A new approach to the synthesis of Biginelli compounds

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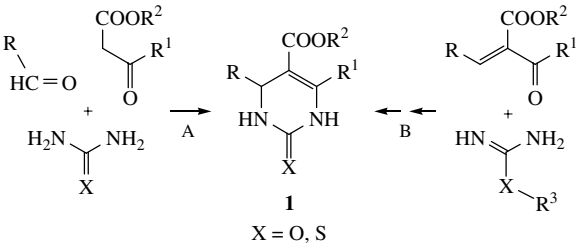
A new synthesis of 4-aryl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid esters is based on the reactions of α-tosyl-substituted phenyl carbamates with the enolates of β-oxoesters followed by treatment with ammonia and dehydration of the resulting 4-hydroxyhexahydropyrimidin-2-ones.

The synthesis of Biginelli compounds, namely, the esters of 2-oxo- and 2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acids **1**, is of considerable interest[1,2] because of diverse biological properties of these compounds. For example, they are active antihypertensive agents,[3,4] kinesin Eg5 inhibitors,[5] α_{1a} adrenoceptor-selective antagonists,[6] *etc*.

The one-step three-component Biginelli condensation (**A**)[7,8] and the multi-stage Atwal procedure (**B**)[9–11] are well-known synthetic methods providing access to pyrimidines **1** (Scheme 1). A limitation of these methods is their low adaptability in obtaining some types of **1**, especially those containing hydrogen atoms or an alkyl group at the 4-position (R = H, alkyl).



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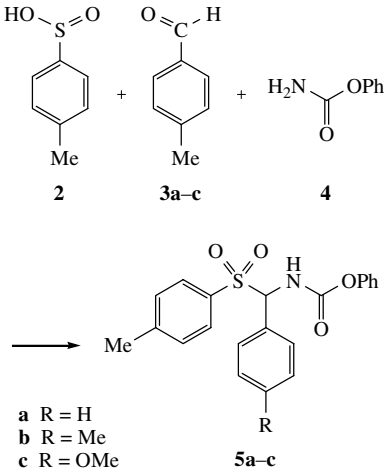
X = O, S

Scheme 1

Recently,[12,13] we developed a new general synthesis of compounds **1** based on the reaction of α-tosyl-substituted ureas or thioureas with enolates of β-oxoesters. Oxoalkyl(thio)ureas, which are intermediates of this reaction, undergo spontaneous cyclization into the corresponding 4-hydroxyhexahydropyrimidin-2-ones/thiones. The latter are dehydrated to give Biginelli compounds. We assumed that the oxoalkyl(thio)ureas can also be generated in the reaction of suitable (thio)carbamates containing an easily leaving group (for example, the phenoxy group) with ammonia or primary amines. Here, we describe preliminary results of the synthesis of **1**.

The key starting compounds, α-tosyl-substituted phenyl carbamates **5a–c**, were prepared by the reactions of *p*-toluenesulfinic acid **2** with aromatic aldehydes **3a–c** and phenyl carbamate **4** in water (Scheme 2). We found that this reaction proceeded at



2 **3a–c** **4**

a R = H
b R = Me
c R = OMe

5a–c

Scheme 2

about 25 °C quite slowly (13–20 days). This may be explained by the low solubility of reagents and intermediate products in an aqueous medium. However, compounds **5a–c** were obtained in very high yields (91–96%). The reaction time decreased with temperature. At 70 °C, the reaction was complete in 10 h to provide **5a–c** in 91–94% yields.†

We found that carbamates **5a–c** readily reacted with the sodium enolates of β-oxoesters (acetonitrile, room temperature, 4–6 h) generated by the treatment of ethyl acetoacetate **6a** or ethyl benzoylacetate **6b** with sodium hydride in dry acetonitrile. As a result of this reaction, the products of nucleophilic substitution of the tosyl group in **5a–c**, namely, corresponding N-substituted phenyl carbamates **7a–f**, were produced in 74–93% yields (Scheme 3).‡

