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SYNTHESIS OF 4-ALKYL-SUBSTITUTED 1,2,3,4-TETRAHYDRO-PYRIMIDIN-2-ONES BY THE BIGINELLI REACTION

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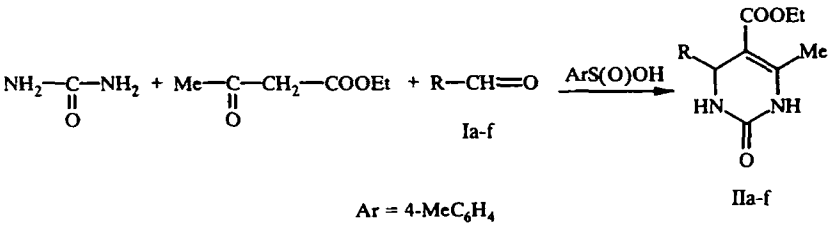
p-*Toluenesulfinic acid is an effective catalyst for condensation of acetoacetic ester with urea and aliphatic or aromatic aldehydes, leading to formation of 4-substituted 6-methyl-5-ethoxycarbonyl-1,2,3,4-tetrahydro-pyrimidin-2-ones.*

5-Functionally substituted 1,2,3,4-tetrahydropyrimidin-2-ones are a very interesting group of organic compounds, and have attracted attention in connection with their considerable practical importance and significant synthetic potential [1]. The main method for obtaining these compounds is the Biginelli reaction, including three-component condensation of urea, a 1,3-dicarbonyl compound, and an aldehyde in the presence of an acid catalyst [1-3]. Rather high yields of target products are achieved only when using aromatic aldehydes in the indicated reaction. In the case of aliphatic aldehydes, the Biginelli reaction does not have such a high preparative value, because of the low yields of pyrimidines and the lack of a universal procedure for their synthesis [3-7]. Thus, the reaction of urea, acetoacetic ester, and heptanoic aldehyde has been carried out with boiling in alcohol in the presence of HCl [4], with prolonged holding in water at 20°C in the presence of HCl [5], and in DMF in the presence of $(CH_3)_3SiCl$ [7]. The yield of 4-hexyl-6-methyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidin-2-one under the indicated conditions was 7.6%, 12.4%, and 37% respectively. The unsatisfactory results when using aliphatic aldehydes in the Biginelli condensation may be explained by the many side reactions of these compounds.

In continuing our investigations on the synthesis of derivatives of hydrogenated nitrogen-containing heterocycles, we set out to develop a preparative procedure for carrying out the Biginelli reaction to obtain 4-alkyl-substituted 1,2,3,4-tetrahydropyrimidin-2-ones. In this work, we have studied the reaction of urea, acetoacetic ester, and aldehydes (Ia-f) in the presence of the readily available *p*-toluenesulfinic acid [8] as the catalyst. We assumed that under the selected reaction conditions, formation *in situ* of reactive α-tosyl-substituted ureas is possible [9, 10], which when reacted with acetoacetic ester and aldehydes I will result in the target tetrahydropyrimidin-2-ones [11, 12]. We have shown that when urea, acetoacetic ester, and aliphatic aldehydes (Ia-e) in the mole ratio 1:1.2:1 are boiled in alcohol in the presence of 0.05-1.00 mole equivalents of *p*-toluenesulfinic acid, then 4-alkyl-substituted 6-methyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidin-2-ones (IIa-e) are formed in 23.0%-41.4% yields.



Ar = 4-MeC_6H_4

I, II a R = Me, b R = Et, c R = Pr, d R = *i*-Pr, e R = *n*-C_6H_{13}, f R = Ph

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TABLE 1. Yields of 1,2,3,4-Tetrahydropyrimidin-2-ones IIa-f (%) Upon Condensation of Urea, Acetoacetic Ester, and Aldehydes Ia-f

Reaction product	*p*-Toluenesulfinic acid* (according to the procedure proposed by the authors)				Literature data
	5	10	25	100	
IIa	—	41,4	40,2	—	25,8 [4], 46,9*[2] [4], 20 [5]
IIb	—	—	38,0	—	15 [5]
IIc	35,5	33,1	33,5	—	—
IId	—	27,2	28,1	34,3	32,4*[3] [6]
IIe	—	—	23,0	—	7,6 [4], 12,4 [5], 37*[4] [7]
IIf	—	—	72,8	—	78,5 [4], 40 [5], 80 [7]

*Amount of acid (in mole % relative to the amount of urea).

