Arch. Pharm. Res. **13**(3), 257-260

Synthesis of Methyl 2, 6-Dimethyl-5-(1', 2'-Dioxo-2'-Ethoxyethyl)-4-(3'-Nitrophenyl)-1,4-Dihydropyridine-3-Carboxylate

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(Received June 16, 1990)

Abstract□Hantzch's type reaction of methyl acetopyruvate (**2a**), methyl 3-aminocrotonate (**3**) and 3-nitrobenzaldehyde (**4**) led to dimethyl 3-acetyl-6-methyl-4-(3'-nitrophenyl)-2,5-dicarboxylate (**5a**) and methyl 2,6-dimethyl-5-(1',2'-dioxo-2'-methoxyethyl)-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**6a**) in 26.7 and 9.2% yield, respectively. On the other hand, methyl 2,6-dimethyl-4-(3'-nitrophenyl)-1, 4-dihydropyridine 3-carboxylate (**9**) was acylated by ethyl oxaly chloride to give methyl 2,6-dimethyl-5-(1',2'-dioxo-2'-ethoxyethyl)-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**6b**) in 76.8% yield.

Keywords□1,4-Dihydropyridines, 1,4-dihydropyridine-5-oxalic acid ester, nifedipine.

Since nifedipine (**1**) was introduced for the treatment of angina pectoris and hypertension[1,2], a number of symmetrically and asymmetrically substituted ester derivatives of 1, 4-dihydropyridine have been synthesized and selected for further development[3,4].

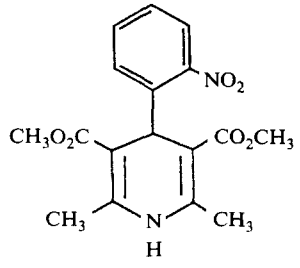
In a recent study the pharmacological activities of the asymmetrically substituted 3-nitrophenyl derivatives were shown to be superior to those of the corresponding symmetrically substituted derivatives in many cases[5,6].

Thus, as a part of our continuing effort to develop novel 1,4-dihydropyridine compounds, we tried to switch over the one of carboxylic acid esters of 1, 4-dihydropyridine to a carbonyl carboxylic acid ester (oxalic acid ester).

For the Hantzch's pyridine synthesis[7,8], methyl acetopyruvate (**2a**) was chosen as a main starting material. **2a** was heated with methyl 3-aminocrotonate (**3**) and 3-nitrobenzaldehyde (**4**) in isopropanol for 24 hours. The solvent was evaporated in vacuo and the residue was separated on silica gel column.

The first eluent gave **5a** in 26.7% yield and the second fraction gave **6a** in 9.2% yield. The IR and NMR spectra of **5a** and **6a** showed little difference in two structures. To elucidate two structures, **5a** was reduced by sodium borohydride. And then, the expected alcohol was cyclized in the reduction process to afford lactone compound **7**.

As the same synthetic proceduce of **5a** and **6a**, the reaction of ethyl acetopyruvate (**2b**), **3** and **4** gave **5b** and **6b** in 15.4 and 6.7% yield, respectively [Scheme 1]. On the other hand, an efficient synthesis of **6b** was carried out. Thus **9** was acylated directly in tetrahydrofuran by ethyl oxalylchloride to give **6b** in 76.8% yield. Compound **9** was synthesized from compound **8** in 70.5% yield [scheme 2].

