A STEREOSELECTIVE SYNTHESIS OF 1,5-DISUBSTITUTED THIENO[3',2':3,4]PIPERIDINO-[1,2-c]OXAZOLIDIN-3-ONES THROUGH N-OXAACYLIMINIUM ION CYCLIZATION

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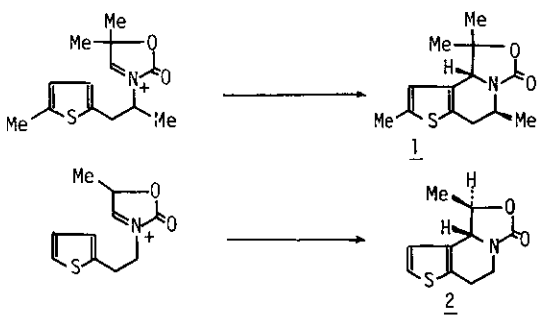
Abstract ——— A stereoselective synthesis of 1-phenyl- (5) and 5-methyl-1-phenyl-thieno[3',2':3,4]piperidino[1,2-c]oxazolidin-3-ones (8a,b) was achieved by reduction of the corresponding N-substituted 5-phenyloxazolidine-2,4-diones (4, 7a,b) with diisobutylaluminum hydride, followed by treatment of the reduction products with formic acid. Reduction of 8a,b with $LiAlH_4$ afforded the corresponding 4-(α-hydroxybenzyl)-6-methylthieno[3,2-c]pyridines (10a,b), respectively.

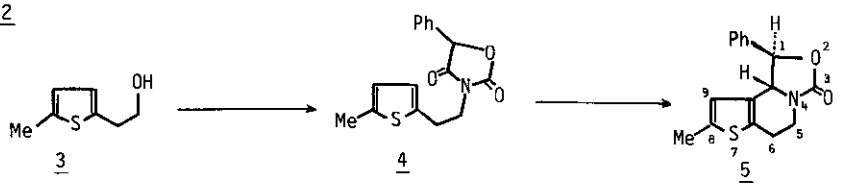
π-Cyclization of N-acyliminium ions has been documented as potent tool in a synthesis of various kinds of heterocyclic systems[1]. Recently, thieno[3,2-c]pyridines fused with oxazolidine[2,3] and pyrazine ring[4] were reported by this method. Thienopyridines are of interest from the point of view of pharmacological evaluation[5] and some of them are rich source of useful drugs[6]. We previously reported a stereoselective synthesis of the 5-methyl- (1)[2] and 1-methylthieno[3',2':3,4]-piperidino[1,2-c]oxazolidin-3-ones (2)[3] through N-oxaacyliminium ion cyclization (see Scheme 1). Although a number of stereochemical feature of these reactions have been delineated[1], the effect of two asymmetric centeres, N-(α)-position and α-position of iminium carbon, on their stereochemical course have received little attention[1,2]. We examined a cyclization of N-oxaacyliminium ions possessing substituents at N-(α)-position and α-position of iminium carbon leading to the title compounds in connection with a stereoselective synthesis of 4-(α-hydroxybenzyl)-6-methyl-thieno[3,2-c]pyridines. The results of our studies are described in this paper.