*[2]Replicating the procedure in [4], the product was obtained in 33.9% yield.

*[3]Replicating the procedure in [6], the product was obtained in 14.7% yield.

*[4]Replicating the procedure in [7], the product was obtained in 6.8% yield.

The yields of the condensation products depend little on the amount of catalyst. For example, in the case of butyric aldehyde, when using 0.05, 0.10, and 0.25 equivalents of *p*-toluenesulfinic acid, the product IIc is formed in 35.5%, 33.1%, and 33.5% yields respectively (see Table 1).

p-Toluenesulfinic acid also catalyzes the Biginelli reaction with aromatic aldehydes, as was demonstrated for the example of benzaldehyde: in the presence of 0.25 equivalents of *p*-toluenesulfinic acid, the product 6-methyl-4-phenyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidin-2-one (IIf) was obtained in 72.8% yield.

To evaluate the procedure proposed in this paper, we should compare it with procedures in the literature which provide the greatest yields of target products (see Table 1). We have repeated some syntheses of compounds IIa, d, e described earlier. In this case, we showed that boiling a mixture of urea, acetoacetic ester, and acetic aldehyde in 1,4-dioxane for 1 h followed by acidification of the reaction mass with hydrochloric acid and boiling again for another 2 h leads to a mixture of pyrimidine IIa and a product which does not dissolve well in alcohol, from which compound IIa was isolated with total yield 33.9%. This procedure for synthesis of compound IIa was described in [4], where it was indicated that this product is obtained in 46.9% yield. Boiling a mixture of urea, acetoacetic ester, and isobutyric aldehyde in alcohol for 6 h in the presence of HCl also led to formation of a mixture of the target pyrimidine IId and a product which does not dissolve well in alcohol. We isolated compound IId with total yield 14.7%, while in [6] it was indicated that under analogous conditions it is obtained in 32.4% yield after filtration of the precipitate from the reaction mass. Finally, we carried out the condensation of urea, acetoacetic ester, and heptanoic aldehyde in DMF in the presence of $(CH_3)_3SiCl$, as was described in [7]. However, when treating the reaction mixture according to the procedure in the cited paper, we could not obtain compound IIe in crystalline form: we obtained an oily material containing a large amount of impurities in addition to the product IIe. We isolated compound IIe from the mixture obtained in only 6.8% yield, while its yield according to data in [7] was 37%. Based on the data obtained, we can conclude that in a number of cases the product yields described in the literature for the Biginelli reaction when using aliphatic aldehydes are overestimated.

Thus *p*-toluenesulfinic acid can be used as a rather effective catalyst for Biginelli synthesis of 4-alkyl-substituted tetrahydropyrimidines. The advantages of the proposed approach to this condensation, compared with the procedures given in the literature, include its universality and its higher and more reproducible yields of the target products.

EXPERIMENTAL

The IR spectra in the 400-3600 cm^{-1} region were recorded on a Shimadzu IR-435 spectrophotometer for suspensions in Vaseline oil. The PMR spectra were recorded on a Bruker MSL-200 spectrometer (200 MHz) for solutions of the samples in DMSO-D_6 or $CDCl_3$. Internal standard, TMS. The course of the reactions and the purity of the products were monitored by TLC on Silufol plates or Kieselgel 60 F_{254} in chloroform–methanol systems, 9:1 or 20:1; the spots were visualized in iodine vapors.

p-Toluenesulfinic acid was obtained by the procedure described in [8], dried over P_2O_5, and stored at 0°C.

In this work, we used freshly distilled aldehydes Ia-f, the acetoacetic ester was dried over $CaCl_2$ and distilled under vacuum. We generally used 95.6% ethanol as the solvent for the Biginelli reaction.

The yields of reaction products were determined by chromatographic purification and a complete match between their IR spectra and the spectra of samples purified by recrystallization.

