SYNTHESIS OF THIENO[3,4-c]PYRIDINE AND THIENO[3,4-c]AZEPINE DERIVATIVES BY N-ACYLIMINIUM ION-INDUCED CYCLIZATION

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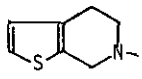
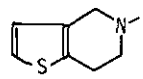
Abstract —— Reduction of N-[2-(3-thienyl)]ethylthiazolidine-2,4-diones (3a and 3b) with diisobutylaluminum hydride followed by treatment of the reduction products with formic acid at 60°C for 14 h yielded the corresponding thieno[3,4-c]pyridines (5a and 5b), respectively. In a similar way, thieno[3,4-c]pyridines (5c-5e) and thieno[3,4-c]azepines (9a, 9b and 9d) were obtained from the corresponding N-substituted hydroxyoxazolidinone, hydroxyimidazolidinones and hydroxythiazolidinones.

The [c]fused systems of thienopyridines, isosteric compounds of isoquinolines, have been of interest to medicinal chemists because of their potential pharmacological activities[1] and considerable number of their derivatives have been prepared[1]. Although thieno[2,3-c]- (1a) and thieno[3,2-c]-pyridines (1b) are easily obtained by the similar methodology to the isoquinoline synthesis[1,2] such as Bischler-Napieralski reaction, Pictet-Spengler reaction, Pictet-Gams reaction and Pomerantz-Fritsch reaction, the [3,4-c]series (1c) are difficult to prepare by those methods[3]. We investigated a facile synthesis of thieno[3,4-c]pyridines (5) and thieno[3,4-c]azepines (9) by π-cyclization of N-acyliminium ion intermediates[4,5]. The results of our studies are described in this paper.



1a



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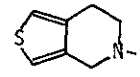
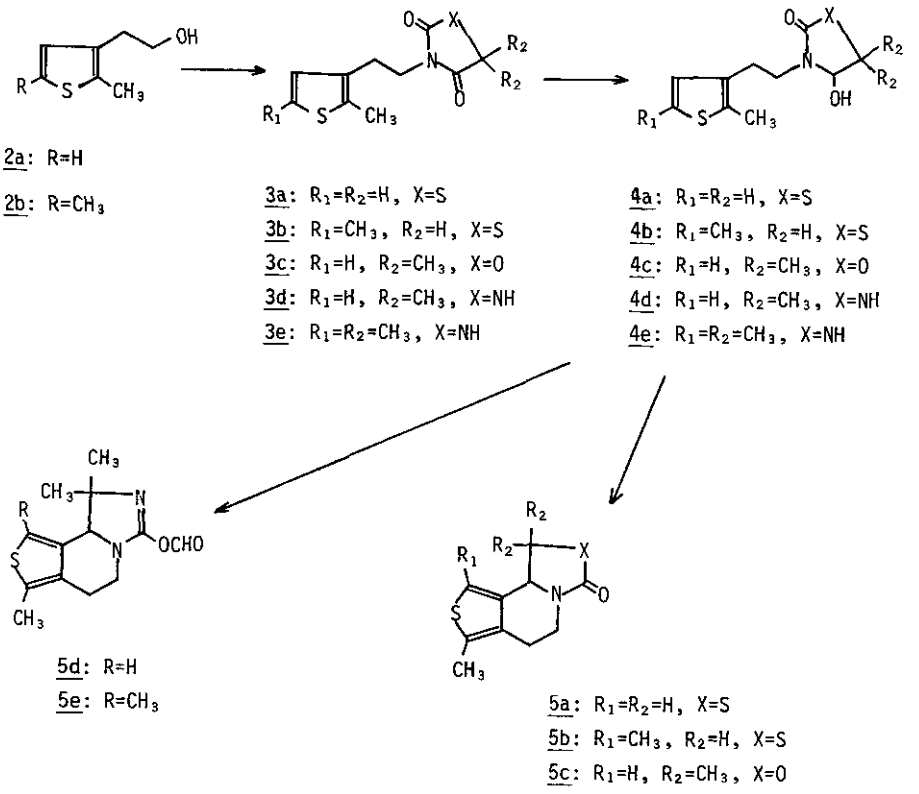


1c

The precursors for the N-acyliminium ions were prepared as follows. Condensation of 2-(3-thienyl)-ethyl alcohols (2a and 2b) with thiazolidine-2,4-dione by the Mitsunobu reaction[6] using diisopropyl azodicarboxylate provided the corresponding N-substituted thiazolidine-2,4-diones (3a and 3b), respectively. In a similar way, N-substituted 5,5-dimethyloxazolidine-2,4-dione (3c) and 5,5-dimethylhydantoins (3d and 3e) were obtained from 5,5-dimethyloxazolidine-2,4-dione and 5,5-dimethylhydantoin. These N-substituted products (3a-3e) were reduced with diisobutylaluminum hydride to give the corresponding 4-hydroxy derivatives (4a-4e), which were used for the following cyclization reaction without purification (see Scheme 1).

