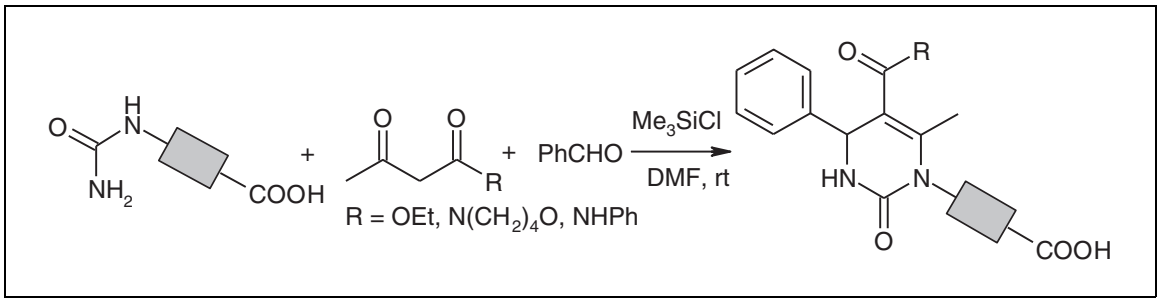
Protecting Group Free Synthesis of Carboxyl-substituted Dihydropyrimidines Through Biginelli Reaction

Eugeniy N. Ostapchuk,[a,b] Andrey S. Plaskon,[a,b] Oleksandr O. Grygorenko,[a,b] Andrey A. Tolmachev,[a,b] and Sergey V. Ryabukhin[a,c]*

[a]Enamine Ltd., Oleksandra Matrosova Street, 23, Kyiv 01103, Ukraine
[b]Kyiv National Taras Shevchenko University, Volodymyrska Street, 64, Kyiv 01033, Ukraine
[c]The Institute of High Technologies, Kyiv National Taras Shevchenko University, 4 Glushkov Street Kyiv 03187, Ukraine
*E-mail: s.v.ryabukhin@gmail.com
Received June 14, 2011
DOI 10.1002/jhet.1568
Published online 00 Month 2013 in Wiley Online Library (wileyonlinelibrary.com).



Chlorotrimethylsilane-promoted Biginelli-type reaction of benzaldehyde, acetoacetic acid derivatives, and various carboxyl-containing ureas was explored. It was found that the steric load of the urea substituents influenced strongly the reaction outcome; in particular, the method was efficient only in the case of unbranched mono-substituted ureas bearing either aliphatic or aromatic groups. The method allows performing a one-pot, protecting group free synthesis of dihydropyrimidines possessing carboxylic functionality.

J. Hetercycl Chem., **00**, 00 (2013).

INTRODUCTION

Multicomponent reactions represent a timely field of organic chemistry for more than a century because they allow huge diversity of rather complicated molecules to be created using one synthetic procedure in an efficient and timesaving manner [1–10]. The Biginelli reaction, one of the most useful multicomponent reactions, offers an efficient way to access multifunctionalized dihydropyrimidine derivatives **1** (Fig. 1) and related heterocyclic compounds through a condensation of an aldehyde, a β-dicarbonyl compound, and urea derivatives [11,12]. Dihydropyrimidine structural unit **1** is an important scaffold in the medical research. It is found in calcium channel modulators, mitotic kinesine inhibitors, adrenergic receptor antagonists, and antibacterial and antiviral agents [13].

Biginelli reaction involving substituted ureas with additional functional groups at their substituents gives rise to functionalized dihydropyrimidines. The latter are useful building blocks for parallel synthesis of combinatorial libraries for high-throughput screening. Notably, the Biginelli reaction is not affected by many functional groups at the urea substituent. This offers a nice opportunity to carry out one-pot, protecting group free [14] syntheses of a number of functionalized dihydropyrimidines.

In this contribution, we describe our results on chlorotrimethylsilane-promoted Biginelli reaction involving substituted ureas bearing the carboxyl functionality at their substituents (**2**). It was shown in a few reports [15–21] that the use of chlorotrimethylsilane as a mild condensation promoter tolerating a wide range of functional groups improved considerably the reaction yields. Therefore, the chlorotrimethylsilane was used in this study. A set of substituted ureas **2a–k** was employed in present syntheses to establish the scope and limitations of the method (Fig. 1).

To the best of our knowledge, only a limited number of examples involving ureas of the type **2** in Biginelli reaction was reported in the literature. In particular, reactions of urea **2e** with ethyl/benzyl acetoacetate and a set of aldehydes promoted by HCl were reported [22–24]. Several examples of analogous transformations of urea **2c** via multistep solid-phase procedures were also reported [25].

The reactions of benzaldehyde with ureas **2a–k** and acetoacetic acid derivatives **3a–c** were performed by keeping the reagents in the presence of Me_3SiCl (5 eq)—DMF system at ambient temperature for 3–4 days (Scheme 1). The results of the experiments are summarized in Table 1.