4,6-Dimethyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidin-2-one (IIa). A solution of 1.166 g (19.42 mmoles) urea, 3.033 g (23.31 mmoles) acetoacetic ester, 0.854 g (19.39 mmoles) acetic aldehyde, and 0.757 g (4.85 mmoles) *p*-toluenesulfinic acid in 6 ml alcohol was boiled with stirring for 5 h and then held at −5°C for 12 h. The precipitate was filtered off, washed with cold alcohol, and then dried. Obtained: 1.369 g of compound IIa. The mother liquor was driven off under vacuum to dryness, and 5 ml of a saturated aqueous solution of sodium bicarbonate and 3 ml alcohol were added to the residue. The mixture was cooled, the residue was filtered off and washed with a cold 3:5 mixture of alcohol and water. An additional 0.175 g of product IIa was obtained. The total yield of compound IIa was 1.544 g (40.2%). Compound IIa was recrystallized from acetonitrile or a 1:1 alcohol−water mixture, mp 198.5-199.5°C (acetonitrile). Lit.: mp 195-196 (alcohol−water) [3]; 189-190 (alcohol−water) [4]; 198-199°C [5]. IR spectrum: 3229, 3104, 1703, 1656, 1235, 1102, 766 cm^{-1}. PMR spectrum (DMSO-D_6): 8.88 (1H, broad s, $N_{(1)}$−H); 7.11 (1H, broad s, $J_{NH,4\text{-}H}$ = 3.2 Hz, $N_{(3)}$−H); 4.13 (1H, m, 4-H), 4.10 (1H, dq, J_{AB} = 10.8 Hz, H_A in OCH_2); 4.06 (1H, dq, H_B in OCH_2); 2.16 (3H, s, 6-CH_3); 1.20 (3H, t, J = 7.2 H_z, CH_3 in OEt); 1.11 ppm (3H, d, J = 6.4 Hz, 4-CH_3).

Compound IIa was obtained by a similar procedure in 41.4% yield (21.8% precipitated when cooling the reaction mixture, and 19.6% was obtained on treatment of the mother liquor) when using *p*-toluenesulfinic acid in the amount of 10 mole % relative to the amount of urea.

6-Methyl-4-ethyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidin-2-one (IIb) was obtained similarly to compound IIa by reaction of acetoacetic ester, urea, and propionic aldehyde in the presence of *p*-toluenesulfinic acid (25 mole % relative to the amount of urea). Total yield, 38.0% (16.2% precipitated when cooling the reaction mixture and 21.8% was obtained on treatment of the mother liquor), mp 184-185°C (alcohol). Lit.: mp 184-185°C [5]. IR spectrum: 3248, 3118, 1730, 1706, 1676, 1647, 1285, 1237, 1119 cm^{-1}. PMR spectrum (DMSO-D_6): 8.84 (1H, broad s, $N_{(1)}$−H); 7.20 (1H, broad s, $N_{(3)}$−H); 4.08 (1H, dq, J_{AB} = 10.8 Hz, H_A in OCH_2); 4.05 (1H, dq, H_B in OCH_2); 3.99-4.10 (1H, m, 4-H); 2.17 (3H, s, 6-CH_3); 1.43 (2H, m, 4-CH_2); 1.19 (3H, t, J = 7.0 Hz, CH_3 in OEt); 0.80 ppm (3H, t, J = 7.3 Hz, CH_3 in 4-Et).

6-Methyl-4-propyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidin-2-one (IIc) was obtained similarly to compound IIa by reaction of acetoacetic ester, urea, and butyric aldehyde in the presence of *p*-toluenesulfinic acid. Total yields of compound IIc, 35.5% (24.0% + 11.5%), 33.1% (24.5% + 8.6%), and 33.5% (26.9% + 6.6%)* when using *p*-toluenesulfinic acid (5, 10, or 25 mole % respectively relative to the amount of urea), mp 184.5-185°C (alcohol). Found, %: C 58.39; H 7.87; N 12.39. $C_{11}H_{18}N_2O_3$. Calculated, %: C 58.39; H 8.02; N 12.38. IR spectrum: 3237, 3104, 1722, 1703, 1671, 1646, 1281, 1238, 1092 cm^{-1}. PMR spectrum ($CDCl_3$): 8.37 (1H, broad s, $N_{(1)}$−H); 6.12 (1H, broad s, $N_{(3)}$−H); 4.29 (1H, m, $J_{4\text{-}H,NH}$ + $J_{4\text{-}H,4\text{-}CH'}$ + $J_{4\text{-}H,4\text{-}CH''}$ = 14.3 Hz, 4-H); 4.17 (1H, dq, J_{AB} = 10.9 Hz, H_A in OCH_2); 4.14 (1H, dq, H_B in OCH_2) 2.26 (3H, s, 6-CH_3); 1.27-1.65 (4H, m, CH_2-CH_2); 1.26 (3H, t, J = 7.2 Hz, CH_3 in OEt); 0.89 ppm (3H, t, J = 6.9 Hz, CH_3 in 4-Pr).