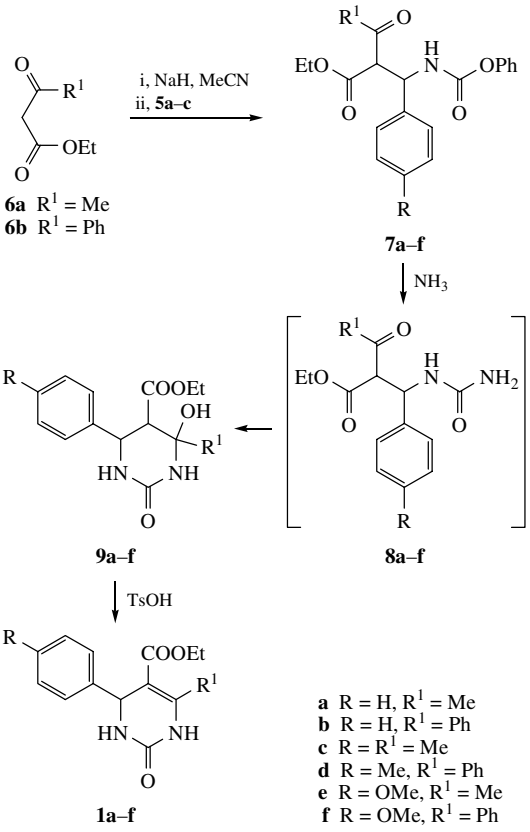
The phenoxy group in **7a–f** was replaced by the amino group upon the treatment of **7a–f** with an excess of ammonia in acetonitrile at room temperature. The reaction time depended on the molar ratio of **7a–f** to ammonia, and it was found to be approximately 24 h at a ratio of 1:13 or 5–6 h at a ratio of 1:60. The products of this reaction, ethyl 4-hydroxy-2-oxohexahydropyrimidine-5-carboxylates **9a–f**, seem to be formed as a result of the heterocyclisation of intermediate oxoalkylureas **8a–f**

† *Synthesis of* **5a**: A 50 ml Erlenmeyer flask with a magnetic stirring bar was charged with water (14.5 ml) and benzaldehyde (1.290 g, 12.16 mmol). Then, *p*-toluenesulfinic acid[18] (1.938 g, 12.41 mmol) was added with stirring, and the resulting mixture was stirred at room temperature for 10 min. Phenyl carbamate **4** (1.667 g, 12.16 mmol) was added to the suspension. The flask was closed with a glass stopper, and the reaction mixture was heated at 70 °C (water bath) with stirring for 9 h 52 min. At the beginning of heating the solid turned into an oil-like substance, which became a mass of fine crystals after 15–20 min. After the reaction was complete, the obtained creamy mixture was cooled to 0 °C, the solid was filtered off, washed with ice water and light petroleum, and dried to give 4.205 g (90.7%) of **5a**.¶

Similarly, compounds **5b**,**c** were prepared by the reaction of phenyl carbamate **4** with *p*-toluenesulfinic acid and 4-methylbenzaldehyde **3b** or 4-methoxybenzaldehyde **3c** in 92.6 and 94.1% yields, respectively. According to ^{1}H NMR data, carbamates **5a–c** contained only a small amount of impurities; therefore, they were used in the synthesis of **7a–f** without further purification. Analytically pure samples of **5a–c** were obtained after recrystallisation from hexane–ethyl acetate (1:1, v/v).

‡ *Synthesis of* **7a**: A solution of ethyl acetoacetate **6a** (0.907 g, 6.97 mmol) in dry acetonitrile (7 ml) was added dropwise to a stirred suspension of NaH (0.167 g, 6.96 mmol) in dry acetonitrile (11 ml) over a period of 2 min at room temperature. After hydrogen evolution finished, to the resulting solution of sodium enolate of ethyl acetoacetate was added carbamate **5a** (2.391 g, 6.27 mmol) and additional 4 ml of dry acetonitrile. The reaction mixture with a white precipitate was stirred for 6 h at room temperature. Then, the solvent was removed under reduced pressure, and a saturated aqueous solution of $NaHCO_3$ (6 ml) and light petroleum (5 ml) were added to a white residue. The mixture with the white precipitate was allowed to stand for 2 h at room temperature and then cooled to 0 °C; the precipitate was filtered off, washed with ice water and light petroleum and dried to give 1.840 g (82.6%) of **7a** as a mixture of two diastereomers.¶