Steric hindrance in the starting urea **2** appeared to be a predominant factor that determined the reaction outcome. In particular, reactions of benzaldehyde, acetoacetic acid

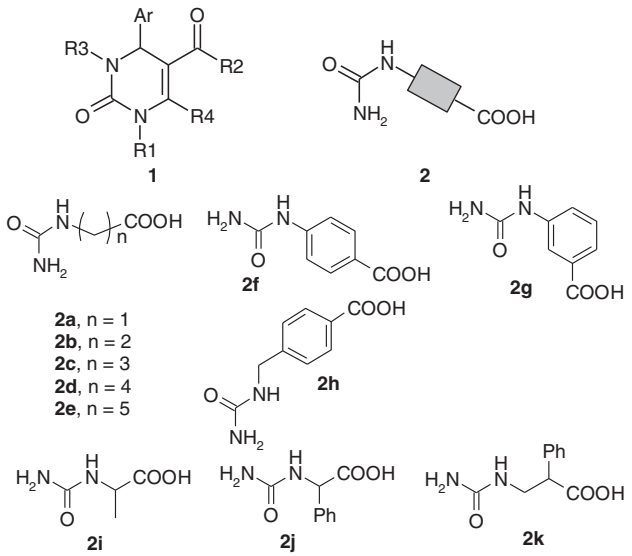
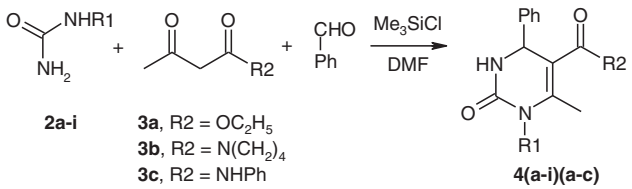


Figure 1. Set of substituted ureas 2a-k.

Scheme 1



derivatives **3a–c**, and ureas **2a–h** resulted in target dihydropyrimidines **4**(**a–h**)(**a–c**) with 60–83% yields. In the case of less reactive ureas **2i–k**, we could not isolate the corresponding dihydropyrimidines **4ia–4ka** from the crude product [18], although their formation (<10%) was detected by NMR and HPLC–MS. It should be noted that lowering the reactivity of β-dicarbonyl component **3** (from **3a** to **3c**) did not affect considerably the outcome of the reaction.

The successful results obtained in the case of ureas **2a–h** bearing small substituents can be explained by a twofold role of the chlorotrimethylsilane. As illustrated in Scheme 2, in our opinion, the chlorotrimethylsilane acts as not only the condensation promoter but also as a dynamic protecting group for the carboxyl moiety [18].

The one-pot, protecting group free chlorotrimethylsilane-promoted Biginelli-type reaction with carboxyl-substituted ureas is an efficient and practical method for the synthesis of dihydropyrimidines from mono-substituted ureas with aliphatic or aromatic groups. Prepared dihydropyrimidines contain the carboxylic functionality valuable for further modification of the molecule.

EXPERIMENTAL

The solvents were purified according to the standard procedures. All the starting materials were purchased from Acros (Geel, Belgium), Merck (Darmstadt, Germany), and Fluka (Dorset, United Kindom). Analytical TLC was performed using Polychrom SI F254 plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 499.9 MHz for protons and 124.9 MHz for carbon-13). Chemical shifts are reported in ppm

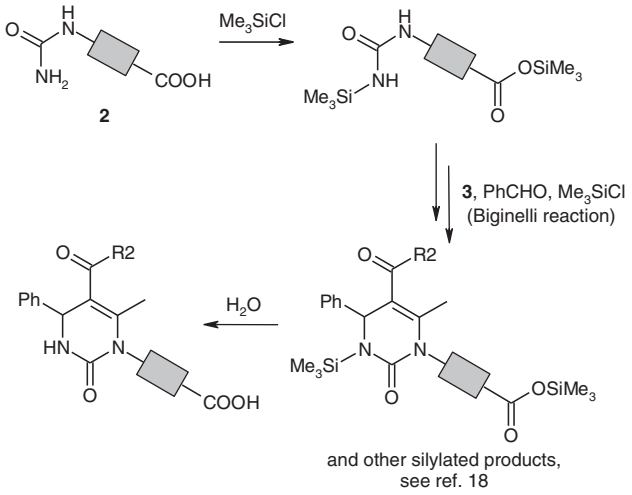
Table 1

Biginelli reactions of benzaldehyde, ureas **2a–k**, and acetoacetic acid derivatives **3a–c**.

