

Synthesis of Antihypertensive Agents via Coupling Reaction of Benzothiazepinone and 1,4-Dihydropyridine Derivatives

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The synthesis of **3a**, **3b**, **7a** and **7b** from Benzothiazepinone and 1,4-dihydropyridine derivatives is described. Benzothiazepinone and 1,4-dihydropyridine derivatives were prepared according to literature procedure. The key reactions involve esterification and amidation of benzothiazepinone and 1,4-dihydropyridine derivatives.

Key words: Antihypertensive agents, Calcium channel blocker, Benzothiazepinone, 1,4-dihydropyridine.

INTRODUCTION

Compounds which interfere with the pathways of calcium utilization (calcium channel blockers) are of particular interest in recent years from both the therapeutic and basic scientific standpoints (Sato *et al.*, 1991; Taketa *et al.*, 1988; Fleckenstein, 1984; Sangiunetti *et al.*, 1984; Matsuki *et al.*, 1993). Therefore extensive efforts have been directed toward the synthesis of calcium channel blockers to allow their development as clinical drug candidates (Ruter *et al.*, 1985; Inoue *et al.*, 1991; Floyd *et al.*, 1992). The major pharmacological effect that selectively inhibits the influx of extracellular calcium through the L-type voltage-operated calcium channels (Taylor, 1987; Abbott, 1988; James *et al.*, 1987; Bondy *et al.*, 1988; Triggle *et al.*, 1987) can be organized into three general categories (Fig. 1).

- 1) 1,4-Dihydropyridines; Nifedipine, Nitrendipine
- 2) Phenylalkylamines; Verapamil
- 3) 1,5-Benzothiazepin-2-ones; Diltiazem

Diltiazem, a benzothiazepinone calcium antagonist which was launched for the first time in Japan 20 years ago, has been used throughout the world as an effective antianginal and antihypertensive agent.

The most extensively studied calcium channel blockers are the 1,4-dihydropyridines. Consequently, several dihydropyridine analogues are already available on the market for therapeutic uses (Annual Drug Data Report 1986~1991).

Our overall goal in this work has been to develop a better understanding of the structural parameters of 1,4-dihydropyridines and 1,5-benzothiazepin-2-ones. In our laboratory, we have prepared some potentially antihypertensive agents by the following structures (Fig. 2).

MATERIALS AND METHODS

General

Reactions requiring anhydrous conditions were performed with precaution for rigorous exclusion of air and moisture. Anhydrous tetrahydrofuran was distilled from sodium benzophenone ketyl prior to use. Thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F254 from EM reagents and visualized with 254-nm UV light or p-anisaldehyde-acetic acid. Flash column chromatography was carried out on silica gel (Merck, 230-400 mesh). The ¹H NMR spectra were recorded on Hitachi R-1100 and Bruker ARX-300. The chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane. Chemicals were purified, when necessary, according to the reported procedure (Perrin *et al.*, 1988).

(±)Cis-2,3-dihydro-5-[2-(dimethylamino)ethyl]-3-[2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid-3-methyl ester-5-carboxy]-2-(4-methoxyphenyl)-1,5-benzothiazepine-4(5H)-one (**3a**)

(±)Cis-2,3-dihydro-5-[2-(dimethylamino)ethyl]-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepine-4(5H)-one (300 mg, 0.8 mmol), 2,6-dimethyl-4-(3'-nitrophenyl)-

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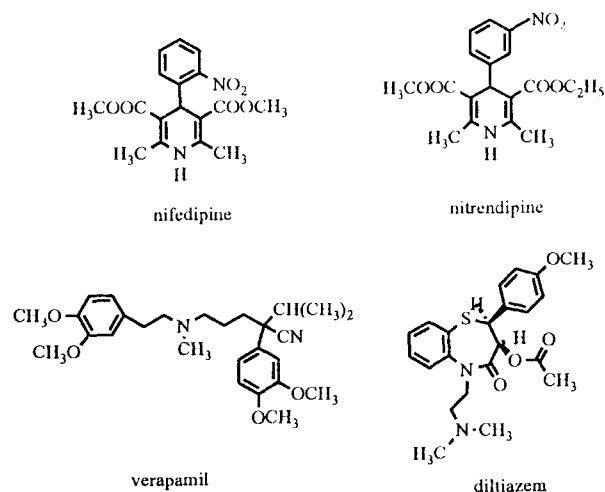


Fig. 1.