Similarly, compounds **7b–f** were prepared by the reactions of **5a** with **6b** and **5b**,**c** with **6a**,**b** in 74–93% yields. According to ^{1}H NMR data, carbamates **7a–f** contained only a small amount of impurities; therefore, they were used in the synthesis of **1a–f** and **9a–f** without further purification. Analytically pure samples of **7a–f** were obtained after recrystallisation from hexane–ethyl acetate (1:1, v/v).



Scheme 3

(Scheme 3). Hydroxypyrimidines **9a–f** were dehydrated without isolation by refluxing in ethanol in the presence of *p*-toluenesulfonic acid (60 mol%) to give target pyrimidines **1a–f**§ in 71–80% yields based on **7a–f**.

The structures of all the obtained compounds were determined by IR, ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.¶

In summary, we developed a new general three-stage method for the synthesis of Biginelli compounds. This method is characterised by high overall yields (up to 70% based on phenyl carbamate **4**) of the target products. In comparison with the known synthetic procedures (see Scheme 1), our approach is more flexible and potentially allows a wide variety of substituents at N(1), C(4), C(5) and C(6) atoms of the pyrimidine ring. In particular, 4-alkyl-substituted and 4-unsubstituted Biginelli compounds, as well as 1,2,3,4-tetrahydropyrimidin-2-ones bearing other functional groups at the C(5) atom, can be readily obtained according to this method.

§ *Synthesis of* **1b**: A 25% aqueous ammonia solution (3.70 ml, 3.35 g, 49.2 mmol) was added to a suspension of **7b** (0.343 g, 0.82 mmol) in acetonitrile (7.4 ml), and the mixture was stirred at room temperature for 9 h 40 min. The solution was evaporated to dryness in a vacuum; the residue was dried in a vacuum dessicator over P_2O_5. Then, TsOH·H_2O (0.094 g, 0.49 mmol) and ethanol (3.5 ml) were added, and the resulting solution was refluxed for 1 h 40 min. The solvent was removed under reduced pressure; water (2 ml) and an aqueous 1 M NaOH solution (2.5 ml) were added to the oil-like residue. The residue was rubbed up with a spatula to complete solidification. The mixture was cooled to 0 °C, the precipitate was filtered off, washed with ice water and light petroleum and dried to give **1b** (0.213 g, 80.4%).

Similarly, compounds **1d**,**f** were prepared using **7d**,**f** as starting materials in 73.6 and 70.8% yields, respectively.

Synthesis of **1a**,**c**,**e**: Syntheses were carried out using **7a**,**c**,**e** as starting materials analogously to the synthesis of **1b**,**d**,**f** with the following exceptions: after the dehydration stage was accomplished, the corresponding reaction mixture was cooled to –10 °C, the resulting precipitate was filtered off, slightly washed with cold (0 °C) ethanol and dried to give **1a**,**c**,**e** in 79.6, 71.0 and 72.4% yields, respectively.

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¶ The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 spectrometer at 300.13 (^{1}H) and 75.476 (^{13}C) MHz as solutions in [$^2H_6$]DMSO. The IR spectra were obtained on a Bruker Equinox 55/S Fourier spectrometer in KBr pellets (for **1a–f**, **5a**) or Nujol (for **7a**).