Entry No.	Urea	R1	Methylene component	R2	Product	Yield, %
1	**2a**	CH_2CO_2H	**3a**	OC_2H_5	**4aa**	83
2	**2a**	CH_2CO_2H	**3b**	$N(CH_2)_4O$	**4ab**	68
3	**2b**	$(CH_2)_2CO_2H$	**3a**	OC_2H_5	**4ba**	72
4	**2c**	$(CH_2)_3CO_2H$	**3a**	OC_2H_5	**4ca**	75
5	**2c**	$(CH_2)_3CO_2H$	**3b**	$N(CH_2)_4O$	**4cb**	63
6	**2d**	$(CH_2)_4CO_2H$	**3a**	OC_2H_5	**4da**	78
7	**2e**	$(CH_2)_5CO_2H$	**3a**	OC_2H_5	**4ea**	70
8	**2e**	$(CH_2)_5CO_2H$	**3b**	$N(CH_2)_4O$	**4eb**	62
9	**2e**	$(CH_2)_5CO_2H$	**3c**	NHPh	**4ec**	71
10	**2f**	*p*-$C_6H_4CO_2H$	**3a**	OC_2H_5	**4fa**	76
11	**2f**	*p*-$C_6H_4CO_2H$	**3b**	$N(CH_2)_4O$	**4fb**	71
12	**2g**	*m*-$C_6H_4CO_2H$	**3a**	OC_2H_5	**4ga**	70
13	**2g**	*m*-$C_6H_4CO_2H$	**3b**	$N(CH_2)_4O$	**4gb**	65
14	**2h**	CH_2(*p*-$C_6H_4CO_2H$)	**3a**	OC_2H_5	**4ha**	69
15	**2h**	CH_2(*p*-$C_6H_4CO_2H$)	**3b**	$N(CH_2)_4O$	**4hb**	63
16	**2i**	$CH(CH_3)CO_2H$	**3a**	OC_2H_5	**4ia**	9[a]
17	**2i**	$CH(CH_3)CO_2H$	**3b**	$N(CH_2)_4O$	**4ib**	5[a]
18	**2i**	$CH(CH_3)CO_2H$	**3c**	NHPh	**4ic**	5[a]
19	**2j**	$CH(C_6H_5)CO_2H$	**3a**	OC_2H_5	**4ja**	9[a]
20	**2k**	$CH_2CH(C_6H_5)CO_2H$	**3a**	OC_2H_5	**4ka**	5[a]

[a]Yields detected by HPLC MS analysis.

Scheme 2



downfield from TMS (^{1}H, ^{13}C) as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Kiev National Taras Shevchenko University. Mass spectra were recorded with Agilent 1100 LCMSD SL instrument (chemical ionization). Flash chromatography was performed on Teledyne ISCO CombiFlash Companion personal flash chromatography system.

General procedure for the reaction of ketones 1a–c and aminoazoles **2a–c**. A mixture of compound **3** (2 mmol), benzaldehyde (2 mmol), urea **2** (2.0–2.2 mmol) in dry DMF (2–3 mL) was sonicated for 1 h at RT to dissolve the starting materials, and then, chlorotrimethylsilane (1.086 g, 10 mmol) was added. The resulting mixture was allowed to stand for 3–4 days and then poured into water (15 mL). The suspension formed was sonicated for 1 h, and the precipitate was filtered and washed with a small amount of diethyl ether (2 mL). If the solid product was not formed, the mixture was extracted with CH_2Cl_2 (2 × 10 mL), the combined extracts were evaporated, and the residue was triturated with small amount of diethyl ether and filtered. The crude product was recrystallized from 2-propanol or purified by flash chromatography (Hexane/Ether 9:1 as an eluent) to yield the dihydropyrimidines **4**.

5-(Ethoxycarbonyl)-6-methyl-2-oxo-4-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl]acetic acid 4aa. Yield 83%. Mp 183°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.09 (t, 3H, $^3J_{H,H}$ = 7.0 Hz, CH_2CH_3), 2.38 (s, 3H, CH_3), 4.00 (m, 2H, CH_2CH_3), 4.32 (d, 1H, $^2J_{H,H}$ = 18.3 Hz, $CH_\alpha H_\beta$), 4.47 (d, 1H, $^2J_{H,H}$ = 18.3 Hz, $CH_\alpha H_\beta$), 5.17 (d, 1H, $^3J_{H,H}$ = 3.0 Hz, 4-H_{DHPM}), 7.23 (t, 1H, $^3J_{H,H}$ = 7.2 Hz, 4-H_{Ph}), 7.30 (m, 4H, 2,3,5,6-H_{Ph}), 8.03 (d, 1H, $^3J_{H,H}$ = 3.0 Hz, NH), 12.84 (br. s, 1H, CO_2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.5, 16.1, 44.5, 53.6, 60.1, 103.4, 127.0, 127.9, 128.8, 144.7, 149.5, 152.8, 166.0, 171.5. *Anal*. Calcd for $C_{16}H_{18}N_2O_5$ C 60.37, H 5.70, N 8.80. Found C 60.62, H 5.97, N 9.13. MS (APCI): *m/z* 319 (MH^+).

[6-Methyl-5-(morpholin-4-ylcarbonyl)-2-oxo-4-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl]acetic acid 4ab. Yield 68%. Mp 253°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.75 (s, 3H, CH_3), 1.99 (m, 1H, NCH), 2.86 (m, 1H, NCH), 2.92–3.12 (m, 3H, NCH_2 + OCH), 3.19 (m, 1H, OCH), 3.54 (m, 1H, OCH), 3.76 (m, 1H, OCH), 4.23 (d, 1H, $^2J_{H,H}$ = 18.1 Hz, $CH_\alpha H_\beta$), 4.42 (d, 1H, $^2J_{H,H}$ = 18.1 Hz, $CH_\alpha H_\beta$), 5.05 (m, 1H, 4-H_{DHPM}), 7.29 (m, 3H, 2,4,6-H_{Ph}), 7.35 (t, 2H, $^3J_{H,H}$ = 7.5 Hz, 3,5-H_{Ph}), 7.67 (br. s, 1H, NH), 12.78 (br. s, 1H, CO_2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 16.1, 41.9, 43.9, 46.6, 56.8, 65.8, 66.3, 106.7, 127.0, 128.2, 129.0, 131.7, 143.8, 153.0, 167.1, 172.1. *Anal*. Calcd for $C_{18}H_{21}N_3O_5$ C 60.16, H 5.89, N 11.69. Found C 59.94, H 5.98, N 11.60. MS (APCI): *m/z* 360 (MH^+).