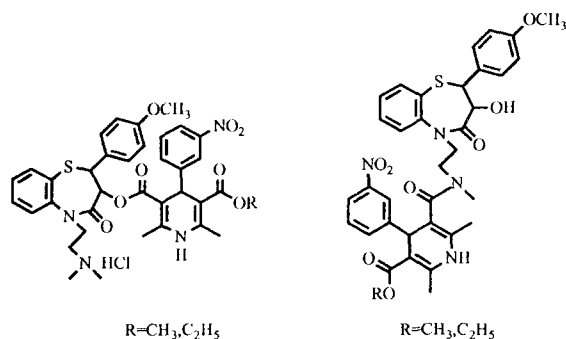


Fig. 2.

nyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-mono methyl ester (265 mg, 0.8 mmol), dicyclohexyl carbodiimide (DCC) (486 mg, 2.36 mmol), and dimethylaminopyridine (DMAP) (64 mg, 0.53 mmol) were dissolved in anhydrous methylene chloride (MC) (5 ml) under nitrogen atmosphere. The mixture was stirred at room temperature for 2 hr and refluxed for 24 hr. After cooling, the yellow crystal was obtained by filtration and the filtrate was evaporated under reduced pressure. The chromatography of residue afforded 300 mg of product (76.7%): IR 3350-3300, 3000, 1685, 1600-1500, 1420-1350, 1250-1200 cm⁻¹, ¹H NMR (CDCl₃) δ 8.0-7.0 (m, 8H), 5.15 (d, J=7.7 Hz, 1H), 4.98 (d, J=7.7 Hz, 1H), 4.5-4.1 (m, 2H), 3.9 (s, 3H), 3.5 (s, 3H), 2.9-2.3 (m, 2H), 2.3-1.9 (s, 6H), 1.7 (s, 6H).

(±) **Cis-2,3-dihydro-5-[2-(dimethylamino)ethyl]-3-[2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid-3-ethyl ester-5-carboxy]-2-(4-methoxyphenyl)-1,5-benzothiazepine-4(5H)-one (3b)**

(±) **Cis-2,3-dihydro-5-[2-(dimethylamino)ethyl]-3-hydroxy-2-(4-methoxy phenyl)-1,5-benzothiazepine-4(5H)-one (4)**

one (300 mg, 0.8 mmol), 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-monoethyl ester (276 mg, 0.8 mmol), DCC (434 mg) and DMAP (64 mg) were dissolved in anhydrous MC (10 ml) under nitrogen atmosphere. The mixture was stirred at room temperature for 2 hr and refluxed for 24 hr. After cooling, the yellow crystal was obtained by filtration and the filtrate was evaporated under reduced pressure. The chromatography of residue afforded 270 mg of product (48.2%): m.p. 98.4°C, IR 3350-3300, 3000, 1685, 1600-1500, 1420-1350, 1250-1200 cm⁻¹, ¹H NMR (CDCl₃) δ 8.0-7.0 (m, 8H), 5.15 (d, J=7.7 Hz, 1H), 4.98 (d, J=7.7 Hz, 1H), 4.5-4.1 (m, 2H), 4.10 (q, J=7.2 Hz, 2H), 3.9 (s, 3H), 2.9-2.3 (m, 2H), 2.3-1.9 (s, 6H), 1.7 (s, 6H), 1.30 (t, J=7.2 Hz, 3H).

(±) **Cis-2,3-dihydro-5-[2-(dimethylamino)ethyl]-3-acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepine-4(5H)-one (4)**

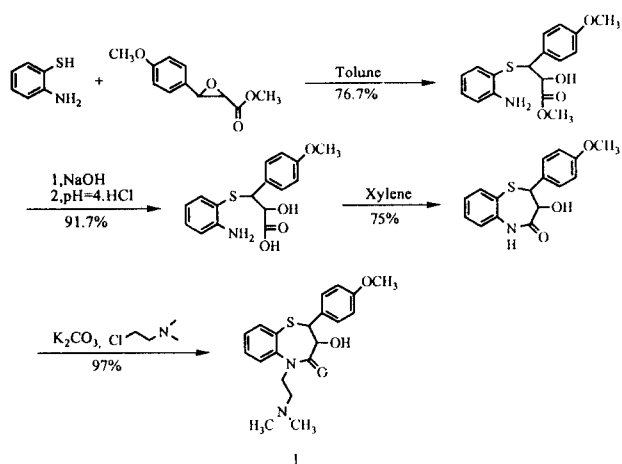
A mixture of (±) **cis-2,3-dihydro-5-[2-(dimethylamino)ethyl]-3-acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepine-4(5H)-one** (600 mg, 1.6 mmol), acetic anhydride (30 ml) and 2-3 drops of pyridine was stirred vigorously at 110-120°C for 3 hr. After cooling, the mixture was evaporated under reduced pressure and the residue was chromatographed on the silicagel column using methanol as an eluent to give product (600 mg, 89.8%): IR 3000, 1600-1500, 1300-1200 cm⁻¹, ¹H-NMR (CDCl₃) δ 8.0-7.0 (m, 3H), 5.2 (d, J=7.7 Hz, 1H), 4.9 (d, J=7.7 Hz, 1H), 4.0-3.8 (m, 2H), 3.7 (s, 3H), 2.7-2.4 (m, 2H), 1.9 (s, 3H).