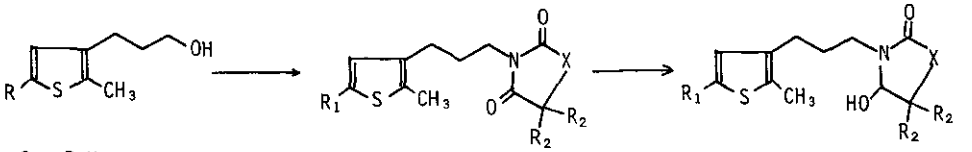
Cyclization of 4a and 4b with formic acid at 60°C[7] for 14 h afforded the thieno[3,4-c]pyridines (5a and 5b), respectively. In a similar way, 4c was also treated with formic acid to give the desired cyclization product (5c). In the cyclization reaction of 4d and 4e, the enol formates (5d and 5e) were obtained[8], respectively.

Scheme 1



This method was extensively applied to a synthesis of thieno[3,4-c]azepine derivatives (9). The N-substituted hydroxythiazolidinones (8a and 8b) and hydroxyimidazolidinones (8c and 8d) were prepared from 6a and 6b according to the method described for 4 from 2 as outlined in the Scheme 2. Cyclization of 8a and 8b was carried out by heating with trifluoroacetic acid[9] at 60°C for 14 h to yield the corresponding thieno[3,4-c]azepine derivatives (9a and 9b), respectively. However, in the case of 8c, dimerization product (10) was obtained and formation of the desired cyclization product (9c) was not observed. It would be most plausible that C-C bond formation for dimerization occurred at the 5-position, since 8d gave the normal cyclization product (9d) by blocking the 5-position with methyl group.

Scheme 2

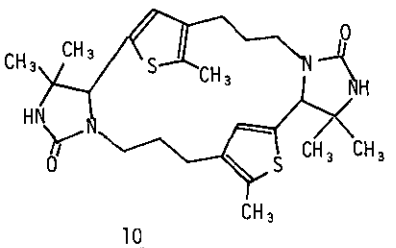


6a: R=H

6b: R=CH_3

7a: R_1=R_2=H, X=S
7b: R_1=CH_3, R_2=H, X=S
7c: R_1=H, R_2=CH_3, X=NH
7d: R_1=R_2=CH_3, X=NH

8a: R_1=R_2=H, X=S
8b: R_1=CH_3, R_2=H, X=S
8c: R_1=H, R_2=CH_3, X=NH
8d: R_1=R_2=CH_3, X=NH



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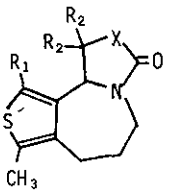

9a: R_1=R_2=H, X=S
9b: R_1=CH_3, R_2=H, X=S
9c: R_1=H, R_2=CH_3, X=NH
9d: R_1=R_2=CH_3, X=NH

EXPERIMENTAL

Melting points are uncorrected. ^{1}H 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.

General Procedure for a Synthesis of 3 and 7 To a stirred mixture of alcohol (2 or 6; 20 mmol), thiazolidine-2,4-dione (2.57 g, 22 mmol), triphenylphosphine (5.76 g, 22 mmol) and THF (30 ml) was added a solution of diisopropyl azodicarboxylate (4.48 g, 22 mmol) under ice-cooling. After the stirring had been continued for 14 h at room temperature, the solvent was evaporated. The resulting residue was chromatographed on silica gel (30 g) by using benzene-hexane (1:1) as an eluent. The products were carefully collected by monitoring with t.l.c. to give the corresponding N-substituted products (3a, 3b, 7a, 7b). 3d, 3e, 7c and 7d were obtained by the same way as above by using 5,5-dimethylhydantoin (2.82 g, 22 mmol) instead of thiazolidine-2,4-dione. For a synthesis of 3c, 5,5-dimethyloxazolidine-2,4-dione (2.84 g, 22 mmol) was used. Yields, mp and ^{1}H NMR ($CDCl_3$) spectral data of 3 and 7 were listed in the Table 1. Mass spectral and analytical data were shown in the Table 2.