Scheme 1



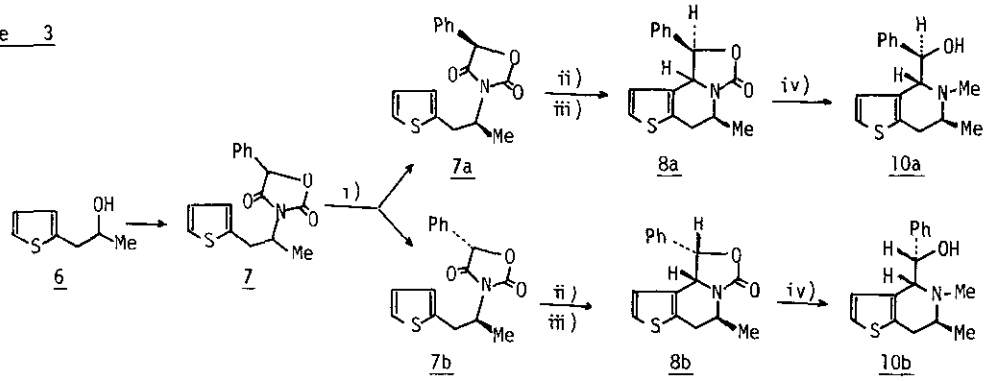
At the first stage, a stereoselective synthesis of 1-phenylthieno[3',2':3,4]piperidino[1,2-c]-oxazolidin-3-one (5) was examined. Condensation of the alcohol (3) with 5-phenyloxazolidine-2,4-dione[7] according to Mitsunobu's method[8] yielded the N-substituted product (4). Reduction of 4 with diisobutylaluminum hydride (DIBAH) in toluene at -78 °C, followed by treatment of the reduction product with formic acid gave 5 as a single product[9]. Thenylation smoothly proceeded from the opposite side of phenyl group and the relative configuration at 1-H and 9b-H could be assigned to be trans[2,3].

Scheme 2

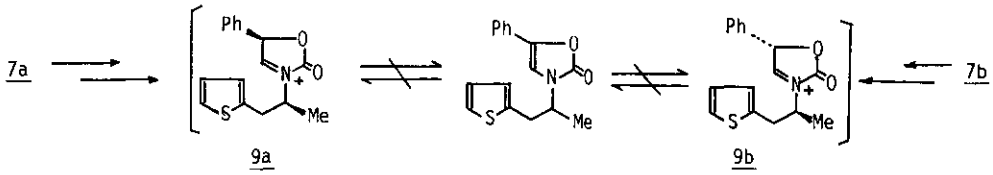


This method was applied to a synthesis of 1,5-disubstituted thieno[3',2':3,4]piperidino[1,2-c]-oxazolidin-3-ones. The alcohol (6) was coupled with 5-phenyloxazolidine-2,4-dione to yield 7 as a mixture of diastereoisomers. Separation of two isomers (7a and 7b) was completed by column chromatography on silica gel. One isomer (7a) was obtained as a crystal and the another one (7b) was as an oil. Treatment of the reduction product of 7a (7a, DIBAH, -78 °C) with formic acid gave 5-methyl-1-phenylthieno[3',2':3,4]piperidino[1,2-c]oxazolidin-3-one (8a) in 80 % yield as a single product. The same reaction starting with 7b afforded 8b in only 8 % yield without formation of 8a. In the formation of 8a and 8b, thenylation proceeded from the opposite side of methyl group. Low yield of 8b should be attributed to the steric hindrance of phenyl group, since thenylation occurred from the same side as phenyl group. The stereochemical assignment for 8a and 8b was based on the comparison of the ^{1}H NMR ($CDCl_3$) spectrum of 8a with that of 8b and their Dreiding stereomodel study. The signal due to 9-H of 8b was observed at considerably higher field (δ 5.80, d, J=5 Hz) relative to that of 8a (δ 6.78, d, J=5 Hz). This higher field shift should be apparently caused by the shielding effect of phenyl group at 1-position. The signal due to 1-H of 8a appeared at higher region (δ 5.14, d, J=8 Hz) than that of 8b (δ 5.87, d, J=8 Hz) owing to the shielding effect of thiophene ring. In the N-acyliminium ion cyclization, it was found that the effect of $A^{(1,3)}$ strain[10] on the stereochemical course could be responsible for the stereoselective synthesis of 8a and 8b. The effect of $A^{(1,3)}$ strain was found to play a more important role than the steric hindrance of phenyl group on the stereoselective N-acyliminium ion cyclization. These results indicate that the relative configuration of methyl and phenyl groups remains unchanged during N-acyliminium ion cyclization. These also demonstrate that iminium ion (9a) is not equilibrium in the another isomer (9a) and the cyclization rate is considerably fast.