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **1a**: mp 204–204.5 °C (from ethanol) (lit.,[8] mp 202.4 °C; lit.,[14] mp 204–205 °C). ^{1}H NMR, δ: 9.20 [s, 1H, N(1)H], 7.74 [br. s, 1H, N(3)H], 7.19–7.37 (m, 5H, Ph), 5.15 (d, 1H, 4-H, $J_{4\text{-H,N-H}}$ 3.1 Hz), 3.98 (q, 2H, OC*H*$_2$Me, *J* 7.1 Hz), 2.25 (s, 3H, 6-Me), 1.09 (t, 3H, OCH$_2$*Me*, *J* 7.1 Hz). ^{13}C NMR, δ: 165.33 (C=O in COOEt), 152.13 [C(2)], 148.35 [C(6)], 144.86 [C(1) in Ph], 128.38 [C(3) and C(5) in Ph], 127.25 [C(4) in Ph], 126.24 [C(2) and C(6) in Ph], 99.25 [C(5)], 59.17 (O*C*H$_2$Me), 53.96 [C(4)], 17.77 (6-Me), 14.06 (OCH$_2$*Me*). IR, ν/cm^{-1}: 3365 (m), 3246 (s), 3116 (s, ν_{N-H}), 1726 (vs, $\nu_{C=O}$ in COOEt), 1702 (vs, amide-I), 1648 (vs, $\nu_{C=C}$), 1601 (w, ν_{CC} in Ph), 1224 (vs), 1092 (vs, ν_{C-O}), 760 (s), 700 (s, $\delta_{C_{arom}-H}$). Found (%): C, 64.67; H, 6.33; N, 10.73. Calc. for $C_{14}H_{16}N_2O_3$ (%): C, 64.60; H, 6.20; N, 10.76.

Ethyl 2-oxo-4,6-diphenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **1b**: mp 157–159 °C (from ethanol) (lit.,[15] mp 157–159 °C). ^{1}H NMR, δ: 9.32 [br. d, 1H, N(1)H, $J_{NH,NH}$ 2.0 Hz], 7.87 [br. dd, 1H, N(3)H, $J_{NH,NH}$ 2.0 Hz, $J_{4\text{-H,NH}}$ 3.5 Hz], 7.25–7.46 (m, 10H, 4-Ph and 6-Ph), 5.24 (d, 1H, 4-H, $J_{4\text{-H,NH}}$ 3.5 Hz), 3.71 (q, 2H, OC*H*$_2$Me, *J* 7.1 Hz), 0.72 (t, 3H, OCH$_2$*Me*, *J* 7.1 Hz). ^{13}C NMR, δ: 165.13 (C=O in COOEt), 152.14 [C(2)], 149.00 [C(6)], 144.42 [C(1) in 4-Ph], 135.08 [C(1) in 6-Ph], 128.89 [C(4) in 6-Ph], 128.55 [C(3) and C(5) in 4-Ph], 128.36 [C(2) and C(6) in 6-Ph], 127.74 [C(3) and C(5) in 6-Ph], 127.44 [C(4) in 4-Ph], 126.32 [C(2) and C(6) in 4-Ph], 100.39 [C(5)], 59.09 (O*C*H$_2$Me), 54.15 [C(4)], 13.38 (OCH$_2$*Me*). IR, ν/cm^{-1}: 3361 (s), 3199 (m), 3080 (m), 3063 (m, ν_{N-H}), 3029 (m, $\nu_{C_{arom}-H}$), 1698 (vs, $\nu_{C=O}$ in COOEt), 1664 (vs, amide-I), 1640 (m, $\nu_{C=C}$), 1599 (m), 1494 (m, ν_{CC} in Ph), 1252 (vs), 1084 (vs, ν_{C-O}), 756 (s), 692 (s, $\delta_{C_{arom}-H}$). Found (%): C, 70.66; H, 5.67; N, 8.68. Calc. for $C_{19}H_{18}N_2O_3$ (%): C, 70.79; H, 5.63; N, 8.69.