3-[5-(Ethoxycarbonyl)-6-methyl-2-oxo-4-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl]propanoic acid 4ba. Yield 72%. Mp 152°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.10 (t, 3H, $^3J_{H,H}$ = 7.1 Hz, CH_2CH_3), 2.44 (m, 1H, $CH_\alpha H_\beta CO_2H$), 2.52 (s, 3H, CH_3), 2.55 (m, 1H, $CH_\alpha H_\beta CO_2H$), 3.80 (m, 1H, $NCH_\alpha H_\beta$), 3.93 (m, 1H, $NCH_\alpha H_\beta$), 4.01 (q, 2H, $^3J_{H,H}$ = 7.1 Hz, CH_2CH_3), 5.14 (d, 1H, $^3J_{H,H}$ = 3.0 Hz, 4-H_{DHPM}), 7.21 (d, 2H, $^3J_{H,H}$ = 7.6 Hz, 2,6-H_{Ph}), 7.24 (t, 1H, $^3J_{H,H}$ = 7.6 Hz, 4-H_{Ph}), 7.31 (t, 2H, $^3J_{H,H}$ = 7.6 Hz, 3,5-H_{Ph}), 7.95 (d, 1H, $^3J_{H,H}$ = 3.0 Hz, NH), 12.32 (br. s, 1H, CO_2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.5, 16.1, 34.3, 38.7, 53.2, 60.1, 103.7, 126.7, 127.8, 128.9, 144.4, 149.9, 152.9, 166.1, 173.0. *Anal*. Calcd for $C_{17}H_{20}N_2O_5$ C 61.44, H 6.07, N 8.43. Found C 61.77, H 6.13, N 8.56. MS (APCI): *m/z* 333 (MH^+).

4-[5-(Ethoxycarbonyl)-6-methyl-2-oxo-4-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl]butanoic acid 4ca. Yield 75%. Mp 222°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.10 (t, 3H, $^3J_{H,H}$ = 7.0 Hz, CH_2CH_3), 1.58 (m, 1H, $CH_2CH_\alpha H_\beta CH_2$), 1.70 (m, 1H, $CH_2CH_\alpha H_\beta CH_2$), 2.13 (t, 2H, $^3J_{H,H}$ = 7.2 Hz, CH_2CO_2H), 2.48 (s, 3H, CH_3), 3.50 (m, 1H, $NCH_\alpha H_\beta$), 3.83 (m, 1H, $NCH_\alpha H_\beta$), 4.01 (q, 2H, $^3J_{H,H}$ = 7.0 Hz, CH_2CH_3), 5.14 (d, 1H, $^3J_{H,H}$ = 3.5 Hz, 4-H_{DHPM}), 7.20 (d, 2H, $^3J_{H,H}$ = 7.6 Hz, 2,6-H_{Ph}), 7.23 (t, 1H, $^3J_{H,H}$ = 7.6 Hz, 4-H_{Ph}), 7.30 (t, 2H, $^3J_{H,H}$ = 7.6 Hz, 3,5-H_{Ph}), 7.93 (d, 1H, $^3J_{H,H}$ = 3.5 Hz, NH), 12.07 (br. s, 1H, CO_2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.5, 16.1, 25.1, 31.1, 41.6, 53.0, 60.1, 103.8, 126.5, 127.8, 128.9, 144.5, 149.9, 153.2, 166.1, 174.4. *Anal*. Calcd for $C_{18}H_{22}N_2O_5$ C 62.42, H 6.40, N 8.09. Found C 62.09, H 6.31, N 7.88. MS (APCI): *m/z* 347 (MH^+)

4-[6-Methyl-5-(morpholin-4-ylcarbonyl)-2-oxo-4-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl]butanoic acid 4cb. Yield 63%. Mp 214°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.71 (m, 2H, $CH_2CH_2CH_2$), 1.84 (s, 3H, CH_3), 2.23 (m, 2H, CH_2CO_2H), 3.04 (m, 2H, NCH_2), 3.21 (m, 2H, NCH_2), 3.41 (m, 2H, OCH_2), 3.54 (m, 2H, OCH_2), 3.71 (m, 2H, NCH_2), 5.03 (d, 1H, $^3J_{H,H}$ = 3.5 Hz, 4-H_{DHPM}), 7.17 (d, 2H, $^3J_{H,H}$ = 7.5 Hz, 2,6-H_{Ph}), 7.29 (t, 1H, $^3J_{H,H}$ = 7.5 Hz, 4-H_{Ph}), 7.35 (t, 2H, $^3J_{H,H}$ = 7.5 Hz, 3,5-H_{Ph}), 7.52 (d, 1H, $^3J_{H,H}$ = 3.5 Hz, NH), 12.04 (br. s, 1H, CO_2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 16.0, 25.4, 31.3, 41.3, 41.9, 46.7, 56.6, 65.9, 66.4, 107.1, 126.6, 128.1, 129.1, 131.8, 143.8, 153.1, 167.4, 174.6. *Anal*. Calcd for $C_{20}H_{25}N_3O_5$ C 62.00, H 6.50, N 10.85. Found C 62.37, H 6.40, N 10.99. MS (APCI): *m/z* 388 (MH^+).

