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DICHLOROACETYLAROYLMETHANES AS TWO-CARBON SYNTHONS IN THE BIGINELLI REACTION

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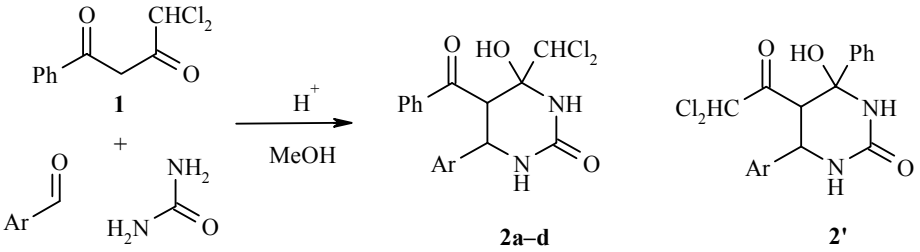
Acid-catalyzed cyclocondensation in a three component system of dichloromethylacetylbenzoylmethanes, urea, and aromatic aldehydes occurred regio- and stereoselectively to give polyfunctional derivatives of perhydropyrimidine.

Keywords: dichloromethylacetylbenzoylmethane, urea, perhydropyrimidines, Biginelli reaction, ^{1}H NMR spectra, cyclocondensation.

Acid-catalyzed cyclocondensation in three component systems of urea, ethyl acetoacetate, and an aldehyde or ketone leading to the formation of derivatives of 1,2,3,4-tetrahydropyrimidine is known as the Biginelli reaction [1]. Until now variations in the aldehydes, ketones, urea derivatives and very rarely keto esters, as sources of a two-carbon unit, have been used with the objective of obtaining various derivatives of pyrimidines [2,3].

We have found that the use dichloromethylaroylmethanes **1** in place of a ketoester as the synthetic equivalent of a two-carbon synthon gave in high or medium yields previously unknown derivatives perhydropyrimidines **2** containing dichloromethyl and benzoyl functional groups in positions 4 and 5, which are capable of various transformations, and which are difficult to introduce into the ring by other routes.



2 a Ar = Ph, **b** Ar = *p*-MeOC$_6$H$_4$, **c** Ar = *p*-BrC$_6$H$_4$, **d** Ar = *p*-IC$_6$H$_4$

Starting from latter suggestions on the mechanism of the Biginelli reaction [4] cyclocondensation of a β-diketone into derivatives of pyrimidine should lead to two regioisomers of perhydropyrimidines with structures **2** and **2'**.

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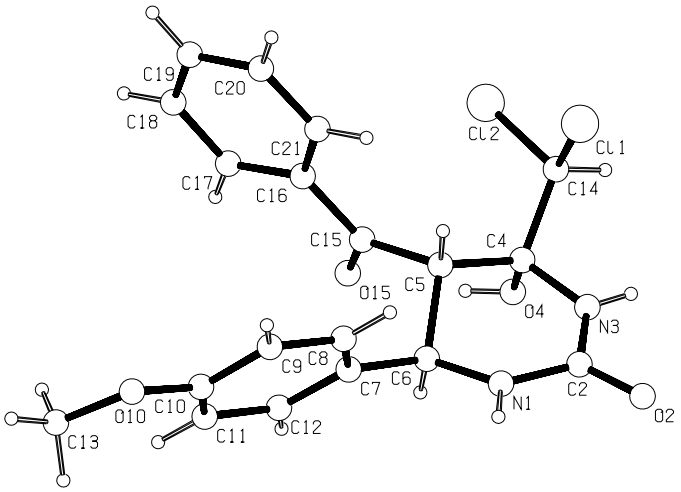

Fig. 1. Geometry of the molecule of compound **2b** in the crystal.
The relative configurations of atoms C-4, C-5, C-6 are *R,S,R* respectively.
The DMF solvent molecule is not shown.