(±) **Cis-2,3-dihydro-5-[2-[(2',2',2'-trichloroethoxy)methylamino]ethyl]-3-acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepine-4(5H)-one (5)**

To a solution of (±) **cis-2,3-dihydro-5-[2-(dimethylamino)ethyl]-3-acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepine-4(5H)-one** (300 mg, 0.72 mmol) in dry toluene (10 ml), trichloroethyl chloroformate (0.165 ml, 1.2 mmol) was added slowly and the mixture was refluxed for 16 hr. After cooling, the reaction mixture was evaporated under reduced pressure. The residue was chromatographed using hexane and ethyl acetate (1:1) to give a product (340 mg, 81.5%): m.p. 156.1°C, IR 3300-3100, 3000, 1720-1700, 1240-1200, 850-680 cm⁻¹, ¹H-NMR (CDCl₃) δ 7.5-6.5 (m, 8H), 5.2 (d, J=7.7 Hz, 1H), 4.9 (d, J=7.7 Hz, 1H), 4.4-3.9 (m, 4H), 4.3 (s, 2H), 3.9 (s, 3H), 1.9 (s, 3H).

(±) **Cis-2,3-dihydro-5-[2-(methylamino)ethyl]-3-acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepine-4(5H)-one (6)**

Zinc dust (65 mg, 1 mmol) was added to a solution of (±) **cis-2,3-dihydro-5-[2-[(2',2',2'-trichloroethoxy)methylamino]ethyl]-3-acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepine-4(5H)-one**

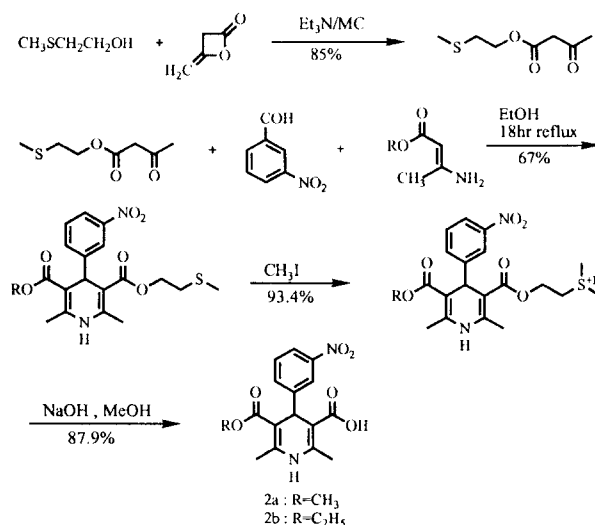


Scheme 1

thylamino] ethyl]-3-acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepine-4(5H)-one (300 mg, 0.59 mmol) in glacial acetic acid (5 ml) and stirred at 50°C for 24 hr. Then zinc dust (75 mg) was added more and the reaction mixture was refluxed for 2 hr. The acetic acid was evaporated under reduced pressure. After the residue was dissolved in ethyl acetate, zinc dust was removed by filtration and the residual mixture was evaporated under reduced pressure. The crude product was chromatographed using methanol to give product (180 mg, 87%): m.p. 111.8°C, IR 3000, 1600-1500, 1300-1200 cm^{-1} , ^1H NMR (CDCl_3) δ 8.0-7.0 (m, 8H), 5.2 (d, $J=7.7$ Hz, 1H), 4.9 (d, $J=7.7$ Hz, 1H), 4.6-4.3 (b, 1H), 4.5-4.1 (m, 2H), 3.9 (s, 3H), 2.5 (s, 3H), 2.9-2.3 (m, 2H), 1.9 (s, 3H).