5-[5-(Ethoxycarbonyl)-6-methyl-2-oxo-4-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl]pentanoic acid 4da. Yield 78%. Mp 141°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.11 (t, 3H, $^3J_{H,H}$ = 7.1 Hz, CH_2CH_3), 1.40 (m, 3H, $CH_\alpha H_\beta CH_2CH_2CO_2H$), 1.50 (m, 1H, $NCH_2CH_\alpha H_\beta CH_2$), 2.19 (t, 2H, $^3J_{H,H}$ = 7.1 Hz, CH_2CO_2H), 2.48 (s, 3H, CH_3), 3.49 (m, 1H, $NCH_\alpha H_\beta$), 3.84 (m, 1H, $NCH_\alpha H_\beta$), 4.03 (q, 2H, $^3J_{H,H}$ = 7.1 Hz, CH_2CH_3), 5.15 (d, 1H, $^3J_{H,H}$ = 3.7 Hz, 4-H_{DHPM}), 7.21 (d, 2H, $^3J_{H,H}$ = 7.6 Hz, 2,6-H_{Ph}), 7.24 (t, 1H, $^3J_{H,H}$ = 7.6 Hz, 4-H_{Ph}), 7.31 (t, 2H, $^3J_{H,H}$ = 7.6 Hz, 3,5-H_{Ph}), 7.92 (d, 1H, $^3J_{H,H}$ = 3.7 Hz, NH), 12.00 (br. s, 1H, CO_2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.5, 16.1, 22.2, 29.3, 33.7, 41.8, 53.0, 60.1, 103.7, 126.5, 127.8, 128.9, 144.6, 149.9, 153.2, 166.1, 174.7. *Anal*. Calcd for $C_{19}H_{24}N_2O_5$ C 63.32, H 6.71, N 7.77. Found C 63.05, H 7.00, N 7.73. MS (APCI): *m/z* 361 (MH^+).

6-[5-(Ethoxycarbonyl)-6-methyl-2-oxo-4-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl]hexanoic acid 4ea. Yield 70%. Mp 152°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.11 (t, 3H, $^3J_{H,H}$ = 7.1 Hz, $CH_2C\underline{H_3}$), 1.14 (m, 2H, CH_2), 1.36 (m, 1H, CH), 1.44 (m, 2H, CH_2), 1.49 (m, 1H, CH), 2.13 (t, 2H, $^3J_{H,H}$ = 7.4Hz, $C\underline{H_2}CO_2H$), 2.48 (s, 3H, CH_3), 3.47 (m, 1H, $NC\underline{H_\alpha}H_\beta$), 3.82 (m, 1H, $NCH_\alpha\underline{H_\beta}$), 4.03 (q, 2H, $^3J_{H,H}$ = 7.1 Hz, $C\underline{H_2}CH_3$), 5.14 (d, 1H, $^3J_{H,H}$ = 3.0 Hz, 4-H_{DHPM}), 7.21 (d, 2H, $^3J_{H,H}$ = 7.6 Hz, 2,6-H_{Ph}), 7.24 (t, 1H, $^3J_{H,H}$ = 7.6 Hz, 4-H_{Ph}), 7.32 (t, 2H, $^3J_{H,H}$ = 7.6 Hz, 3,5-H_{Ph}), 7.94 (d, 1H, $^3J_{H,H}$ = 3.0 Hz, NH), 11.99 (br. s, 1H, CO_2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.5, 16.1, 24.7, 26.2, 29.5, 34.1, 42.0, 52.9, 60.1, 103.7, 126.5, 127.8, 128.9, 144.5, 150.0, 153.2, 166.1, 174.8. *Anal*. Calcd for $C_{20}H_{26}N_2O_5$ C 64.16, H 7.00, N 7.48. Found C 63.89, H 7.26, N 7.41. MS (APCI): *m/z* 375 (MH^+).

6-[6-Methyl-5-(morpholin-4-ylcarbonyl)-2-oxo-4-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl]hexanoic acid 4eb. Yield 62%. Mp 112°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.24 (m, 2H, CH_2), 1.51 (m, 4H, $2CH_2$), 1.83 (s, 3H, CH_3), 2.19 (t, 2H, $^3J_{H,H}$ = 7.2 Hz, $C\underline{H_2}CO_2H$), 2.77 (m, 1H, NCH), 3.05 (m, 1H, 2NCH), 3.12 (m, 1H, NCH), 3.23 (m, 1H, OCH), 3.40 (m, 1H, $NC\underline{H_\alpha}H_\beta$), 3.54 (m, 2H, 2OCH), 3.70 (m, 1H, OCH), 3.76 (m, 1H, $NCH_\alpha\underline{H_\beta}$), 5.02 (m, 1H, 4-$H_{DHPM}$), 7.17 (d, 2H, $^3J_{H,H}$ = 7.5 Hz, 2,6-H_{Ph}), 7.28 (t, 1H, $^3J_{H,H}$ = 7.5 Hz, 4-H_{Ph}), 7.36 (t, 2H, $^3J_{H,H}$ = 7.5 Hz, 3,5-H_{Ph}), 7.49 (br. s, 1H, NH), 11.96 (br. s, 1H, CO_2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 16.0, 24.8, 26.3, 29.8, 34.2, 41.7, 41.9, 46.8, 56.5, 65.8, 66.2, 104.1, 126.6, 128.1, 129.0, 131.1, 143.8, 153.1, 167.4, 174.8. *Anal*. Calcd for $C_{22}H_{29}N_3O_5$ C 63.60, H 7.04, N 10.11. Found C 63.27, H 6.74, N 10.40. MS (APCI): *m/z* 416 (MH^+).