Ethyl 6-methyl-4-(4-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **1c**: mp 214–214.5 °C (from ethanol) (lit.,[16] mp 215–216 °C; lit.,[17] mp 170–171 °C). ^{1}H NMR, δ: 9.16 [s, 1H, N(1)H], 7.69 [br. s, 1H, N(3)H], 7.12 (s, 4H, C_6H_4), 5.11 (d, 1H, 4-H, $J_{4\text{-H,NH}}$ 3.2 Hz), 3.98 (q, 2H, OC*H*$_2$Me, *J* 7.1 Hz), 2.26 and 2.24 (2s, 2×3H, 6-Me, 4-*Me*C$_6$H$_4$), 1.10 (t, 3H, OCH$_2$*Me*, *J* 7.1 Hz). ^{13}C NMR, δ: 165.34 (C=O in COOEt), 152.16 [C(2)], 148.13 [C(6)], 141.94 [C(1) in 4-MeC$_6$H$_4$], 136.34 [C(4) in 4-MeC$_6$H$_4$], 128.87 [C(3) and C(5) in 4-MeC$_6$H$_4$], 126.13 [C(2) and C(6) in 4-MeC$_6$H$_4$], 99.40 [C(5)], 59.13 (O*C*H$_2$Me), 53.61 [C(4)], 20.62 (4-*Me*C$_6$H$_4$), 17.74 (6-Me), 14.08 (OCH$_2$*Me*). IR, ν/cm^{-1}: 3246 (s), 3117 (s, ν_{N-H}), ~1721 (sh, $\nu_{C=O}$ in COOEt), 1705 (vs, amide-I), 1650 (vs, $\nu_{C=C}$), 1513 (m, ν_{CC} in C_6H_4), 1225 (vs), 1091 (vs, ν_{C-O}). Found (%): C, 65.60; H, 6.81; N, 10.11. Calc. for $C_{15}H_{18}N_2O_3$ (%): C, 65.68; H, 6.61; N, 10.21.

Ethyl 4-(4-methylphenyl)-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **1d**: mp 164.5–167 °C (from ethanol). ^{1}H NMR, δ: 9.22 [s, 1H, N(1)H], 7.77 [br. s, 1H, N(3)H], 7.24–7.44 (m, 5H, 6-Ph), 7.27 [m, 2H, AA′ part of AA′XX′ spin system, C(2)H and C(6)H in 4-MeC$_6$H$_4$, J_{ortho} 8.1 Hz], 7.18 [m, 2H, XX′ part of AA′XX′ spin system, C(3)H and C(5)H in 4-MeC$_6$H$_4$, J_{ortho} 8.1 Hz], 5.20 (d, 1H, 4-H, $J_{4\text{-H,NH}}$ 3.5 Hz), 3.71 (q, 2H, OC*H*$_2$Me, *J* 7.1 Hz), 2.29 (s, 3H, 4-*Me*C$_6$H$_4$), 0.72 (t, 3H, OCH$_2$*Me*, *J* 7.1 Hz). ^{13}C NMR, δ: 165.12 (C=O in COOEt), 152.15 [C(2)], 148.74 [C(6)], 141.52 [C(1) in 4-MeC$_6$H$_4$], 136.54 [C(4) in 4-MeC$_6$H$_4$], 135.11 [C(1) in Ph], 129.03 [C(3) and C(5) in 4-MeC$_6$H$_4$], 128.83 [C(4) in Ph], 128.33 [C(2) and C(6) in Ph], 127.71 [C(3) and C(5) in Ph], 126.20 [C(2) and C(6) in 4-MeC$_6$H$_4$], 100.58 [C(5)], 59.04 (O*C*H$_2$Me), 53.84 [C(4)], 20.67 (4-*Me*C$_6$H$_4$), 13.39 (OCH$_2$*Me*). IR, ν/cm^{-1}: 3305 (s), 3223 (s), 3114 (s, ν_{N-H}), 3055 (m), 3029 (m, $\nu_{C_{arom}-H}$), 1705 (vs, $\nu_{C=O}$ in COOEt), 1667 (vs, amide-I), 1640 (m, $\nu_{C=C}$), 1598 (m), 1512 (m, ν_{CC} in Ph and C_6H_4), 1246 (vs), 1097 (s, ν_{C-O}), 840 (m, $\delta_{C_{arom}-H}$ in C_6H_4), 767 (m), 701 (m, $\delta_{C_{arom}-H}$ in Ph). Found (%): C, 71.19; H, 5.94; N, 8.27. Calc. for $C_{20}H_{20}N_2O_3$ (%): C, 71.41; H, 5.99; N, 8.33.