(\pm) Cis-2,3-dihydro-5-[2-[[2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid-3-methyl ester-5-carbonyl] methylamino] ethyl]-3-acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepine-4(5H)-one (7a)

(\pm) Cis-2,3-dihydro-5-[2-(methylamino)ethyl]-3-acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepine-4(5H)-one (300 mg, 0.75 mmol), 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-monomethylester (250 mg, 0.75 mmol) and DCC (480 mg) were dissolved in anhydrous MC (10 ml) under nitrogen atmosphere. After Et_3N (25 μl) was added, the mixture was refluxed for 36 hr. The reaction mixture was evaporated under reduced pressure and chromatographed using MC and acetone (10:1) to give product (219 mg, 40.8%): m.p. 158.7°C, IR 3350-3300, 3000, 1690-1680, 1520-1500, 1410-1390, 1300-1200 cm^{-1} , ^1H NMR (CDCl_3) δ 8.0-7.0 (m, 12H), 5.14 (d, $J=7.7$ Hz, 1H), 5.05 (d, $J=7.7$ Hz, 1H), 4.4 (s, 3H), 4.2-4.0 (m, 4H), 3.7 (s, 3H), 3.5 (s, 3H), 2.2 (s, 6H), 1.9 (s, 6H).



Scheme 2

(\pm) Cis-2,3-dihydro-5-[2-[[2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid-3-ethyl ester-5-carbonyl] methylamino] ethyl]-3-acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepine-4(5H)-one (7b)

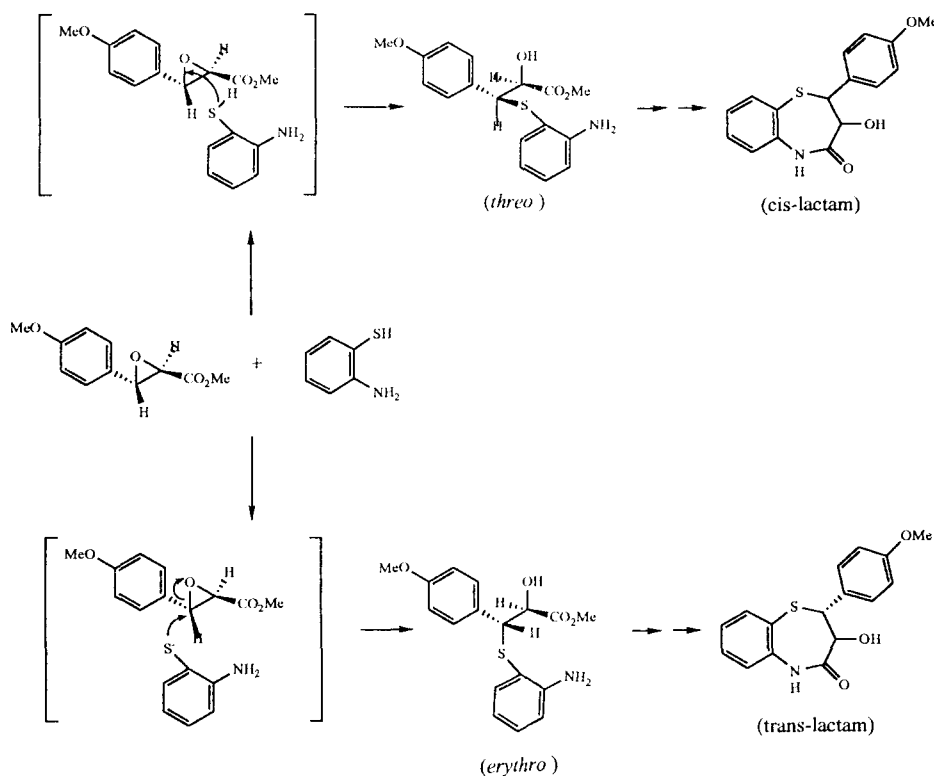
(\pm) Cis-2,3-dihydro-5-[2-(methylamino)ethyl]-3-acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepine-4(5H)-one (300 mg, 0.75 mmol), 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-monomethylester (260 mg, 0.75 mmol) and DCC (480 mg) were dissolved in anhydrous MC (10 ml) under nitrogen atmosphere. After Et_3N (25 μl) was added, the mixture was refluxed for 36 hr. The reaction mixture was evaporated under reduced pressure and chromatographed using MC and acetone (10:1) to give product (180 mg, 32.9%): m.p. 164.7°C, IR 3350-3300, 3000, 1690-1680, 1520-1500, 1410-1390, 1300-1200 cm^{-1} , ^1H NMR (CDCl_3) δ 8.0-7.0 (m, 12H), 5.14 (d, $J=7.7$ Hz, 1H), 5.05 (d, $J=7.7$ Hz, 1H), 4.4 (s, 1H), 4.15 (q, $J=7.2$ Hz, 2H), 4.0-3.5 (m, 4H), 3.7 (s, 3H), 2.2 (s, 6H), 1.9 (s, 3H), 1.34 (t, $J=7.2$ Hz, 3H).