6-[5-(Anilinocarbonyl)-6-methyl-2-oxo-4-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl]hexanoic acid 4ec. Yield 71%. Mp 244°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.21 (m, 2H, CH_2), 1.43 (m, 1H, CH), 1.50 (m, 3H, CH), 2.15 (s, 3H, CH_3), 2.18 (t, 2H, $^3J_{H,H}$ = 7.2 Hz, $C\underline{H_2}CO_2H$), 3.39 (m, 1H, $NC\underline{H_\alpha}H_\beta$), 3.81 (m, 1H, $NCH_\alpha\underline{H_\beta}$), 5.25 (s, 1H, 4-$H_{DHP}$), 7.02 (t, 1H, $^3J_{H,H}$ = 7.4 Hz, 4-$H_{Ph'}$), 7.21–7.29 (m, 5H, 3,4,5-H_{Ph} + 2,6-$H_{Ph'}$), 7.32 (t, 2H, $^3J_{H,H}$ = 7.4 Hz, 3,5-$H_{Ph'}$), 7.56 (d, 2H, $^3J_{H,H}$ = 8.1 Hz, 2,6-H_{Ph}), 7.66 (br. s, 1H, NH), 9.82 (s, 1H, CONHPh), 12.00 (br. s, 1H, CO_2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 16.7, 24.8, 26.3, 29.8, 34.1, 41.7, 54.6, 110.7, 120.1, 123.8, 126.7, 127.8, 128.9, 129.1, 138.5, 139.6, 144.2, 153.6, 166.5, 174.9. *Anal*. Calcd for $C_{24}H_{27}N_3O_4$ C 68.39, H 6.46, N 9.97. Found C 68.08, H 6.22, N 10.13. MS (APCI): *m/z* 422 (MH^+).

4-[5-(Ethoxycarbonyl)-6-methyl-2-oxo-4-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl]benzoic acid 4fa. Yield 76%. Mp 234°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.12 (t, 3H, $^3J_{H,H}$ = 7.1 Hz, $CH_2C\underline{H_3}$), 2.03 (s, 3H, CH_3), 4.05 (q, 2H, $^3J_{H,H}$ = 7.1 Hz, $C\underline{H_2}CH_3$), 5.29 (d, 1H, $^3J_{H,H}$ = 3.0 Hz, 4-H_{DHPM}), 7.30 (t, 1H, $^3J_{H,H}$ = 7.6 Hz, 4-H_{Ph}), 7.34–7.42 (m, 6H, 2,3,5,6-H_{Ph} + 3,5-H_{Ar}), 8.00 (d, 2H, $^3J_{H,H}$ = 8.5 Hz, 2,6-H_{Ar}), 8.23 (d, 1H, $^3J_{H,H}$ = 3.0 Hz, NH), 13.07 (br. s, 1H, CO_2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.5, 18.6, 53.7, 60.3, 104.8, 126.8, 128.1, 129.2, 130.4, 130.7, 130.9, 142.2, 144.3, 148.7, 152.2, 165.8, 167.2. *Anal*. Calcd for $C_{21}H_{20}N_2O_5$ C 66.31, H 5.30, N 7.36. Found C 66.05, H 5.51, N 7.62. MS (APCI): *m/z* 381 (MH^+).

4-[6-Methyl-5-(morpholin-4-ylcarbonyl)-2-oxo-4-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl]benzoic acid 4fb. Yield 71%. Mp 298°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.42 (s, 3H, CH_3), 2.11 (m, 1H, NCH), 2.90–3.15 (m, 3H, 3NCH), 3.24 (m, 1H, OCH), 3.44 (m, 1H, OCH), 3.55 (m, 1H, OCH), 3.77 (m, 1H, OCH), 5.17 (m, 1H, 4-H_{DHPM}), 7.34 (m, 3H, 3,4,5-H_{Ph}), 7.42 (m, 4H, 3,5-H_{Ar} + 2,6-H_{Ph}), 7.88 (br. s, 1H, NH), 7.99 (d, 2H, $^3J_{H,H}$ = 8.6 Hz, 2,6-H_{Ar}), 12.94 (br. s, 1H, CO_2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 17.7, 42.0, 46.8, 56.9, 66.3, 108.0, 126.9, 128.3, 129.2, 130.2, 130.4, 130.9, 142.6, 143.4, 145.4, 152.3, 166.8, 167.3. *Anal*. Calcd for $C_{23}H_{23}N_3O_5$ C 65.55, H 5.50, N 9.97. Found C 65.27, H 5.49, N 10.14. MS (APCI): *m/z* 422 (MH^+).