4-Isopropyl-6-methyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidin-2-one (IId) was obtained similarly to compound IIa by reaction of acetoacetic ester, urea, and isobutyric aldehyde in the presence of *p*-toluenesulfinic acid. Total yields of compound IId were 27.2% (23.8% + 3.4%), 28.1% (8.4% + 19.7%), and 34.3% (10.9% + 23.4%) when using *p*-toluenesulfinic acid (respectively 10, 25, and 100 mole % relative to the amount of urea), mp 205-206.5°C (alcohol). Lit. mp 198°C (methanol) [6]. IR spectrum: 3228, 3101, 1724, 1702, 1644, 1284, 1235, 1083 cm^{-1}. PMR spectrum ($CDCl_3$): 8.31 (1H, broad s, $N_{(1)}$−H); 6.00 (1H, broad s, $J_{NH,4\text{-}H}$ = 3.5 Hz, $N_{(3)}$−H); 4.21 (1H, dd, $J_{4\text{-}H,4\text{-}CH}$ = 3.5 Hz, 4-H); 4.17 (1H, dq, J_{AB} = 10.8 Hz, H_A in OCH_2); 4.14 (1H, dq, H_B in OCH_2); 2.27 (3H, s, 6-CH_3); 1.85 (1H, m, 4-CH); 1.26 (3H, t, J = 7.2 Hz, CH_3 in OEt); 0.90 (3H, d, J = 6.9 Hz, CH_3 in *i*-Pr); 0.84 ppm (3H, d, J = 6.9 Hz, CH_3 in *i*-Pr).

4-Hexyl-6-methyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidin-2-one (IIe) was obtained similarly to compound IIa with total yield 23.0% (13.6% precipitated when cooling the reaction mixture and 9.4% was obtained on treatment of the mother liquor) in the presence of *p*-toluenesulfinic acid (25 mole % relative to the amount of urea), mp 158-159°C (ace-

*The first number inside the parentheses means the yield of product precipitating from the reaction mixture; the second number is the yield on treatment of the mother liquor.

tonitrile), lit. mp 151-152 (alcohol–water) [4]; 150-152°C (alcohol) [7]. IR spectrum: 3233, 3108, 1729, 1705, 1649, 1238, 1085, 773 cm^{-1}. PMR spectrum ($CDCl_3$): 8.47 (1H, broad s, $N_{(1)}$–H); 6.07 (1H, broad s, $N_{(3)}H$); 4.27 (1H, m, $J_{4\text{-H,NH}} + J_{4\text{-H,4-CH}'} + J_{4\text{-H,4-CH}''} = 13.8$ Hz, 4-H); 4.17 (1H, dq, $J_{AB} = 11.0$ Hz, H_A in OCH_2); 4.14 (1H, dq, H_B in OCH_2); 2.26 (3H, s, 6-CH_3); 1.17-1.63 (10H, m, 5CH_2); 1.26 (3H, t, $J = 7.1$ Hz, CH_3 in OEt); 0.84 ppm (3H, t, $J = 6.2$ Hz, CH_3 in 4-C_6H_{13}).

6-Methyl-4-phenyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidin-2-one (IIf) was obtained similarly to compound IIa with total yield 72.8% (61.6% precipitated on cooling the reaction mixture and 11.2% was obtained on treatment of the mother liquor) in the presence of *p*-toluenesulfinic acid (25 mole % relative to the amount of urea), mp 212.5-213.5°C (alcohol). Lit. mp 202-204°C [4]; 203-204°C [5]; 206-208°C (alcohol) [7]. IR spectrum: 3228, 3100, 1728, 1702, 1645, 1600, 1287, 1226, 1091, 754, 695 cm^{-1}.

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