in 90—95% yields.

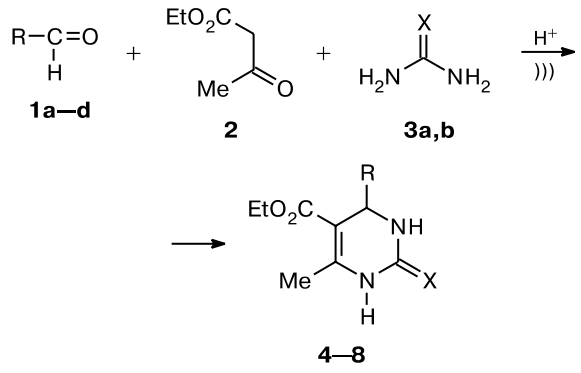
Key words: Biginelli reactions, ethyl 4-R-6-methyl-2-oxo- and 4-R-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates, ultrasound effect.

Multicomponent reactions leading to a variety of molecular structures are of special interest for combinatorial chemistry. For instance, the Biginelli reaction (condensation between aldehyde **1**, ethyl acetoacetate (**2**), and urea or thiourea (**3**)) affords a broad range of substituted 2-oxo- and 2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **4**—**8**, which are known as calcium channel blockers of the nifedipine type.[1,2] Biginelli compounds are conventionally synthesized either by prolonged (2—3 days) stirring of the reactants in EtOH in the presence of HCl[3] or by refluxing them for 3—4 h.[4] Microwave radiation with an active carrier reduces the Biginelli reaction time to several minutes;[5] however, the target products are more difficult to isolate and, moreover, urea has been reported[6] to decompose by microwave rays.

The ultrasound effect on the Biginelli reaction has been described in only one paper and found to reduce the reaction time from 8—12 to 3—7 h, with ammonium cerium nitrate as a neutral catalyst.[7]

We discovered that the classical Biginelli reaction (ethanol, HCl as a catalyst) is accelerated by ultrasound 40 and more times. After the reaction mixture was exposed to ultrasound for 2 to 5 min and the solvent was removed, the target compounds **4**—**8** were obtained in 90—95% yields, irrespective of the aldehyde nature. In most cases, no additional purification (recrystallization) is needed because of high selectivity of the reaction which reduces the quantity of by-products (Scheme 1).

Scheme 1



	R		X	R		X	R
1a	Ph	**3a**	O	—	**6**	O	Me
1b	Me	**3b**	S	—	**7**	O	CH=CH—Ph
1c	CH=CH—Ph	**4**	O	Ph	**8**	O	2-thienyl
1d	2-thienyl	**5**	S	Ph			

Experimental

Melting points were determined on a combined Boetius microscope stage and are given uncorrected. ^{1}H NMR spectra were recorded on a Bruker DRX-400 instrument in $CDCl_3$ or DMSO-d_6 with Me_4Si as the internal standard. Elemental analysis was carried out on a Carlo Erba 1108 instrument; TLC was performed on Silufol UV-254 plates (ethanol—chloroform, 1 : 9). The domestic UZDN-A ultrasound disperser was used (20 kHz, 80 W).

Synthesis of compounds 4—8 (general procedure). The emitter of the ultrasound disperser was immersed in a suspension of ethyl acetoacetate **2** (10 mmol), urea (thiourea) **3** (10 mmol), and a corresponding aldehyde **1** (10 mmol) in 20 mL of EtOH acidified with conc. HCl (1—2 drops). The emitter was on until the reaction was completed (2—5 min). The solvent was removed, and the residue was washed with water or acetonitrile. While isolating compound **5**, the solvent was removed, and the residue was triturated with water, filtered off, and recrystallized from dioxane.