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Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **1e**: mp 205–206 °C (from ethanol) (lit.,[14] mp 204–205 °C; lit.,[16] mp 202–204 °C). ^{1}H NMR, δ: 9.15 [br. d, 1H, N(1)H, $J_{NH,NH}$ 2.1 Hz], 7.67 [br. dd, 1H, N(3)H, $J_{4\text{-}H,NH}$ 3.2 Hz, $J_{NH,NH}$ 2.1 Hz], 7.14 [m, 2H, AA′ part of AA′XX′ spin system, C(2)H and C(6)H in 4-MeOC_6H_4, J_{ortho} 8.7 Hz], 6.87 [m, 2H, XX′ part of AA′XX′ spin system, C(3)H and C(5)H in 4-MeOC_6H_4, J_{ortho} 8.7 Hz], 5.09 (d, 1H, 4-H, $J_{4\text{-}H,NH}$ 3.2 Hz), 3.98 (q, 2H, OC*H*$_2$Me, *J* 7.1 Hz), 3.71 (s, 3H, OMe), 2.24 (s, 3H, 6-Me), 1.10 (t, 3H, OCH$_2$*Me*, *J* 7.1 Hz). ^{13}C NMR, δ: 165.37 (C=O in COOEt), 158.43 [C(4) in 4-MeOC_6H_4], 152.16 [C(2)], 148.01 [C(6)], 137.05 [C(1) in 4-MeOC_6H_4], 127.39 [C(2) and C(6) in 4-MeOC_6H_4], 113.69 [C(3) and C(5) in 4-MeOC_6H_4], 99.55 [C(5)], 59.14 (O*C*H$_2$Me), 55.04 (OMe), 53.33 [C(4)], 17.75 (6-Me), 14.10 (OCH$_2$*Me*). IR, ν/cm^{-1}: 3244 (s), 3113 (s, ν_{N-H}), 1725 (vs, $\nu_{C=O}$ in COOEt), 1706 (vs, amide-I), 1651 (vs, $\nu_{C=C}$), 1613 (m), 1584 (m), 1513 (m, ν_{CC} in C_6H_4), 1224 (vs), 1091 (vs, ν_{C-O}), 841 (m, $\delta_{C_{arom}-H}$). Found (%): C, 62.25; H, 6.30; N, 9.68. Calc. for $C_{15}H_{18}N_2O_4$ (%): C, 62.06; H, 6.25; N, 9.65.

Ethyl 4-(4-methoxyphenyl)-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **1f**: mp 162.5–163.5 °C (from ethanol). ^{1}H NMR, δ: 9.26 [s, 1H, N(1)H], 7.79 [unsolved br. d, 1H, N(3)H], 7.26–7.45 [m, 7H, 6-Ph and C(2)H, C(6)H in 4-MeOC_6H_4], 6.94 [m, 2H, XX′ part of AA′XX′ spin system, C(3)H and C(5)H in 4-MeOC_6H_4, J_{ortho} 8.7 Hz], 5.18 (d, 1H, 4-H, $J_{4\text{-}H,NH}$ 3.4 Hz), 3.74 (s, 3H, OMe), 3.71 (q, 2H, OC*H*$_2$Me, *J* 7.1 Hz), 0.72 (t, 3H, OCH$_2$*Me*, *J* 7.1 Hz). ^{13}C NMR, δ: 165.12 (C=O in COOEt), 158.56 [C(4) in 4-MeOC_6H_4], 152.12 [C(2)], 148.62 [C(6)], 136.57 [C(1) in 4-MeOC_6H_4], 135.14 [C(1) in Ph], 128.81 [C(4) in Ph], 128.33 [C(2) and C(6) in Ph], 127.71 [C(3) and C(5) in Ph], 127.47 [C(2) and C(6) in 4-MeOC_6H_4], 113.84 [C(3) and C(5) in 4-MeOC_6H_4], 100.70 [C(5)], 59.03 (O*C*H$_2$Me), 55.07 (OMe), 53.54 [C(4)], 13.39 (OCH$_2$*Me*). IR, ν/cm^{-1}: 3316 (s), 3202 (s), 3085 (s, ν_{N-H}), 3032 (w), 3012 (w, $\nu_{C_{arom}-H}$), 1692 (vs, $\nu_{C=O}$ in COOEt), 1677 (vs, amide-I), 1634 (m, $\nu_{C=C}$), 1608 (m), 1587 (w), 1510 (m, ν_{CC} in Ph and C_6H_4), 1236 (vs), 1086 (s, ν_{C-O}), 836 (m, $\delta_{C_{arom}-H}$ in C_6H_4), 769 (m), 696 (m, $\delta_{C_{arom}-H}$ in Ph). Found (%):C, 68.15; H, 5.69; N, 7.87. Calc. for $C_{20}H_{20}N_2O_4$ (%): C, 68.17; H, 5.72; N, 7.95.