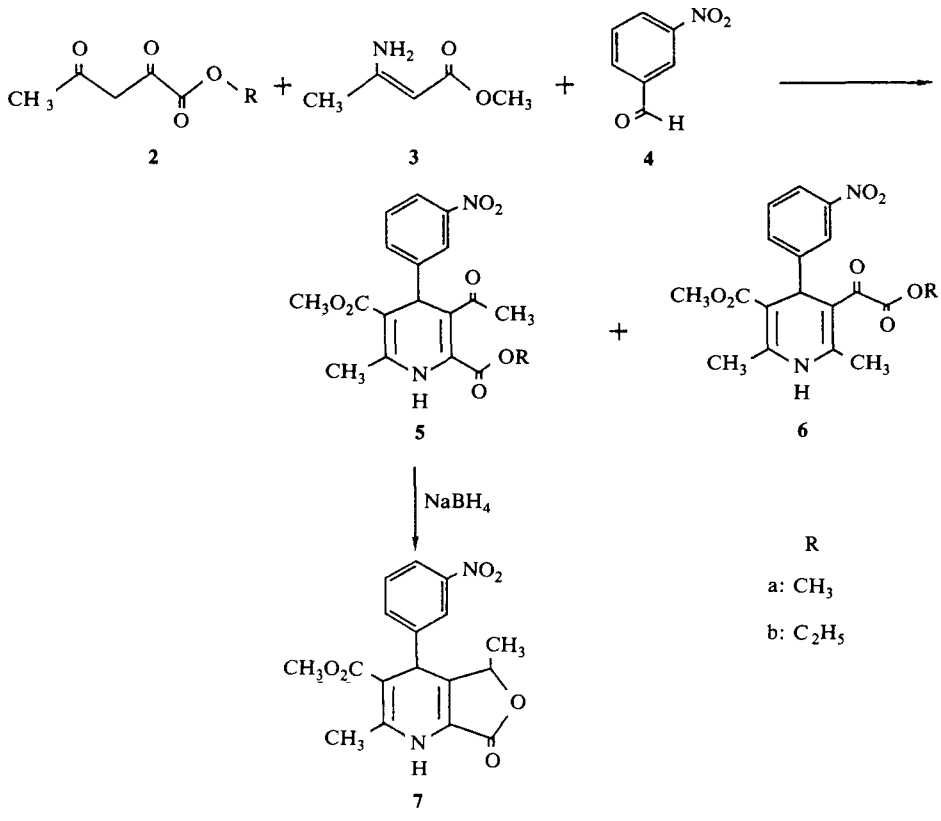


Nifedipine

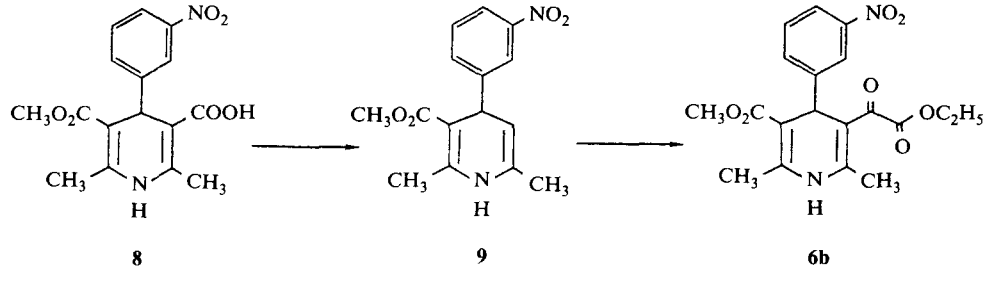
None of the synthesized compounds showed significant vasodilating activities on the vascular smooth muscles in *in vitro* preparations of experimental animals[9].

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Capilary melting point apparatus and are uncorrected. The pmr spectra were recorded on a Varian VXR-5200 (200 MHz). Chemical shifts are recorded in ppm with tetramethylsilane as the internal standard. The IR spectra were recorded with a Shimazu IR-435 spectrometer. The elemental analyses (C,H,N) were carried out with a Carlo Erba model 1106 Elemental Analyzer.



Scheme 1



Scheme 2

Dimethyl 3-acetyl-6-methyl-4-(3'-nitrophenyl)-2, 5-dicarboxylate (5a) and Methyl 2,6-dimethyl-5-(1', 2'-dioxo-2'-methoxyethyl)-4-(3'-nitrophenyl)-1, 4-dihydropyridine-3-carboxylate (6a)

A mixture of methyl 3-aminocrotonate (**3**, 2.3g, 0.02 mol), 3-nitrobenzaldehyde (**4**, 3g, 0.02 mol) and methyl acetopyruvate (**2a**, 2.88g, 0.02 mol) in isopropanol (5 m*l*) was heated to reflux under nitrogen stream for 24 hours.

The reaction mixture was cooled and the solvent was evaporated in vacuo. The residue was separated on silica gel column (EtOAc/n-Hexane = 1:2).

The first eluent gave dimethyl 3-acetyl-6-methyl-4-(3'-nitrophenyl)-2, 5-dicarboxylate (**5a**).

yield: 2g (26.7%), mp: 155-156°C; IR (KBr): 3344 (NH), 1727 (C=O), 1700 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.01 (s, 3H, $-CH_3$), 2.25 (s, 3H, $-CH_3$), 3.58 (s, 3H, $-OCH_3$),3.79 (s, 3H, $-OCH_3$), 5.06 (s, 1H, C_4-H), 7.55-8.08 (m, 4H, Ar-H), 9.79 (s, 1H, NH)

Anal. Calcd. for $C_{18}H_{18}N_2O_7$: C, 57.75; H, 4.85; N, 7.49. Found: C, 58.11; H, 4.90; N, 7.46.

The second eluent gave methyl 2, 6-dimethyl-5-(1',2'-dioxo-2'-methoxyethyl)-(3'-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**6a**).

yield: 0.68g (9.2%), mp: 174-175°C; IR (KBr): 3273 (NH), 1735 (C=O), 1713 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.16 (s, 3H, $-CH_3$), 2.33 (s, 3H, $-CH_3$), 3.57 (s, 3H, $-OCH_3$), 3.75 (s, 3H, $-OCH_3$), 5.02 (s, 1H, C_4-H), 7.49-8.03 (m, 4H, Ar-H), 9.73 (s, 1H,NH)

Anal. Calcd. for $C_{18}H_{18}N_2O_7$: C, 57.75; H, 4.85; N, 7.49. Found: C, 57.91; H, 4.88; N, 7.37.