Scheme 3



i) Separation, ii) DIBAH, iii) HCOOH, iv) $LiAlH_4$



Reduction of 8a and 8b with $LiAlH_4$ gave the corresponding 4-(α-hydroxybenzyl)-6-methylthieno[3,2-c]pyridines (10a and 10b), respectively, the hydroxyl group of which formed a hydrogen bond with eq.-oriented lone pair of electrons on N. In these compounds, methyl group at N takes ax.-oriented configuration. In the ^1H NMR ($CDCl_3$) spectrum of 10a, 3-H resonated at the much higher region (δ 5.20, d, J=6 Hz) relative to 3-H of 10b (δ 6.20, d, J=6 Hz) and 9-H of 8a (δ 6.78, d, J=5 Hz) because of the shielding effect of benzene ring. The signal due to 3-H of 10b appeared at down field relative to 9-H of 8b by releasing the shielding effect of benzene ring.

The results presented here might be applicable to a stereoselective synthesis of some poly-substituted nitrogen heterocycles.

EXPERIMENTAL

Melting points are uncorrected. ^1H NMR spectra were recorded on a Varian EM-390 instrument. Mass spectra were taken at an ionizing voltage of 70 eV on a Hitachi RMU-7L instrument. THF was distilled from $LiAlH_4$ before use. Toluene was dried over CaH_2 under reflux and distilled before use.

Synthesis of 4, 7a and 7b To a stirred mixture of alcohol (3)(2.84 g, 20 mmol), triphenylphosphine (5.76 g, 22 mmol), 5-phenyloxazolidine-2,4-dione (3.89 g, 22 mmol) and THF (30 ml) was added a solution of diisopropyl azodicarboxylate (4.48 g, 22 mmol) in THF (10 ml) under ice-cooling. In the preparation of 7, 6 (2.84 g, 20 mmol) was used instead of 3. After the stirring had been continued for 14 h at room temperature, the solvent was evaporated. The remaining residue was chromatographed on silica gel (30 g). For 4, elution with benzene-hexane (1:1) gave 4.7 g (78 %).

For preparation of 7a and 7b, ethyl acetate-hexane (1:4) was used as an eluent. Evaporation of the initial fraction (about 50 ml) yielded 7a. Successive fraction (about 45 ml) afforded a mixture of 7a and 7b. Finally, 7b was obtained as a pure state as an oil. Yields and physical data are summarized in the Tables 1 and 2.

General Procedure of Synthesis of 5, 8a and 8b To a stirred solution of 4 (or 7) (1.5 g, 5 mmol) in toluene (30 ml) was added DIBAH (1.28 g, 9 mmol, 6.1 ml of 25 % toluene solution) at -78 °C. After the stirring had been continued for 1 h at the same temperature, the mixture was decomposed with 5 % H_2SO_4 (40 ml) and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and evaporated. The remaining residue was treated with formic acid (15 ml) under stirring for 14 h at room temperature. The mixture was made basic with 28 % NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and evaporated. The remaining residue was chromatographed on silica gel (20 g). Elution with benzene gave 5 (or 8a,b). Yields and physical data are summarized in the Tables 1 and 2.

The 4-(α-Hydroxybenzyl)-6-methylthieno[3,2-c]pyridine (10a and 10b) To a stirred solution of $LiAlH_4$ (185 mg, 5 mmol) in THF (30 ml) was added a solution of 8a (or 8b) (285 mg, 1 mmol) in THF (10 ml) under ice-cooling. After the stirring had been continued for 14 h at room temperature, the mixture was decomposed with 10 % NaOH. After removal of the inorganic substance by filtration, the solvent was evaporated to yield 10a (or 10b). Yields and physical data are listed in the Tables 1 and 2.