3-[5-(Ethoxycarbonyl)-6-methyl-2-oxo-4-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl]benzoic acid 4ga. Yield 70%. Mp 239°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.13 (t, 3H, $^3J_{H,H}$ = 7.1 Hz, $CH_2C\underline{H_3}$), 2.02 (s, 3H, CH_3), 4.06 (q, 2H, $^3J_{H,H}$ = 7.1 Hz, $C\underline{H_2}CH_3$), 5.31 (d, 1H, $^3J_{H,H}$ = 3.0 Hz, 4-H_{DHPM}), 7.32 (t, 1H, $^3J_{H,H}$ = 7.5 Hz, 4-H_{Ph}), 7.39 (d, 2H, $^3J_{H,H}$ = 7.5 Hz, 2,6-H_{Ph}), 7.42 (t, 2H, $^3J_{H,H}$ = 7.5 Hz, 3,5-H_{Ph}), 7.69 (m, 2H, 4,5-H_{Ar}), 7.96 (d, 1H, $^3J_{H,H}$ = 7.2 Hz, 6-H_{Ar}), 8.16 (d, 1H, $^4J_{H,H}$ = 1.4 Hz, 2-H_{Ar}), 8.22 (d, 1H, $^3J_{H,H}$ = 3.0 Hz, NH), 13.01 (br. s, 1H, CO_2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.5, 18.6, 53.6, 60.3, 104.6, 126.7, 128.1, 129.2, 129.4, 129.5, 129.8, 131.8, 132.2, 133.3, 138.4, 144.3, 152.5, 165.9, 167.7. *Anal*. Calcd for $C_{21}H_{20}N_2O_5$ C 66.31, H 5.30, N 7.36. Found C 66.27, H 4.98, N 7.71. MS (APCI): *m/z* 381 (MH^+).

3-[6-Methyl-5-(morpholin-4-ylcarbonyl)-2-oxo-4-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl]benzoic acid 4gb. Yield 65%. Mp > 300°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.41 (s, 3H, CH_3), 2.11 (m, 1H, NCH), 2.91–3.15 (m, 3H, 3NCH), 3.24 (m, 1H, OCH), 3.54 (m, 2H, 2OCH), 3.77 (m, 1H, OCH), 5.17 (m, 1H, 4-H_{DHPM}), 7.34 (d + t, 3H, $^3J_{H,H}$ = 7.5 Hz, 2,4,6-H_{Ph}), 7.42 (t, 2H, $^3J_{H,H}$ = 7.5 Hz, 3,5-H_{Ph}), 7.56 (m, 2H, 4,5-H_{Ar}), 7.81 (s, 1H, 2-H_{Ar}), 7.87 (br. s, 1H, NH), 7.94 (d, 1H, $^3J_{H,H}$ = 7.2Hz, 6-H_{Ar}), 13.15 (br. s, 1H, CO_2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 17.8, 41.9, 46.7, 57.0, 66.3, 107.4, 126.9, 128.3, 129.1, 129.2, 129.5, 131.3, 131.4, 132.0, 135.1, 138.8, 143.5, 152.5, 166.9, 167.3. *Anal*. Calcd for $C_{23}H_{23}N_3O_5$ C 65.55, H 5.50, N 9.97. Found C 65.37, H 5.29, N 10.10. MS (APCI): *m/z* 422 (MH^+).

4-{[5-(Ethoxycarbonyl)-6-methyl-2-oxo-4-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl]methyl}benzoic acid 4ha. Yield 69%. Mp 224°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.10 (t, 3H, $^3J_{H,H}$ = 7.1 Hz, $CH_2C\underline{H_3}$), 2.35 (s, 3H, CH_3), 4.03 (q, 2H, $^3J_{H,H}$ = 7.1 Hz, $C\underline{H_2}CH_3$), 4.94 (d, 1H, $^2J_{H,H}$ = 17.3 Hz, $C\underline{H_\alpha}H_\beta$), 5.14 (d, 1H, $^2J_{H,H}$ = 17.3 Hz, $CH_\alpha\underline{H_\beta}$), 5.27 (d, 1H, $^3J_{H,H}$ = 3.0 Hz, 4-H_{DHPM}), 7.17 (d, 2H, $^3J_{H,H}$ = 7.6 Hz, 3,5-H_{Ar}), 7.27 (d, 2H, $^3J_{H,H}$ = 7.7 Hz, 2,6-H_{Ph}), 7.28 (t, 1H, $^3J_{H,H}$ = 7.7 Hz, 4-H_{Ph}), 7.35 (t, 2H, $^3J_{H,H}$ = 7.7 Hz, 3,5-H_{Ph}), 7.86 (d, 2H, $^3J_{H,H}$ = 7.6 Hz, 2,6-H_{Ar}), 8.21 (d, 1H, $^3J_{H,H}$ = 3.0 Hz, NH), 12.91 (br. s, 1H, CO_2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.5, 16.5, 45.5, 52.9, 60.2, 104.3, 126.7, 127.4, 127.9, 128.9, 129.8, 129.9, 130.0, 144.3, 149.7, 153.5, 166.0, 167.5. *Anal*. Calcd for $C_{22}H_{22}N_2O_5$ C 66.99, H 5.62, N 7.10. Found C 67.22, H 5.60, N 7.43. MS (APCI): *m/z* 395 (MH^+).