2-Ethyl 5-methyl 3-acetyl-6-methyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-2,5-dicarboxylate (5b) and Methyl 2, 6-dimethyl-5-(1',2'-dioxo-2'-ethoxy-ethyl)-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (6b).

As the same procedure of **5a** and **6a**, the first eluent gave 2-ethyl 5-methyl 3-acetyl-6-methyl-4-(3'-nitrophenyl)-1, 4-dihydropyridine-2, 5-dicarboxylate (**5b**).

yield: 1.2g (15.4%), mp: 109-111°C; IR (KBr): 3262 (NH), 1717 (C=O), 1668 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.26 (t, 3H, $-CH_2CH_3$), 2.02 (s, 3H, $-CH_3$), 2.25 (s, 3H, $-COCH_3$), 3.58 (s, 3H, $-OCH_3$), 4.26 (q, 2H, $-CH_2CH_3$), 5.06 (s, 1H, C_4-H), 7.59-8.07 (m, 4H, Ar-H), 9.74 (s, 1H,NH)

Anal. Calcd. for $C_{19}H_{20}N_2O_7$: C, 58.76; H, 5.19; N, 7.21. Found: C, 58.99; H, 5.21; N, 6.98.

The second eluent gave methyl 2, 6-dimethyl-5-(1', 2'-dioxo-2'-ethoxyethyl)-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**6b**).

yield: 0.5g (6.7%), mp: 161-163°C; IR (KBr): 3290 (NH), 1732 (C=O), 1710 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.21 (t, 3H, $-CH_2CH_3$), 2.18 (s, 3H, $-CH_3$), 2.32 (s, 3H, $-CH_3$), 3.57 (s, 3H, $-OCH_3$), 4.23 (q, 2H, $-CH_2CH_3$), 5.01 (s, 1H, C_4-H), 7.55-8.03 (m, 4H, Ar-H), 9.73 (s, 1H, NH)

Anal. Calcd. for $C_{19}H_{20}N_2O_7$: C, 58.76; H, 5.19; N, 7.21. Found: C, 58.68; H, 5.19; N, 7.12.

Reduction of 5a

5a (0.5g, 1.5 mmole) was dissolved in ethanol (50 m*l*).

To the solution was added $NaBH_4$ (0.07g) at room temperature. The reaction mixture was stirred overnight and then the pale yellow precipitates were filtered and washed with water. The solid was dried in vacuo to give dimethyl 3-(2'-hydroxyethyl)-6-methyl-4-(3'-nitrophenyl)-1, 4-dihydropyridine-2, 5-dicarboxylate lactone (**7**).

yield: 0.21g (40.7%), mp: 209-211°C; IR (KBr): 3320 (NH), 1760 (C=O), 1710 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 0.76 (d, J=6 Hz, 3H, $-CH_3$), 2.32 (s, 3H, $-CH_3$), 3.46 (s, 3H, $-OCH_3$), 5.09 (s, 1H, C_4-H), 5.12 (q, J=6 Hz, 1H, -H), 7.56-8.10 (m, 4H, Ar-H), 9.56 (s, 1H, NH)

Anal. Calcd. for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.32; H, 4.68; N, 7.90.

Methyl 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (9)

A mixture of 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine 3,5-dicarboxylic acid 3-monomethyl ester (**8**, 2.5g) and 2-amino-1-butanol (2.5 m*l*) in toluene (50 m*l*) was heated to reflux for 4 hours. The solvent was evaporated in vacuo and the residue was separated on silica gel column (EtOAc/n-Hexane=1:2). The eluent was evaporated and the yellow solid was recrystalized from methanol.

yield: 1.53g (70.5%), mp: 114-117°C; IR (KBr): 3362 (NH), 1697 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.8 (s, 3H, $-CH_3$), 2.34 (s, 3H, $-CH_3$), 3.54 (s, 3H, $-OCH_3$), 4.6 (d, 2H, CH-CH), 5.34 (s, 1H, NH), 7.3-8.1 (m, 4H, Ar-H).

Synthesis of 6b by Friedel-Crafts acylation

To a solution of BF_3-etherate (3 m*l*, 2.4 eq.) in tetrahydrofuran (30 m*l*) was added ethyl oxalychloride (1.34 m*l*, 1.2 eq.). The reaction mixture was stirred for 30 min. To the mixture was added methyl 2,6-dimethyl-4-(3'-nitrophenyl)-1, 4-dihydropyridine-3-carboxylate (**9**, 2.88g, 0.01 mole) and then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched with water and the mixture was extracted with EtOAc (100 m*l*). The EtOAc layer was washed with water, brine and then dried over $MgSO_4$. The solvent was concentrated to give yellow solid. Recrystallized from ethanol.

yield: 2.98g (76.8%), mp: 158-160°C.

ACKNOWLEDGEMENT

This research was partially supported by the special research project, Ministry of Science and Technology, Korea.

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