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4). Yield 95%, m.p. 202—204 °C (*cf.* Ref. 8: 202—204 °C). Found (%): C, 64.80; H, 6.15; N, 10.79. $C_{14}H_{16}N_2O_3$. Calculated (%): C, 64.60; H, 6.20; N, 10.76. ^{1}H NMR (DMSO-d_6), δ: 1.14 (t, 3 H, $\underline{Me}CH_2$, J = 7.0 Hz); 2.26 (s, 3 H, Me); 3.91 (q, 2 H, $MeC\underline{H}_2$, J = 7.0 Hz); 5.12 (d,

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1 H, C(4)H, J = 4.5 Hz); 7.30 (s, 5 H, Ph); 7.67 (d, 1 H, NH, J = 4.5 Hz); 9.09 (br.s, 1 H, NH).

Ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5). Yield 90%, m.p. 203—205 °C (*cf.* Ref. 5: 205—206 °C). Found (%): C, 60.76; H, 5.86; N, 9.93. $C_{14}H_{16}N_2O_2S$. Calculated (%): C, 60.85; H, 5.84; N, 10.14. ^{1}H NMR (DMSO-d_6), δ: 1.18 (t, 3 H, MeCH_2, J = 4.0 Hz); 2.30 (s, 3 H, Me); 4.00 (m, 2 H, MeCH_2); 5.18 (d, 1 H, C(4)H, J = 3.6 Hz); 7.25 (m, 5 H, Ph); 9.50 (d, 1 H, NH, J = 3.6 Hz); 10.15 (s, 1 H, NH).

Ethyl 4,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6). Yield 91.5%, m.p. 181—182 °C (*cf.* Refs. 8, 9: 181—184 °C). Found (%): C, 54.33; H, 7.73; N, 14.59. $C_9H_{14}N_2O_3$. Calculated (%): C, 54.54; H, 7.12; N, 14.14. ^{1}H NMR ($CDCl_3$), δ: 1.26 (d, 3 H, MeCH, J = 10.2 Hz); 1.28 (t, 3 H, MeCH_2, J = 6.2 Hz); 2.29 (s, 3 H, Me); 4.02 (m, 2 H, MeCH_2); 4.07 (m, 1 H, C(4)H); 5.59 (br.s, 1 H, NH); 7.89 (s, 1 H, NH).

Ethyl 6-methyl-2-oxo-4-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7). Yield 94.5%, m.p. 238—240 °C (*cf.* Ref. 7: 241—243 °C). Found (%): C, 67.14; H, 6.48; N, 9.47. $C_{16}H_{18}N_2O_3$. Calculated (%): C, 67.13; H, 6.34; N, 9.78. ^{1}H NMR ($CDCl_3$), δ: 1.30 (t, 3 H, MeCH_2, J = 7.2 Hz); 2.48 (s, 3 H, Me); 4.20 (m, 2 H, MeCH_2); 6.40 (d, 1 H, C(4)H, J = 15.0 Hz); 6.01 (dd, 1 H, CH=CHPh, J = 7.0 Hz, J = 15.0 Hz); 6.47 (d, 1 H, CH=CHPh, J = 7.0 Hz); 7.25 (m, 5 H, Ph); 7.36, 8.91 (both s, 1 H each, NH).

Ethyl 6-methyl-2-oxo-4-(2-thienyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (8). Yield 92.5%, m.p. 205—207 °C (*cf.* Ref. 7: 206—208 °C). Found (%): C, 54.25; H, 5.94; N, 10.70. $C_{12}H_{14}N_2O_3S$. Calculated (%): C, 54.13; H, 5.30; N, 10.52. ^{1}H NMR (DMSO-d_6), δ: 1.21 (t, 3 H, MeCH_2, J = 7.2 Hz); 2.22 (s, 3 H, Me); 4.04 (q, 2 H, MeCH_2, J = 7.2 Hz); 5.40 (d, 1 H, C(4)H, J = 3.6 Hz); 7.17 (m, 3 H, thiophene); 7.76 (d, 1 H, NH, J = 3.6 Hz); 9.18 (s, 1 H, NH).

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