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Synthesis of Bis-1,4-Dihydropyridine Derivatives

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Synthesis of Bis-1,4-Dihydropyridine Derivatives

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Abstract: A series of bis-1,4-dihydropyridine derivatives were synthesized by the reaction of *p*-phenylenedialdehyde or *m*-phenylenedialdehyde and active methylene compounds.

Keywords: Bis-1,4-dihydropyridine, synthesis

1,4-Dihydropyridines (1,4-DHPs) are well known as a consequence of their pharmacological profile as the most important calcium channel

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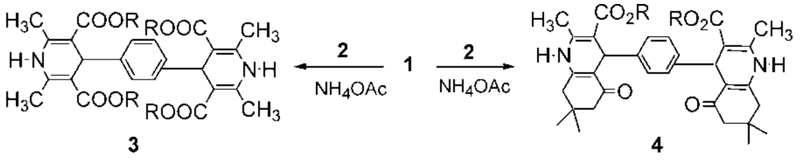
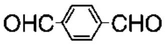
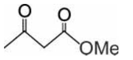
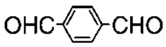
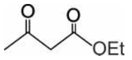
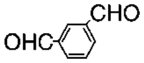
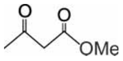
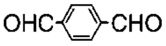
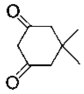
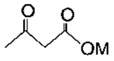
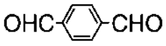
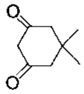
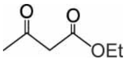
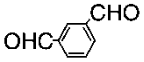
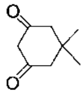
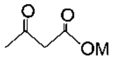
modulators.[1−7] Extensive efforts have been exerted to develop methodology for the modification of the 1,4-DHP ring.[8] 4-Aryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate derivatives are widely used for the treatment of cardiovascular diseases (such as hypertension, angina pectoris, and infarction).[9,10] 1,4-DHPs that have different ester groups on the 3 and 5 positions possess a stereogenic carbon on the 4-position in the 1,4-DHP nucleus, and their two enantiomers often show different biological activities.[11] It is well established that slight structural modifications on the DHP ring may bring remarkable changes of pharmacological effects. However, so far attention has mainly been paid to the synthesis of monofunctional 1,4-DHP derivatives, and the bisfunctional ones are seldom investigated. Here we would like to report the synthesis of bis-1,4-dihydropyridine derivatives (Scheme 1).



Scheme 1.

The results are listed in Table 1.

Table 1. Synthesis of bis-1,4-DHP derivatives

	Starting material					
Entry	1	2		Ratio	Product	Yield (%)
1			—	1:4	**3a**	75
2			—	1:4	**3b**	78
3			—	1:4	**3c**	70
4				1:2:2	**4a**	92
5				1:2:2	**4b**	90
6				1:2:2	**4c**	89

EXPERIMENTAL

Melting points were determined in a capillary tube and are uncorrected. The ^{1}H NMR spectra were recorded on a DPX 300 MHz Spectrometer with TMS as internal standard. The IR spectra were obtained with an SE-1730 instrument as potassium bromide pellets.

General Procedure

A mixture of *p*-phenylenedialdehyde or *m*-phenylenedialdehyde **1** (2 mmol), active methylene compounds **2** (in proper ratio), ammonium acetate (4 mmol), and acetic acid (15 mL) was kept stirring for 4–6 h at 100°C (TLC). Then the mixture was cooled and poured into 100 mL of water. The solid products were filtered, dried, and recrystallized from ethanol.

1,4-bis(2,6-dimethyl-3,5-dimethoxylcarbonyl-1,4-dihydropyridine-4-yl)benzene 3a: mp > 300°C; Y = 75%; IR (KBr, ν, cm^{-1}): 3354, 2954, 2864, 1652, 1483, 1220, 1122, 1017; ^{1}H NMR (DMSO-d_6) (δ, ppm): 2.24 (6H, s, $2 \times CH_3$), 2.50 (6H, s, $2 \times CH_3$), 3.55 (12H, s, $4 \times CH_3$), 4.46 (2H, s, $2 \times CH$), 6.97 (4H, s, ArH), 8.60 (2H, s, $2 \times NH$); CHN analysis: %C (calcd. 64.11, found 63.92); %H (calcd. 6.15, found 5.88); %N (calcd. 5.34, found 5.10).

