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SHORT COMMUNICATIONS

Chloro(trimethyl)silane-Catalyzed Three-Component Condensation of Diethyl 3,3′-(1,3-Phenylene)bis(3-oxopropanoate) with Aromatic Aldehyde and Urea. New Synthesis of Diethyl 4,4′-(1,3-Phenylene)bis(2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylates)

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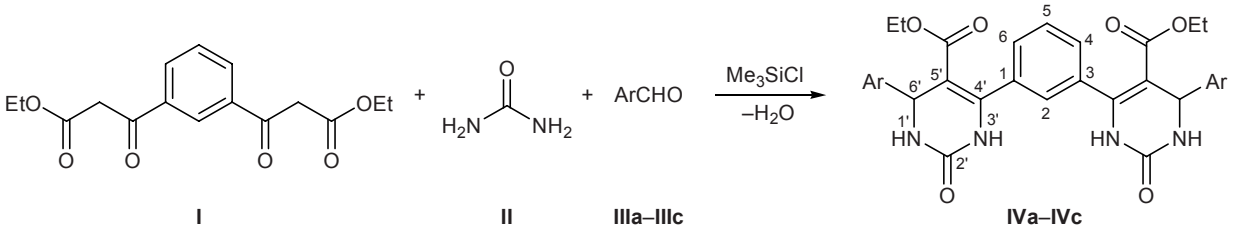
Condensation of ethyl acetoacetate with aldehyde and urea (Biginelli reaction) [1] underlies one of the most efficient procedures for the synthesis of 3,4-dihydropyrimidines. Various derivatives of these compounds attract considerable interest due to their therapeutic and pharmacological properties, in particular antiviral, antitumor, antibacterial, antiphlogistic, etc. [2, 3]. In the recent years, numerous publications were concerned with improvement of procedures for the Biginelli reaction; however, these studies were limited mainly to variation of the aldehyde or ketone component, while variation of the keto ester component as source of two-carbon fragment for pyrimidine ring was a very rare case [4–9].

We have found only two publications [10, 11] in which the use of bis-reagents, i.e., those possessing two similar functionalities necessary for the Biginelli reaction, has been described. Zhidovinova et al. [10] reported on a one-step synthesis of podands having dihydropyrimidinone and dihydroazolopyrimidine terminal fragments from 1,7-bis(2-formylphenyl)-1,4,7-trioxaheptane and of related structures with dihydropyrimidinone and dihydropyrimidinethione fragments from 1,5-bis(ureido)-3-oxapentane. Tu et al. [11] proposed a one-step procedure for the synthesis of 1,3- and 1,4-bis(oxopyrimidinyl)benzenes using isophthalaldehyde and terephthalaldehyde.

Up to now, Biginelli reactions were not performed with compounds having two keto ester moieties (two-carbon fragments for building up a pyrimidine ring) in a single molecule. We have found that reactions of diethyl 3,3′-(1,3-phenylene)bis(3-oxopropanoate) (**I**) with urea (**II**) and aromatic aldehydes **IIIa**–**IIIc** in a 1:2 mixture of dimethylformamide with acetonitrile in the presence of chloro(trimethyl)silane lead to the formation of previously unknown 1,3-bis(2-oxo-1,2,3,6-tetrahydropyrimidin-4-yl)benzene derivatives **IVa**–**IVc** in good yields (Scheme 1).

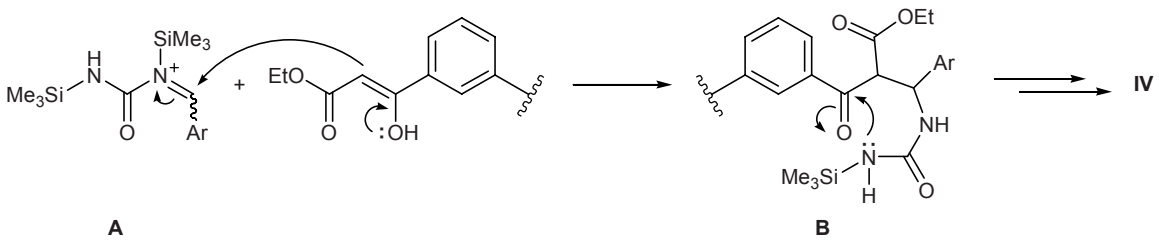
Scheme 1.



I **II** **IIIa–IIIc** **IVa–IVc**

Ar = Ph (**a**), 4-ClC_6H_4 (**b**), 4-$Me_2NC_6H_4$ (**c**).

Scheme 2.



When the condensation was performed according to a classical procedure (by stirring the reactant mixture in ethanol in the presence of HCl for 2–3 days or in acetic acid for 30 days or by heating in EtOH–AcOH for 3–4 h), the target bis-pyrimidines **IVa**–**IVc** were not obtained in a good yield. Presumably, chloro(trimethyl)silane activates [12] reactions involving nitrogen-centered nucleophiles. Nucleophilic addition of intermediate N-silylated acyliminium cation **A** to the enol tautomer (probably predominating) of β-dicarbonyl compound **I** gives intermediate **B**, and intramolecular cyclization of the latter with elimination of Me_3SiOH leads to the final product (Scheme 2).