Phenyl [(aryl)(tosyl)methyl]carbamates **5a–c** gave expected spectral and analytical data. As an example for **5a**: ^{1}H NMR, δ: 9.61 (d, 1H, NH, $J_{NH,CH}$ 10.8 Hz), 7.81 [m, 2H, AA′ part of AA′XX′ spin system, C(2)H and C(6)H in 4-MeC_6H_4, J_{ortho} 8.2 Hz], 7.66–7.74 (m, 2H, Ph–C), 7.50 [m, 2H, XX′ part of AA′XX′ spin system, C(3)H and C(5)H in 4-MeC_6H_4, J_{ortho} 8.2 Hz], 7.41–7.48 (m, 3H, Ph–C), 7.34 [m, 2H, C(3)H and C(5)H in OPh], 7.19 [m, 1H, C(4)H in OPh], 6.79 [m, 2H, C(2)H and C(6)H in OPh], 6.06 (d, 1H, CH–N, $J_{NH,CH}$ 10.8 Hz), 2.45 (s, 3H, Me). ^{13}C NMR, δ: 153.65 (C=O), 150.38 [C(1) in OPh], 144.90 [C(4) in 4-MeC_6H_4], 133.65 [C(1) in 4-MeC_6H_4], 129.84 [C(1) in Ph], 129.75, 129.69, 129.40, 129.33 [C(2), C(6) and C(3), C(5) in 4-MeC_6H_4 and Ph], 129.49 [C(4) in Ph], 128.21 [C(3) and C(5) in OPh], 125.46 [C(4) in OPh], 121.43 [C(2) and C(6) in OPh], 74.73 (CH–N), 21.12 (Me). IR, ν/cm^{-1}: 3398 (m), 3355 (m), 3299 (m, ν_{N-H}), 3063 (w), 3036 (w, $\nu_{C_{arom}-H}$), 1722 (vs, $\nu_{C=O}$), 1593 (m), 1510 (m, ν_{CC} in C_6H_4, Ph and OPh), 1318 (s, ν_{as} SO_2), 1146 (vs, ν_s SO_2), 815 (s, $\delta_{C_{arom}-H}$ in C_6H_4), 757 (m), 702 (s, $\delta_{C_{arom}-H}$ in Ph and OPh). Found (%): C, 66.05; H, 5.09; N, 3.60. Calc. for $C_{21}H_{19}NO_4S$ (%): C, 66.12; H, 5.02; N, 3.67.