For pyrimidines with three asymmetric carbon atoms in the molecule there are four possible diastereoisomers and additionally their four enantiomeric forms. However analysis of ^{1}H and ^{13}C NMR spectra of the products before purification and after recrystallization indicates the formation of only a single enantiomeric pair of the regioisomers **2** with the benzoyl group in position 5, while the coupling constants of protons H-5 and H-6 (J = 10.0-10.8 Hz) in the ^{1}H NMR spectra indicate the equatorial positions of the aryl and benzyl substituents. The latter conclusions were confimed by X-ray crystallography on crystals of three representative perhydropyrimidines. As an example, Fig. 1 demonstrates the geometry of molecules of compound **2b** in the crystal.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker WM-400 spectrometer (400 and 100 MHz respectively). The residual signals of the solvent (DMSO-d_6) (δ_H 2.54 and δ_C 40.45 ppm) were used as internal standards. IR spectra of nujol mulls were recorded on a Bruker Vector-22 spectrometer over the range 400-3600 cm^{-1}.

5-Benzoyl-4-dichloromethyl-4-hydroxy-6-phenylperhydropyrimidin-2-one (2a). Benzaldehyde (0.23 g, 2.16 mmol) and urea (0.26 g, 4.33 mmol) were added to a solution of the 1,3-diketone **1** (0.50 g, 2.16 mmol) in ethanol (or methanol) (10 ml) and acetic acid (25 ml). The reaction mixture was boiled for 4 h. The solvents were removed in vacuum, the semicrystalline mass was triturated with ether, the crystals were filtered off, dried in air and recrystallized. Yield 90.7%; mp 171-173°C (DMF). IR spectrum, ν, cm^{-1}: 3438, 3322, 3230, 3062, 2924, 2855, 2596, 2531, 1700, 1650, 1597, 1511, 1458, 1378, 1279, 1246, 1170, 1062, 1013, 797, 750, 702. ^{1}H NMR spectrum, δ, ppm (J, Hz): 4.70 (1H, d, J = 10.1, H-5); 5.06 (1H, d, J = 10.1, H-6); 6.08 (1H, s, $CHCl_2$); 6.15 (1H, br.s, OH); 6.75 (1H, br.s, NH); 6.83 (1H, br. s, NH); 7.13-7.90 (10H, m, C_6H_5 + C_6H_5). ^{13}C {^{1}H} NMR spectrum: 50.03, 56.89, 77.28, 86.15, 129.00, 129.10, 129.27, 129.28, 129.29, 134.23, 138.77, 139.45, 155.33, 199.33. Found, %: C 57.00; H 4.21; Cl 18.86; N 7.42. $C_{18}H_{16}Cl_2N_2O_3$. Calculated, %: C 57.03; H 4.22; Cl 18.70; N 7.39.

Compounds 2b-d were obtained analogously.

5-Benzoyl-4-dichloromethyl-4-hydroxy-6-(*p*-methoxyphenyl)perhydropyrimidin-2-one (2b). Yield 92%; mp 181-183°C (DMF). IR spectrum, ν, cm^{-1}: 3441, 3392, 3333, 3228, 3100, 2925, 2854, 1681, 1615, 1597, 1499, 1464, 1361, 1251, 1173, 1115, 1077, 1021, 801, 790. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.59 (3H, s, CH_3O); 4.42 (1H, d, *J* = 10.8, H-5); 4.85 (1H, d, *J* = 10.8, H-5); 5.92 (1H, s, $CHCl_2$); 6.61 (1H, br. s, OH); 6.61 (2H, d, *J* = 8.6, *m*-H in *p*-$MeOC_6H_4$); 6.95 (1H, br. s, NH); 7.1 (1H, br. s, NH); 7.21 (2H, d, *J* = 8.6, *o*-H in *p*-$MeOC_6H_4$); 7.33 (2H, dd, *J* = 7.5, *J* = 7.4, H *m*-Ph); 7.48 (2H, dd, *J* = 7.5, *J* = 7.4, H *p*-Ph); 7.64 (2H, d, *J* ~ 7.4, H *o*-Ph). Found, %: C 55.76; H 4.40; Cl 17.32; N 6.84. $C_{19}H_{18}Cl_2N_2O_4$. Calculated, %: C 55.78; H 4.40; Cl 17.33; N 6.85.