RESULTS AND CONCLUSION

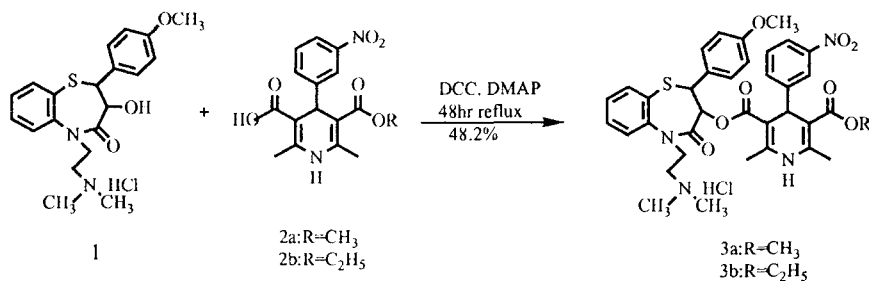
Compound **1** was prepared according to literature procedure (Takeda *et al.*, 1986) (Scheme 1).

The 1,4-dihydropyridine derivatives **2** were synthesized in 4 steps from diketene by the method of Scheme 2 (Suh *et al.*, 1989; Suh *et al.*, 1991). The reaction of 2-aminothiophenol with the glycidate afforded one stereoisomer of the ester in 76.7% yield. The stereochemistry of the ester could be determined on the basis of the ^1H NMR spectra of their corresponding lactams.

According to Inoue (Inoue *et al.*, 1984), the vicinal



Scheme 3



Scheme 4

coupling constant between the methine at C₂ and C₃ of lactams is about 6 Hz and 11 Hz for *cis*- and *trans*-isomers, respectively. From ¹H NMR analysis of our lactam, we concluded that *cis* isomer was produced almost exclusively (coupling constant of methine at C₂ and C₃ of lactam=7.7 Hz). The stereochemistry has shown that the reaction of glycidate with 2-aminothiophenol mainly gave the *threo*-ester, the *cis*-opening product resulting from attack of the thiol group from the open side of the oxirane ring (Inoue *et al.*, 1985) (Scheme 3).

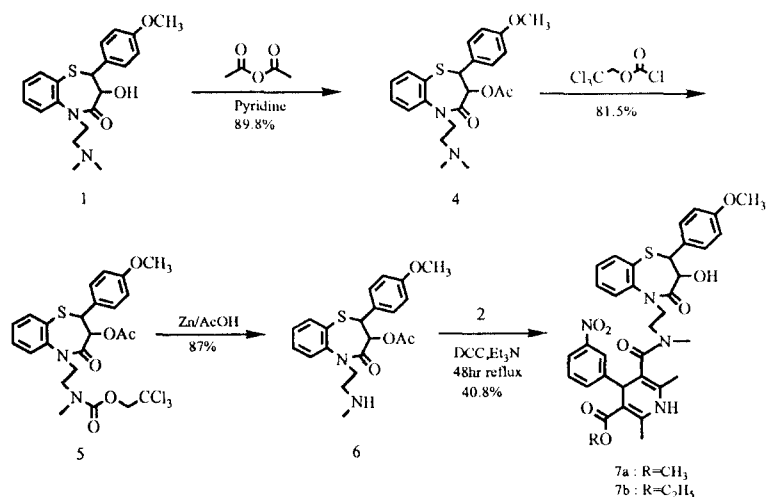
Treatment of **1** with **2a** (**2b**) in refluxing CH₂Cl₂ in the presence of DCC and DMAP afforded the desired compound **3a** (**3b**) in 48% yield (Scheme 4). The compound **7a** and **7b** shown were prepared by the pro-

cedure outlined in Scheme 5.

Acetylation of **1** is performed in acetic anhydride in the presence of the catalytic amount of pyridine at 110-120°C for 3 hr. Crude product from this reaction was refluxed with 2',2',2'-trichloroethyl chloroformate in toluene for 16 hr, followed by treatment of Zn in glacial acetic acid for 24 hr at 50°C to give **6**. The monomethylamine **6** was reacted with **2a** (**2b**) to give **7a** (**7b**).

ACKNOWLEDGEMENT

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Scheme 5

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