Table 1. Yields, mp and ^1H NMR Spectral Data of 3 and 7

Compound	Yield (%)	mp (°C)	^1H NMR ($CDCl_3$) δ
3a	74	78-79	2.41 (3H, s), 2.76-2.93 (2H, m), 3.69-3.90 (2H, m), 3.90 (2H, s), 6.90 (1H, d, J=6 Hz), 7.08 (1H, d, J=6 Hz)
3b	75	76-77	2.33 (3H, s), 2.40 (3H, s), 2.67-2.89 (2H, m), 3.68-3.84 (2H, m), 3.78 (2H, s), 6.56 (1H, s)
3c	68	oil	1.37 (6H, s), 2.41 (3H, s), 2.37-3.03 (2H, m), 3.66-3.82 (2H, m), 6.87 (1H, d, J=6 Hz), 7.08 (1H, d, J=6 Hz)
3d	70	oil	1.33 (6H, s), 2.42 (3H, s), 2.83-3.00 (2H, m), 3.64-3.81 (2H, m), 6.91 (1H, d, J=6 Hz), 7.08 (1H, d, J=6 Hz)
3e	72	87-88	1.37 (6H, s), 2.34 (3H, s), 2.38 (3H, s), 2.40-2.57 (2H, m), 3.59-3.77 (2H, m), 6.54 (1H, s)
7a	76	53-54	1.76-2.01 (2H, m), 2.37 (3H, s), 2.50-2.67 (2H, m), 3.60-3.80 (2H, m), 3.87 (2H, s), 6.87 (1H, s, J=6 Hz), 7.06 (1H, d, J=6 Hz)
7b	73	oil	1.74-2.04 (2H, m), 2.27-2.58 (2H, m), 2.27 (3H, s), 2.38 (3H, s), 3.58-3.73 (2H, m), 3.84 (2H, s), 6.51 (1H, s)
7c	70	77-78	1.42 (6H, s), 1.76-2.09 (2H, m), 2.37 (3H, s), 2.49-2.67 (2H, m), 3.49-3.66 (2H, m), 6.90 (1H, d, J=6 Hz), 7.07 (1H, d, J=6 Hz)
7d	70	86-87	1.39 (6H, s), 1.70-2.04 (2H, m), 2.28 (3H, s), 2.38 (3H, s), 2.28-2.56 (2H, m), 3.47-3.62 (2H, m), 6.52 (1H, s)

Table 2. Mass Spectral (M^+) and Analytical Data of 3 and 7

Compound	Formula	MS m/e (M^+)	Microanalysis (Calcd.) C (%)	H (%)	N (%)
3a	$C_{10}H_{11}NO_2S_2$	241	49.92 (49.77)	4.64 (4.59)	5.71 (5.80)
3b	$C_{11}H_{13}NO_2S_2$	255	51.91 (51.74)	5.22 (5.13)	5.38 (5.49)
3c	$C_{12}H_{15}NO_3S$	253			
3d	$C_{12}H_{16}N_2O_2S$	252			
3e	$C_{13}H_{18}N_2O_2S$	266	58.57 (58.62)	6.78 (6.81)	10.49 (10.52)
7a	$C_{11}H_{13}NO_2S_2$	255	51.48 (51.74)	5.08 (5.13)	5.53 (5.49)
7b	$C_{12}H_{15}NO_2S_2$	269			
7c	$C_{13}H_{18}N_2O_2S$	266	58.39 (58.62)	6.77 (6.81)	10.41 (10.52)
7d	$C_{14}H_{20}N_2O_2S$	280	59.90 (59.97)	7.21 (7.19)	10.11 (9.99)

General Procedure for a Synthesis of 5, 9 and 10 To a stirred solution of 3 (or 7) (10 mmol) in toluene (40 ml) was added diisobutylaluminum hydride (2.41 g, 11.48 ml of 25 % toluene solution, 17 mmol) 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 (50-60 ml) and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and evaporated. The remaining residue, without purification, was treated with formic acid (20 ml) at 60°C for 14 h. For a synthesis of 9 and 10, trifluoroacetic acid was used instead of formic acid at the same temperature. After the reaction, 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 (10 g) by using benzene as an eluent. Removal of the solvent gave the corresponding cyclization products. Yields, mp and ^{1}H NMR of 5, 9 and 10 were listed in the Table 3 and mass spectral and analytical data were shown in the Table 4.