Compounds **IVa**–**IVc** showed in the ^{1}H NMR spectra signals from protons in the phenyl and phenylene fragments, two broadened singlets from four NH protons (equivalent in pairs) at δ 7.81–7.98 and 8.84–8.95 ppm, and a doublet at δ 5.19–5.31 ppm ($^3J_{NH,CH}$ = 3.1–3.4 Hz) from the 6-H proton. In addition, signals from protons in the ester ethoxy groups were present.

The condensation of diethyl 3,3′-(1,3-phenylene)-bis(3-oxopropanoate) (**I**) with other aromatic aldehydes and structural specificity and properties of the products will be the subjects of our further studies.

Diethyl 4,4′-(1,3-phenylene)bis(2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-5-carboxylate) (IVa). Chloro(trimethyl)silane, 0.71 g (6.53 mmol), was added dropwise to a mixture of 0.50 g (1.63 mmol) of diester **I**, 0.39 g (6.53 mmol) of urea (**II**), 0.34 g (3.26 mmol) of benzaldehyde (**IIIa**), 6 ml of acetonitrile, and 3 ml of dimethylformamide. The mixture was heated for 25 h at 80°C, the solvent was removed under reduced pressure, the residue (a semicrystalline material) was treated with diethyl ether–methanol (4:1), and the precipitate was filtered off and dried in air. Yield 0.52 g (56%), colorless crystals, mp 298–299°C. IR spectrum, ν, cm^{-1}: 3338, 3224, 3105, 1704, 1667, 1343, 1302, 1270, 1251, 1204, 1095, 827, 812, 781, 753, 709, 699, 654, 472. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.89 t (6H, C**H**$_3$CH$_2$, J = 7.0 Hz), 3.82–3.88 m (4H, CH$_2$O), 5.31 d (2H, 6′-H, J = 3.4 Hz), 7.31 d.d (2H, *p*-H, J = 7.0, 7.0 Hz), 7.37 d.d (1H, 5-H, J = 7.7, 7.7 Hz), 7.38–7.46 m (11H, 2-H, 4-H, 6-H, *o*-H, *m*-H), 7.95 br.s (2H, 1′-H), 8.92 br.s (2H, 3′-H). Found, %: C 67.80; H 5.35; N 9.92. $C_{32}H_{30}N_4O_6$. Calculated, %: C 67.83; H 5.34; N 9.89.

Diethyl 4,4′-(1,3-phenylene)bis[6-(4-chlorophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylate] (IVb) was synthesized in a similar way from 0.50 g (1.63 mmol) of diester **I**, 0.29 g (4.89 mmol) of urea (**II**), and 0.57 g (3.26 mmol) of 4-chlorobenzaldehyde (**IIIb**). Yield 0.68 g (66%), colorless crystals, mp 304–306°C. IR spectrum, ν, cm^{-1}: 3228, 3103, 1704, 1681, 1645, 1490, 1445, 1412, 1369, 1338, 1293, 1262, 1243, 1198, 1092, 1014, 839, 798, 772, 702, 649, 465. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.88 t (6H, C**H**$_3$CH$_2$, J = 7.0 Hz), 3.84 q (4H, CH$_2$O, J = 7.0 Hz), 5.31 d (2H, 6′-H, J = 3.1 Hz), 7.37 d.d (1H, 5-H, J = 7.7, 7.7 Hz), 7.43–7.47 m (11H, 2-H, 4-H, 6-H, ClC$_6$H$_4$), 7.98 br.s (2H, 1′-H), 8.95 br.s (2H, 3′-H). Found, %: C 60.42; H 4.49; Cl 11.13; N 8.82. $C_{32}H_{28}Cl_2N_4O_6$. Calculated, %: C 60.48; H 4.44; Cl 11.16; N 8.82.

Diethyl 4,4′-(1,3-phenylene)bis[6-(4-dimethylaminophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylate] (IVc) was synthesized in a similar way from 0.50 g (1.63 mmol) of compound **I**, 0.29 g (4.89 mmol) of urea **II**, and 0.49 g (3.26 mmol) of 4-dimethylaminobenzaldehyde (**IIIc**). Yield 0.64 g (60%), colorless crystals, mp 282–284°C. IR spectrum, ν, cm^{-1}: 3232, 3098, 1700, 1617, 1525, 1445, 1367, 1343, 1278, 1244, 1199, 1167, 1093, 1012, 798, 782, 704, 651, 465. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.90 t (6H, C**H**$_3$CH$_2$, J = 7.0 Hz), 2.89 s (12H, NCH$_3$), 3.81–3.88 m (4H, CH$_2$O), 5.19 d (2H, 6′-H, J = 3.1 Hz), 6.74 d (4H, *m*-H, J = 8.4 Hz), 7.22 d (4H, *o*-H, J = 8.6 Hz), 7.36 d.d (1H, 5-H, J = 7.6, 7.6 Hz), 7.40–7.42 m (3H, 2-H, 4-H, 6-H), 7.81 br.s (2H, 1′-H), 8.84 br.s (2H, 3′-H). Found, %: C 66.20; H 6.21; N 12.85. $C_{36}H_{40}N_6O_6$. Calculated, %: C 66.24; H 6.18; N 12.87.

The melting points were determined on a Boetius melting point apparatus. The IR spectra were recorded in the frequency range from 400 to 3600 cm^{-1} on

a Bruker Vector-22 spectrometer with Fourier transform from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Bruker Avance-600 spectrometer at 600.13 MHz using the residual proton signal of the solvent as reference (DMSO, δ 2.52 ppm).

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