4-{[6-Methyl-5-(morpholin-4-ylcarbonyl)-2-oxo-4-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl]methyl}benzoic acid 4hb. Yield 63%. Mp 244°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.72 (s, 3H, CH_3), 2.08 (m, 1H, NCH), 2.77 (m, 1H, NCH), 3.00 (m, 3H, NCH_2 + OCH), 3.18 (m, 1H, OCH), 3.52 (m, 1H, OCH), 3.74 (m, 1H, OCH), 4.90 (d, 1H, $^2J_{H,H}$ = 17.3 Hz, $C\underline{H_\alpha}H_\beta$), 5.01 (d, 1H, $^2J_{H,H}$ = 17.3 Hz, $CH_\alpha\underline{H_\beta}$), 5.18 (d, 1H, $^3J_{H,H}$ = 3.0 Hz, 4-H_{DHPM}), 7.25 (d, 2H, $^3J_{H,H}$ = 7.5 Hz, 3,5-H_{Ar}), 7.31 (m, 3H, 2,4,6-H_{Ph}), 7.38 (t, 2H, $^3J_{H,H}$ = 7.5 Hz, 3,5-H_{Ph}), 7.77 (d, 1H, $^3J_{H,H}$ = 3.0 Hz, NH), 7.94 (d, 2H, $^3J_{H,H}$ = 7.6 Hz, 2,6-H_{Ar}), 12.91 (br. s, 1H, CO_2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 16.2, 41.9, 45.1, 46.6, 56.7,

65.8, 66.2, 107.2, 126.5, 126.8, 127.4, 128.2, 129.1, 129.9, 130.2, 143.5, 145.2, 153.4, 167.1, 167.6. *Anal*. Calcd for $C_{24}H_{25}N_3O_5$ C 66.19, H 5.79, N 9.65. Found C 66.02, H 5.84, N 9.60. MS (APCI): *m*/*z* 436 (MH^+).

Acknowledgments. The authors thank Mr. Vitaliy V. Polovinko for NMR measurements and Mrs. Olga V. Manoylenko for chromatographic separations.

REFERENCES AND NOTES

[1] Zhu, J.; Bienaymé, H. Multicomponent Reactions. Wiley-VCH: Weinheim, Germany, 2005.

[2] Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. Acc Chem Res 1996, 29, 123.

[3] Tietze, L. F.; Lieb, M. E. Curr Opin Chem Biol 1998, 2, 363.

[4] Domling, A. Comb Chem High Throughput Screen 1998, 1, 1.

[5] Dax, S. L.; McNally, J. J.; Youngman, M. A. Curr Med Chem 1999, 6, 255.

[6] Tietze, L. F.; Modi, A. Med Res Rev 2000, 20, 304.

[7] Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. Chem Eur J 2000, 6, 3321.

[8] Ugi, I.; Heck, S. Comb Chem High Throughput Screen 2001, 4, 1.

[9] Weber, L. Drug Discov Today 2002, 7, 143.

[10] Domling, A. Curr Opin Chem Biol 2002, 6, 306.

[11] Biginelli, P. Gazz Chim Ital 1893, 23, 360.

[12] Kappe, C. O. Acc Chem Res 2000, 33, 879.

[13] Kappe, C. O. Eur J Med Chem 2000, 35, 1043.

[14] Young, I. S.; Baran, P. S. Nature Chem 2009, 1, 193.

[15] Volochnyuk, D. M.; Ryabukhin, S. V.; Plaskon, A. S.; Grygorenko, O. O. Synthesis 2009, 3719.

[16] Ryabukhin, S. V.; Plaskon, A. S.; Ostapchuk, E. N.; Volochnyuk, D. M.; Shishkin, O. V.; Shivanyuk, A. N.; Tolmachev, A. A. Org Lett 2007, 9, 4215.

[17] Ryabukhin, S. V.; Plaskon, A. S.; Ostapchuk, E. N.; Volochnyuk, D. M.; Shishkin, O. V.; Tolmachev, A. A. J Fluorine Chem 2008, 129, 625.

[18] Ryabukhin, S. V.; Plaskon, A. S.; Ostapchuk, E. N.; Volochnyuk, D. M.; Tolmachev, A. A. Synthesis 2007, 417.

[19] Zhu, Y.-L.; Pan, Y.-J.; Huang, S.-L. Synth Commun 2004, 34, 3167.

[20] Zhu, Y.-L.; Huang, S.-L.; Pan, Y.-J. Eur J Org Chem 2005, 2354.

[21] Zhu, Y.-L.; Pan, Y.-J.; Huang, S.-L. Heterocycles 2005, 65, 133.

[22] Werner, S.; Turner, D. M.; Lyon, M. A.; Huryn, D. M.; Wipf, P. Synlett 2006, 2334.

[23] Wright, C. M.; Chovatiya, R. J.; Jameson, N. E.; Turner, D. M.; Zhu, G.; Werner, S.; Huryn, D. M.; Pipas, J. M.; Day, B. W.; Wipf, P.; Brodsky, J. L. Bioorg Med Chem 2008, 16, 3291.

[24] Chiang, A. N.; Valderramos, J.-C.; Balachandran, R.; Chovatiya, R. J.; Mead, B. P.; Schneider, C.; Bell, C. L.; Klein, M. G.; Huryn, D. M.; Chen, X. S.; Day, B. W.; Fidock, D. A.; Wipf, P.; Brodsky, J. L. Bioorg Med Chem 2009, 17, 1527.

[25] Wipf, P.; Cunningham, A. Tetrahedron Lett 1995, 36, 7819.