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LETTERS TO THE EDITOR

Synthesis of Some 1,4-Dihydropyridines under the Microwave Irradiation

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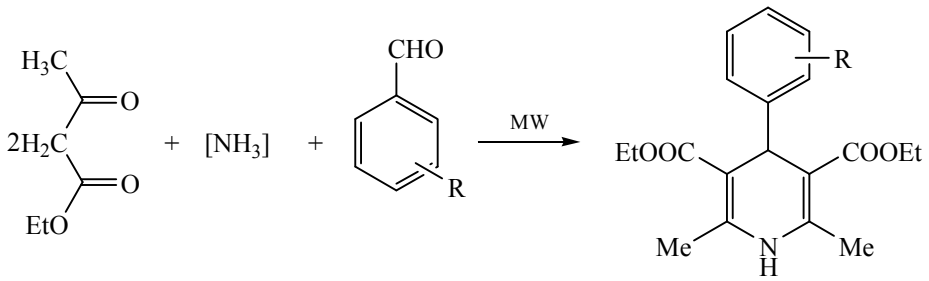
More than 30 years the derivatives of 1,4-dihydropyridines class are widely used in medicine as calcium channel blockers. Features of the structure and unique action make these compounds irreplaceable for treating hypertonic and cardiovascular diseases, prevention and treatment of strokes [1]. However the described in the literature convection synthesis approach to 1,4-dihydropyridines have an essential drawback: duration of the reaction [2–5].

We studied the synthesis method of the symmetric 1,4-dihydropyridines by the three-component reaction of ammonia donor, ethyl acetoacetate, and aromatic aldehydes under the microwave irradiation conditions:



R = Ph (**I**), 4-$NO_2C_6H_4$ (**II**), $CH_3OC_6H_4$ (**III**).

In the reaction we used a stoichiometric ratio of ethyl acetoacetate and the corresponding aldehyde. As ammonia donors we used 25% ammonia aqueous solution, ammonium acetate in acetic acid, and ammonium carbonate. As evident from the method *a*, the best results were obtained if the reaction with ammonium acetate was carried out in acetic acid.

Method *a***.** Into the flat-bottom flask of thermostable glass (250 ml) were placed 0.01 mol of the corresponding aldehyde, 10 ml of 25% aqueous ammonia, and 2.6 g (0.02 mol) of ethyl acetoacetate. The reaction mixture was subjected to microwave irradiation of 150 W for 5 min with off and on through each 1–2 min. The precipitate formed after cooling the reaction mixture was recrystalled from ethanol. Yields 70% (**I**), 86% (**II**), 65% (**III**).

Method *b***.** Into the flat-bottom flask of thermostable glass (250 ml) was placed 5 ml of glacial acetic acid, then was gradually added 15 ml of 25% aqueous ammonia under stirring. Thereafter to the reaction mixture were added 0.01 mol of the corresponding aldehyde and 2.6 g (0.02 mol) of ethyl acetoacetate. The reaction mixture was subjected to microwave irradiation of 150 W for 5–10 min off and on through each 1–2 min. The reaction progress was monitored by TLC. The precipitate formed after the reaction mixture cooling was recrystalled from ethanol. Yields 68% (**I**), 83% (**II**), 70% (**III**).

Method *c*. Into the flat-bottom flask of thermostable glass (250 ml) were placed 0.015 mol of the corresponding aldehyde, 2.6 g (0.02 mol) of ethyl acetoacetate and 0.72 g (0.0075 mol) of ammonium carbonate. The reaction mixture was subjected to microwave irradiation of 150 W for 15–20 min off and on through each 5 min. The reaction progress was monitored by TLC. The precipitate formed after cooling the reaction mixture was recrystalled from ethanol. Yields 62% (**I**), 82% (**II**), 53% (**III**).

The IR spectra were recorded on a Nicolet 5700 spectrophotometer (KBr). The ^{1}H NMR spectra were registered on a Bruker DRX500 device (500.13 MHz).

4-Phenyl-2,6-dimethyl-3,5-dicarbethoxy-1,4-dihydropyridine (Ia): mp 145–146°C. IR spectrum, ν, cm^{-1}: 3324, 3060, 2982, 1688, 1647, 1487, 1050, 827, 703. ^{1}H NMR spectrum (DMSO-d_5), δ, ppm: 1.13 t (6H), 2.50 s (6H), 4.00 s (4H), 4.85 m (1H), 8.7 s (1H), 7.25–7.35 m (5H). Found, %: C 69.25; H 7.11. $C_{19}H_{23}NO_4$. Calculated, %: C 69.28; H 7.04.

4-(2-Nitrophenyl)-2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine (IIb): mp 120–122°C. IR spectrum (KBr), ν, cm^{-1}: 3330, 3101, 2996, 2952, 2849, 1682, 1647, 1495, 1052, 829, 712. ^{1}H NMR spectrum (DMSO-d_5), δ, ppm: 1.13 t (6H), 2.35 s (6H), 3.98 m (4H), 5.1 s (1H), 7.25–7.31 m (4H), 9.1 s (1H). Found, %: C 60.91; H 5.98. $C_{19}H_{22}N_2O_6$. Calculated, %: C 60.95; H 5.92.

4-(4-Methoxy)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine (IIIc): mp 170–172°C. IR spectrum (KBr), ν, cm^{-1}: 3365, 3096, 2950, 2838, 1680, 1653, 1265, 1131, 1049, 942, 745. ^{1}H NMR spectrum (DMSO-d_5), δ, ppm: 2.33 s (6H), 3.65 s (6H), 3.75 s (3H), 4.94 s (1H), 8.87 s (1H), 7.11–7.35 m (4H). Found, %: C 65.31; H 6.40. $C_{18}H_{21}NO_5$. Calculated, %: C 65.24; H 6.39.

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