Table 3. Yields, mp and ^{1}H NMR Spectral Data of 5, 9 and 10

Compound	Yield (%)	mp (°C)	^{1}H NMR ($CDCl_3$) δ
5a	74	144-145	2.37 (3H, s), 2.66-2.88 (2H, m), 3.10-3.33 (2H, m), 3.57-3.77 (1H, m), 4.30-4.52 (1H, m), 4.91 (1H, d,d, J=7 and 9 Hz), 6.92 (1H, s)
5b	70	oil	2.28 (3H, s), 2.37 (3H, s), 2.59-2.87 (2H, m), 3.01-3.27 (2H, m), 3.60-3.80 (1H, m), 4.33-4.53 (1H, m), 4.90 (1H, d,d, J=6 and 10 Hz)
5c	68	138-139	1.04 (3H, s), 1.67 (3H, s), 2.38 (3H, s), 2.61-3.04 (3H, m), 4.09-4.31 (1H, m), 4.70 (1H, s), 6.80 (1H, s)
5d	58	154-155	1.37 (3H, s), 1.90 (3H, s), 2.37 (3H, s), 2.62-3.10 (3H, m), 4.24-4.44 (1H, m), 4.58 (1H, s), 6.90 (1H, s)
5e	55	112-113	1.05 (3H, s), 1.93 (3H, s), 2.27 (3H, s), 2.38 (3H, s), 2.54-2.68 (3H, m), 4.22-4.42 (1H, m), 4.70 (1H, s)
9a	63	120-122	1.67-1.93 (2H, m), 2.37 (3H, s), 2.63-3.39 (3H, m), 3.47-3.57 (2H, m), 4.17-4.41 (1H, m), 4.95 (1H, t, J=7 Hz), 7.00 (1H, s)
9b	60	194-195	1.86-2.11 (2H, m), 2.32 (3H, s), 2.36 (3H, s), 2.53-2.93 (3H, m), 3.19-3.31 (2H, m), 3.88-4.24 (1H, m), 5.10 (1H, d,d, J=7 and 10 Hz)
9d	55	238-239	0.99 (3H, s), 1.47 (3H, s), 2.30 (3H, s), 2.34 (3H, s), 2.56-2.72 (5H, m), 3.71-3.97 (1H, m), 4.77 (1H, s)
10	55	> 280	1.03 (6H, s), 1.32 (6H, s), 1.56-1.94 (4H, m), 2.27 (6H, s), 2.38-2.59 (6H, m), 3.23-3.58 (2H, m), 6.54 (2H, m)

Table 4. Mass Spectral (M^+) and Analytical Data of 5, 9 and 10

Compound	Formula	MS m/e (M^+)	Microanalysis (Calcd.) C (%)	H (%)	N (%)
5a	$C_{10}H_{11}NOS_2$	225	53.25 (53.30)	4.88 (4.92)	6.32 (6.22)
5b	$C_{11}H_{13}NOS_2$	239			
5c	$C_{12}H_{15}NO_2S$	237	60.68 (60.73)	6.31 (6.37)	5.98 (5.90)
5d	$C_{13}H_{16}N_2O_2S$	264	59.00 (59.06)	6.17 (6.10)	10.57 (10.60)
5e	$C_{14}H_{18}N_2O_2S$	278	60.32 (60.40)	6.56 (6.51)	9.99 (10.06)
9a	$C_{11}H_{13}NOS_2$	239	55.25 (55.19)	5.44 (5.47)	5.83 (5.85)
9b	$C_{12}H_{15}NOS_2$	253	56.64 (56.88)	5.90 (5.97)	5.61 (5.53)
9d	$C_{14}H_{20}N_2OS$	264	63.67 (63.50)	7.64 (7.63)	10.64 (10.60)
10	$C_{26}H_{36}N_4O_2S_2$	500	62.15 (62.36)	7.25 (7.25)	11.19 (11.19)

REFERENCES AND NOTES

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2. For recent examples; J.-P Maffarand and R. Boigegrain, Heterocycles, 12, 1479 (1979); K. Satake, T. Imai, M. Kimura, and S. Morosawa, Heterocycles, 16, 1271 (1981).
3. The [3,4-c]series have been prepared from 3,4-disubstituted pyridines or 3,4-disubstituted thiophenes through cyclization of thiophene ring or pyridine ring, respectively.
4. J. A. M. Hamersma and W. N. Speckamp, Tetrahedron, 38, 3255 (1982), and references cited therein.
5. H. Kohn and Z.-K. Liao, J. Org. Chem., 47, 2787 (1982).
6. O. Mitsunobu, M. Wada, and T. Sano, J. Am. Chem. Soc., 94, 679 (1972).
7. The cyclization products were not obtained at room temperature but dehydration products were yielded.
8. This reaction was examined several times under the same conditions. In only one case, small quantity of the normal cyclization products without formylation were obtained accompaning with 5d and 5e.
9. In this reaction, the use of formic acid afforded the dehydration product.

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