1,4-bis(2,6-dimethyl-3,5-diethoxylcarbonyl-1,4-dihydropyridine-4-yl)benzene 3b: mp > 300°C; Y = 78%; IR (KBr, ν, cm^{-1}): 3349, 2985, 1696, 1488, 1369, 1300, 1241, 1207, 1122, 1093, 1052, 1020, 859, 808, 739, 688; ^{1}H NMR (DMSO-d_6) (δ, ppm): 1.09 (12H, t, $J = 6.8$ Hz, $4 \times CH_3$), 2.23 (12H, s, $4 \times CH_3$), 3.97 (8H, q, $J = 6.8$ Hz, $4 \times OCH_2$), 4.77 (2H, s, $2 \times CH$), 6.96 (4H, s, ArH), 8.75 (2H, s, $2 \times NH$); CHN analysis: %C (calcd. 66.19, found 65.88); %H (calcd. 6.94, found 5.69); %N (calcd. 4.82, found 4.63).

1,3-bis(2,6-dimethyl-3,5-diethoxylcarbonyl-1,4-dihydropyridine-4-yl)benzen 3c: mp > 300°C; Y = 70%; IR (KBr, ν, cm^{-1}): 3341, 2981, 2361, 1700, 1648, 1483, 1372, 1330, 1299, 1210, 1114, 1050, 1023, 780, 759, 686, 634; ^{1}HNMR (DMSO-d_6) δ: 1.11 (12H, t, $J = 6.8$ Hz, $4 \times CH_3$), 2.23 (12H, s, $4 \times CH_3$), 3.96 (8H, q, $J = 6.8$ Hz, $4 \times OCH_2$), 4.79 (2H, s, $2 \times CH$), 6.86–7.00 (4H, m, ArH), 8.74 (2H, s, $2 \times NH$); CHN analysis: %C (calcd. 64.11, found 63.87); %H (calcd. 6.15, found 5.84); %N (calcd. 5.34, found 5.09).

1,4-bis(3-methoxylcarbonyl-1,4,5,6,7,8-hexahydro-5-oxo-2,7,7-trimethylquinoline-4-yl)benzene 4a: mp > 300°C; Y = 92%; IR (KBr, ν, cm^{-1}): 3291, 3082, 2955, 1698, 1604, 1488, 1381, 1310, 1281, 1213, 1187, 1168, 1142, 1110, 1078, 1016, 800, 739, 609, 592, 533; ^{1}H NMR (DMSO-d_6) (δ, ppm):

0.79 (6H, s, 2 × CH_3), 0.97 (6H, s, 2 × CH_3), 1.94–2.49 (8H, m, 4 × CH_2), 2.25 (6H, s, 2 × CH_3), 3.50 (6H, s, 2 × CH_3), 4.77 (2H, s, 2 × CH), 6.90 (4H, s, ArH), 9.00 (2H, s, 2 × NH); CHN analysis: %C (calcd. 71.31, found 71.05); %H (calcd. 7.04, found 6.79); %N (calcd. 4.89, found 4.62).

1,4-bis(3-ethoxylcarbonyl-1,4,5,6,7,8-hexahydro-5-oxo-2,7,7-trimethylquinoline-4-yl)benzene 4b: mp > 300°C; Y = 90%; IR (KBr, ν, cm^{-1}): 3291, 3082, 2955, 1698, 1605, 1488, 1381, 1311, 1281, 1214, 1187, 1168, 1142, 1111, 1078, 1016, 800, 739, 609, 592, 533; ^{1}HNMR (DMSO-d_6) δ: 0.86 (6H, s, 2 × CH_3), 1.04 (6H, s, 2 × CH_3), 1.08 (6H, t, $J = 6.8$ Hz, 2 × CH_3), 1.91–2.41 (8H, m, 4 × CH_2), 2.23 (6H, s, 2 × CH_3), 3.50 (4H, q, $J = 6.8$ Hz, 2 × OCH_2), 4.76 (2H, s, 2 × CH), 6.83–6.94 (4H, m, ArH), 9.00 (2H, s, 2 × NH); %C (calcd. 71.97, found 71.78); %H (calcd. 7.38, found 7.15); %N (calcd. 4.66, found 4.37).

1,3-bis(3-methoxylcarbonyl-1,4,5,6,7,8-hexahydro-5-oxo-2,7,7-trimethylquinoline-4-yl)benzene 4c: mp > 300°C; Y = 89%; IR (KBr, ν, cm^{-1}): 3293, 3083, 2956, 2361, 1701, 1615, 1498, 1380, 1312, 1283, 1222, 1171, 1148, 1112, 1077, 1009, 788, 701, 527; ^{1}H NMR (DMSO-d_6) (δ, ppm): 0.82 (6H, s, 2 × CH_3), 0.99 (6H, s, 2 × CH_3), 1.90–2.43 (8H, m, 4 × CH_2), 2.23 (6H, s, 2 × CH_3), 3.50 (6H, s, 2 × CH_3), 4.76 (2H, s, 2 × CH), 6.83–6.94 (4H, m, ArH), 9.00 (2H, s, 2 × NH); %C (calcd. 71.31, found 71.03); %H (calcd. 7.09, found 6.75); %N (calcd. 4.89, found 4.68).

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