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Synthesis of Pyrido [4,3-f]-1,5-thiazepine as a Potential Antihypertensive Agent

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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. Its major pharmacological effect arises from the selective inhibition of 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). Therefore extensive efforts have been directed toward the development of more powerful antihypertensive drug by synthesis of various diltiazem derivatives as calcium channel blockers (Floyd, *et al.*, 1992; Inoue, *et al.*, 1991; Sato, *et. al.*, 1991).

Of the various developed diltiazem analogues, especially 8-chloro-1,5-benzodiazepin derivative, Clentiazem maleate (Inoue, *et al.*, 1991), showed more potent pharmalogical effect and longer half-life duration than diltiazem due to the introduction of electron withdrawing group on the phenyl moiety, presumably resulting in low electron density and high polarity. With the aim at this result and continuing our work (Ham *et. al.*, 1994), we herein report the efficient synthesis of the new diltiazem derivative with pyridine moiety instead of phenyl one because pyridine assumed an aspect of lower electron density and higher polarity in comparison with phenyl ring.

4-Amino-3-thiopyridine (7), which will be part of the new diltiazem derivative, was synthesized from 4-aminopyridine (3) as a starting material. In order to ortholithiate and introduce sulfur at 3 position, we protected 4-amino pyridine (3) with *tert*-butyldicarbonate in THF to give N-BOC pyridine (4) in 98% yield. This protected pyridine (4) was ortho-lithiated with *t*-BuLi in THF at -78°C -20°C and quenched with sulfur at -78°C followed by acidification to afford the N-BOC-4-amino-3-thiopyridine (6) via the intermediate anion (5), which was hydrolyzed with HCl to 4-amino-3-thiopyridine HCl salt (7) in 70% overall yield (Scheme 1).

4-Amino-3-thiopyridine HCl salt (7) was coupled with methyl *trans*-(±)-(4-methoxyphenyl) glycidate (Matsuki, *et al.*, 1993) in toluene and methanol to give one stereoisomer of the ester (8) which was hydrolyzed with KOH to the corresponding acid (9) in 51% overall yield. The stereochemistry of the acid (9) could be determined on the basis of the ^{1}H NMR spectra of its corresponding lactam.

In order to cyclize the acid (9) intramolecularly, we followed the standard method (Takeda, *et al.*, 1986) for synthesis of diltiazem by refluxing in xylene. However we failed the intramolecular cyclization by the above method due to the poor solubility of our compound in xylene. We carried out various methods using amide coupling reagents ($NaHCO_3$/DPPA in DMF (Boger, *et al.*, 1990), 1-HOBT/DCC in DMF/MC (Inoue, *et al.*, 1990),etc.) and finally we accomplished the cyclization by utilizing 1-hydroxybenzotriazole (1-

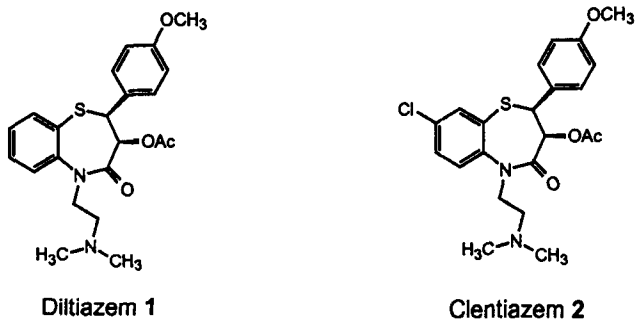

Fig. 1.