5-Benzoyl-6-(*p*-bromophenyl)-4-dichloromethyl-4-hydroxyperhydropyrimidin-2-one (2c). Yield 80.1%; mp 174-176°C (DMF). IR spectrum, ν, cm^{-1}: 3466, 3332, 3235, 3086, 2954, 2924, 2854, 1698, 1665, 1597, 1523, 1507, 1490, 1460, 1446, 1275, 1241, 1076, 1014, 802, 789, 729, 677, 683. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.44 (1H, d, *J* = 10.6, H-5); 4.90 (1H, d, *J* = 10.6, H-6); 6.63 (1H, br. s, OH); 6.92 (1H, br. s, NH); 7.17 (1H, br. s, NH); 7.25 (2H, d, *J* = 8.7, *m*-H in *p*-BrC_6H_4); 7.34 (2H, d , *J* = 8.7, *o*-H in *p*-BrC_6H_4); 7.36 (2H, m, H *m*-Ph); 7.50 (1H, dd, *J* = 7.5, *J* = 7.5, H *o*-Ph); 7.65 (2H, d, *J* = 7.5, H *o*-Ph). Found, %: C 47.20; H 3.20; Br 17.51; Cl 15.51; N 6.14. $C_{18}H_{15}BrCl_2N_2O_3$. Calculated, %: C 47.26; H 3.28; Br 17.46; Cl 15.49; N 6.12.

5-Benzoyl-4-dichloromethyl-4-hydroxy-6-(*p*-iodophenyl)-2-perhydropyrimidin-2-one (2d). Yield 70.8%; mp 166-172°C (1:1 DMF + MeCN). IR spectrum, ν, cm^{-1}: 3495, 3337, 3246, 2924, 2854, 1691, 1652, 1486, 1378, 1064, 1009, 798. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.43 (1H, d, *J* = 10.7, H-5); 4.89 (1H, d, *J* = 10.7, H-6); 5.90 (1H, s, $CHCl_2$); 6.57 (1H, s, OH); 6.81 (1H, s, NH); 7.10 (1H, s, NH); 7.13-7.69 (9H, m, C_6H_5, Ar). Found, %: C 42.85; H 2.79; Cl 14.09; I 25.18; N 5.65. $C_{18}H_{14}Cl_2IN_2O_3$. Calculated, %: C 42.80; H 2.99; Cl 14.04; I 25.12; N 5.55.

X-ray Structural Analysis of Compound 2b (Ar = *p*-$MeOC_6H_5$) was carried out with an Enraf-Nonius CAD-4 automatic four-circle diffractometer. Crystals of $C_{19}H_{18}Cl_2N_2O_4 \cdot C_3H_7NO$ are triclinic. At 20°C: *a* = 9.836(2), *b* = 10.023(7), *c* = 13.510(10) Å; α = 91.95(6), β = 103.48(6), γ = 113.47(8)°; *V* = 1176(1) $Å^3$; *Z* = 2; d_{calc} = 1.36 g/cm^3; space group *P*-1. The cell parameters and the intensities of 5091 reflexions, 2296 with $I \geq 3\sigma$, were measured at 20°C (λCuKα, graphite monochromator, ω/2θ scanning, θ ≤ 74.31°). There was no decrease in intensities of three control reflexions during the time of the experiment. Absorption was calculated empirically (μCu 28.37 cm^{-1}). The structure was solved by direct method using the SIR program [5] and refined initially isotropically and then in the anisotropic approximation using the WinGX suite of programs [6]. Atoms H-3,4,5 and H-14 were resolved from electron density difference syntheses and were included in the last least squares cycles and refined in the isotropic approximation. The remaining hydrogen atoms were refined by the "riding" scheme in the SHELXL program [7]. The final residual factors were $R = 0.061$ and $R_w = 0.149$ for 2489 independent reflexions with $F^2 \geq 2\sigma$. Treatment of the experimental data used the MoIEN suite of programs [8] on an AlphaStation 200.

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