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Phenyl [1-aryl-2-(ethoxycarbonyl)-3-oxobutyl]carbamates **7a–f** gave expected spectral and analytical data. As an example for **7a** (mixture of two diastereomers, 57:43): ^{1}H NMR spectrum of the major isomer, δ: 8.47 (d, 1H, NH, $J_{NH,CH}$ 8.9 Hz), 7.24–7.42 [m, 7H, Ph and C(3)H, C(5)H in OPh, the signals overlapped with signals of corresponding protons of the minor isomer], 7.15–7.22 [m, 1H, C(4)H in OPh, the signals overlapped with signals of corresponding protons of the minor isomer], 6.99–7.04 (m, 2H, C(2)H, C(6)H in OPh, the signals overlapped with signals of corresponding protons of the minor isomer), 5.18 (dd, 1H, C*H*–Ph, $J_{NH,CH}$ 8.9 Hz, $J_{CH,CH}$ 11.3 Hz), 4.19 (d, 1H, C*H*–Ac, $J_{CH,CH}$ 11.3 Hz), 4.21 (m, 1H, A part of ABX_3 spin system, OC*H*$_A$H$_B$Me, J_{AB} 10.8 Hz, J_{AX} 7.1 Hz), 4.16 (m, 1H, B part of ABX_3 spin system, OCH$_A$*H*$_B$Me, J_{AB} 10.8 Hz, J_{BX} 7.1 Hz), 2.32 (s, 3H, Ac), 0.89 (t, 3H, OCH$_2$*Me*, *J* 7.1 Hz). ^{1}H NMR spectrum of minor isomer, δ: 8.44 (d, 1H, NH, $J_{NH,CH}$ 9.5 Hz), 7.24–7.42 [m, 7H, Ph and C(3)H, C(5)H in OPh, the signals overlapped with signals of corresponding protons of the major isomer], 7.15–7.22 [m, 1H, C(4)H in OPh, the signals overlapped with signals of corresponding protons of the major isomer], 6.99–7.04 [m, 2H, C(2)H, C(6)H in OPh, the signals overlapped with signals of corresponding protons of the major isomer], 5.24 (dd, 1H, C*H*–Ph, $J_{NH,CH}$ 9.5 Hz, $J_{CH,CH}$ 10.8 Hz), 4.33 (d, 1H, C*H*–Ac, $J_{CH,CH}$ 10.8 Hz), 3.87 (q, 2H, OC*H*$_2$Me, *J* 7.1 Hz), 2.01 (s, 3H, Ac), 1.21 (t, 3H, OCH$_2$*Me*, *J* 7.1 Hz). ^{13}C NMR spectrum of major isomer, δ: 200.38 (C=O in Ac), 166.05 (*C*OOEt), 153.42 (NH–C=O), 150.78 [C(1) in OPh], 139.80 [C(1) in Ph], 129.32 [C(3) and C(5) in Ph], 128.39 [C(3) and C(5) in OPh], 127.81 [C(4) in Ph], 127.36 [C(2) and C(6) in Ph], 125.08 [C(4) in OPh], 121.53 [C(2) and C(6) in OPh], 64.38 (*C*H–Ac), 61.13 (O*C*H$_2$Me), 54.12 (CH–N), 29.50 (CO*Me*), 13.53 (OCH$_2$*Me*). ^{13}C NMR spectrum of the minor isomer, δ: 200.60 (C=O in Ac), 166.79 (*C*OOEt), 153.42 (NH–C=O), 150.85 [C(1) in OPh], 139.77 [C(1) in Ph], 129.32 [C(3) and C(5) in Ph], 128.50 [C(3) and C(5) in OPh], 127.76 [C(4) in Ph], 127.39 [C(2) and C(6) in Ph], 125.08 [C(4) in OPh], 121.53 [C(2) and C(6) in OPh], 64.09 (*C*H–Ac), 61.31 (O*C*H$_2$Me), 53.86 (CH–N), 30.06 (CO*Me*), 13.94 (OCH$_2$*Me*). IR, ν/cm^{-1}: 3380 (s, ν_{N-H}), 3058 (w), 3044 (w), 3031 (w, $\nu_{C_{arom}-H}$), 1719 (vs, $\nu_{C=O}$ in COOEt), 1705 (vs, $\nu_{C=O}$ in Ac and NH–C=O), 1491 (s, ν_{CC} in Ph and OPh), 1222 (s), 1215 (s), 1041 (m, ν_{C-O}), 762 (m), 705 (s, $\delta_{C_{arom}-H}$). Found (%): C, 67.55; H, 5.91; N, 3.87. Calc. for $C_{20}H_{21}NO_5$ (%): C, 67.59; H, 5.96; N, 3.94.