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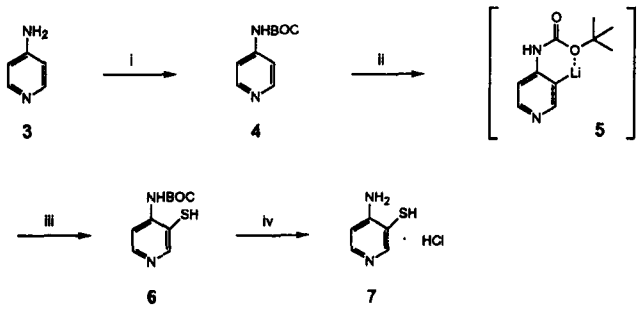
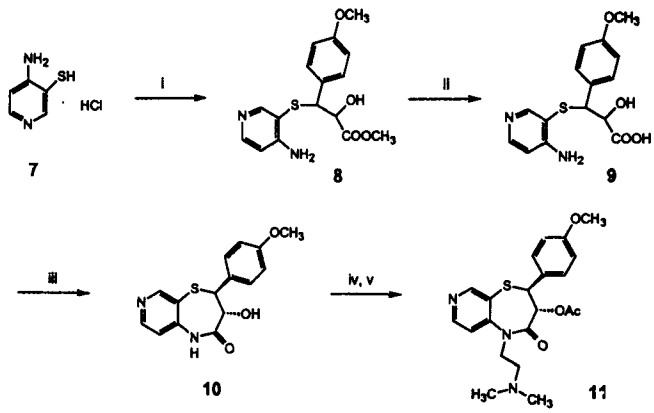


Reagents: i) $(BOC)_2O$, THF, reflux, 1.5hr (98%); ii) tert-BuLi, THF, -78°C, 15min, -20°C, 2hr; iii) S, THF, -78°C - rt, 1hr (72%); iv) 9.6M HCl, MeOH/H_2O, rt, 30min (97%).

Scheme 1.



Reagents: i) Methyl trans-3-(4-methoxyphenyl) glycidate, toluene/ methanol, reflux, 72hr; ii) KOH, EtOH, rt, 24hr (51%); iii) EDC, HOBT, DMF, rt, 16hr (26%); iv) N,N-Dimethylethyl chloride hydrochloride, K_2CO_3, DMF, 70-75°C, 20hr (63%); v) Acetic anhydride, pyridine, 60-65°C, 8hr (48%).

Scheme 2.

HOBT) and 1-ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride in DMF at room temperature to afford the desired lactam (10) in 26% yield.

According to Inoue (Inoue *et al.*, 1984), the vicinal coupling constant between the methine at C_2 and C_3 of lactams is about 6 Hz and 11 Hz for *cis*- and *trans*-isomer, respectively. From ^{1}H NMR analysis of our lactam, we concluded that trans isomer was produced almost exclusively (coupling constant of methine at C_2 and C_3 of lactam=11 Hz). The stereochemistry has shown that the reaction of glycidate with 4-amino-3-thiopyridine HCl salt (7) mainly gave the *erythro*-ester (8) by the trans-opening rather than *cis*-opening of the epoxide. This result was quite different with that Inoue reported about the synthesis of diltiazem previously (Inoue *et. al.*, 1985).

The lactam (10) was finally N-alkylated with N,N-dimethylethyl chloride in DMF and O-acylated with acetic anhydride in pyridine to afford the desired pyrido [4,3-f]-1,5-thiazepine-4(5H)-one (11) (mp 106-108°C; ^{1}H-NMR spectrum ($CDCl_3$): δ 2.03 (s, 3 H, $OCOCH_3$), 2.37 (s, 6 H, $N(CH_3)_2$), 2.58-2.64 (m, 2 H, CH_2), 2.77-2.88 (m, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 4.61 (d, 1 H, J=11 Hz, CH), 4.97 (d, 1 H, J=11 Hz, CH), 6.81-8.76 (m, 7 H, ArH); IR spectrum (KBr): 3620-3120, 2860, 1730, 1675, 1610 cm^{-1}.) in 30% overall yield (Scheme 2).

In summary, we synthesized the new diltiazem derivative, pyrido [4,3-f]-1,5-thiazepine-4(5H)-one, and developed the mild and efficient intramolecular macro cyclization method. Application of this general synthetic strategy to the synthesis of various diltiazem derivatives including heterocycle moiety is currently being pursued.

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