Table 1. Yields, Mps and ^1H NMR Spectral Data of 4, 5, 7, 8 and 10

Compound	Yield (%)	mp (°C)	^1H NMR ($CDCl_3$) δ
4	78	74-75	2.40 (3H, s), 2.91-3.33 (2H, m), 3.83-3.93 (2H, m), 5.67 (1H, s), 6.58-6.69 (2H, m), 7.34-7.53 (5H, m)
5	80	119-120	2.37 (3H, s), 4.07-4.42 (3H, m), 4.78-4.87 (1H, m), 4.82 (1H, d, J=8 Hz), 5.13 (1H, d, J=8 Hz), 6.37 (1H, s), 7.51 (5H, s)
7a	25	74-75	1.53 (3H, d, J=7 Hz), 3.03-3.27 (1H, m), 3.49-3.77 (1H, m), 4.36-4.61 (1H, m), 5.53 (1H, s), 6.78-7.49 (8H, m)
7b	20	oil	1.53 (3H, d, J=7 Hz), 3.03-3.27 (1H, m), 3.53-3.82 (1H, m), 4.36-4.61 (1H, m), 5.57 (1H, s), 6.78-7.49 (8H, m)
8a	80	132-133	1.23 (3H, d, J=7 Hz), 2.62-2.80 (1H, m), 2.91-3.23 (1H, m), 4.49-4.80 (1H, m), 4.93 (1H, d, J=8 Hz), 5.14 (1H, d, J=8 Hz), 6.78 (1H, d, J=5 Hz), 7.24 (1H, d, J=5 Hz), 7.50-7.63 (5H, m)
8b	8	185-186	1.24 (3H, d, J=7 Hz), 2.53-2.71 (1H, m), 3.13-3.39 (1H, m), 4.48-4.79 (1H, m), 5.18 (1H, d, J=8 Hz), 5.80 (1H, d, J=5 Hz), 5.87 (1H, d, J=8 Hz), 6.82 (1H, d, J=5 Hz), 7.12-7.38 (5H, m)
10a	93	151-152	1.34 (3H, d, J=7 Hz), 2.39 (3H, s), 2.64-2.73 (2H, m), 3.37-3.78 (1H, m), 3.60 (1H, d, J=10 Hz), 4.50 (1H, d, J=10 Hz), 5.20 (1H, d, J=6 Hz), 6.83 (1H, d, J=6 Hz), 7.39 (5H, broad s)
10b	92	oil	0.99 (3H, d, J=7 Hz), 2.44 (3H, s), 2.56-2.64 (2H, m), 2.94-3.18 (1H, m), 3.88 (1H, d, J=5 Hz), 5.09 (1H, d, J=5 Hz), 6.26 (1H, d, J=6 Hz), 6.96 (1H, d, J=6 Hz), 7.41 (5H, s)

Table 2. Mass Spectral (M^+) and Analytical Data of 4, 5, 7, 8 and 10

Compound	Formula	MS m/e (M^+)	Microanalyses (Calcd.) C	H	N
4	$C_{16}H_{15}O_3NS$	301	63.55 (63.77)	4.90 (5.02)	4.60 (6.65)
5	$C_{16}H_{15}O_2NS$	285	67.24 (67.34)	5.23 (5.30)	4.85 (4.91)
7a	$C_{16}H_{15}O_3NS$	301	63.53 (63.77)	4.93 (5.02)	4.60 (4.65)
7b	$C_{16}H_{15}O_3NS$	301[a]			
8a	$C_{16}H_{15}O_2NS$	285	67.20 (67.34)	5.22 (5.30)	4.83 (4.91)
8b	$C_{16}H_{15}O_2NS$	285	67.35 (67.34)	5.16 (5.30)	4.75 (4.91)
10a	$C_{16}H_{19}ONS$	273	70.23 (70.29)	7.02 (7.01)	5.10 (5.12)
10b	$C_{16}H_{19}ONS$	b			

a High resolution MS, m/e 301.0763 (M^+); Calcd for $C_{16}H_{15}O_3NS$: 301.0771.

b Electron impact MS did not give M^+, but CI MS gave M^++1 at m/z 274.

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