CONDENSED THIENOPYRIMIDINES 5.[1a] STUDIES ON THE THERMAL CYCLIZATION OF VARIOUS ORTHO-FORMYLTHIOPHENECARBAMATES WITH ETHANOLAMINE

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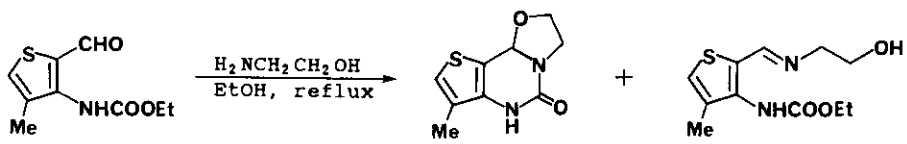
Abstract——Condensation of various ortho-formylthiophene-carbamates with ethanolamine afforded angular annelated tricyclic oxazolothienopyrimidine derivatives, 2,3,6,9b-tetrahydro-5H-oxazolo[3,2-c]thieno[2,3-e]-, and [3,2-e]pyrimidin-5-ones (2), which have new heterocyclic ring systems. The reaction mechanism on the formation of 2 is discussed.

It is well known that a number of thienopyrimidine analogues show various biological activities.[2] Recently we reported the synthesis of 2,3-dihydro-5H-oxazolo[3,2-a]thieno[3,2-d]pyrimidin-5-one derivatives having gastric anti-secretory activity.[1b]

In the course of the synthesis of 2,3-dihydro-5H-oxazolo[3,2-a]thienopyrimidine derivatives, we found that the reactions of some ortho-formylthiophenecarbamates with ethanolamine under refluxing in EtOH gave angular annelated tricyclic oxazolothienopyrimidine derivatives besides the anticipated Schiff's bases.[1a] The reaction of ethyl N-(2-formyl-4-methyl-3-thienyl)carbamate (1c) with ethanolamine, for example, gave 7-methyl-2,3,6,9b-tetrahydro-5H-oxazolo[3,2-c]thieno[2,3-e]-pyrimidin-5-one (2c) and the desired Schiff's base (3c) in 71% and 19% yields, as illustrated in Chart 1. However, there have been no systematic studies on the



1c 2c 3c

Chart 1

formation of this type of angular annelated oxazolothienopyrimidine derivatives.

The present paper describes the reactions between various ortho-formylthiophene-carbamates and ethanolamine in detail.

Initially, in order to clarify the defferences in reactivity between thiophene derivative and benzene one, the reaction of ethyl N-(2-formylphenyl)carbamate (4)[3] or 1 with ethanolamine was carried out (Chart 2). The reaction of 4 with ethanolamine under refluxing in EtOH afforded 2-hydroxyethylimine derivative (5). The Schiff's base (5) was heated under refluxing in N,N-dimethylformamide (DMF) to give a tricyclic compound (6).

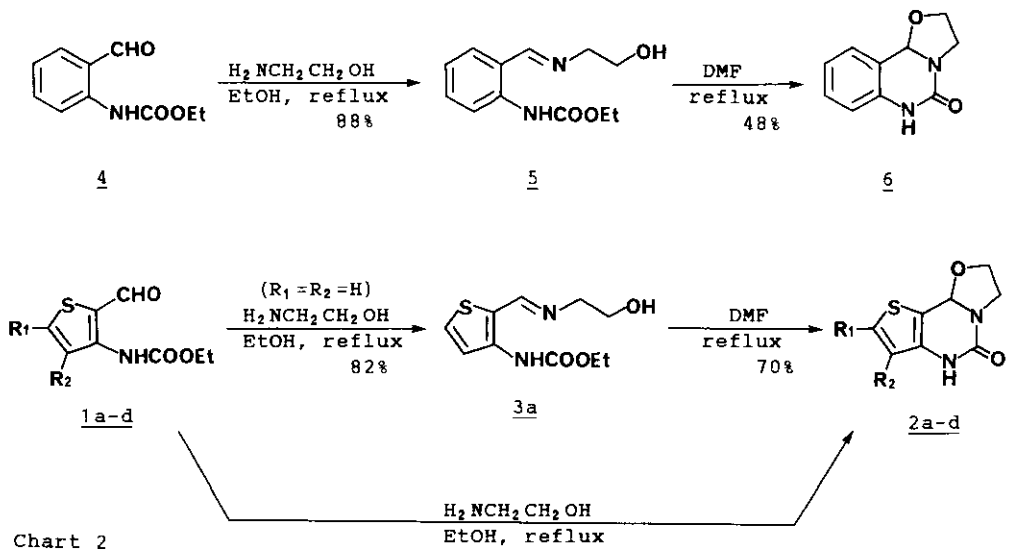
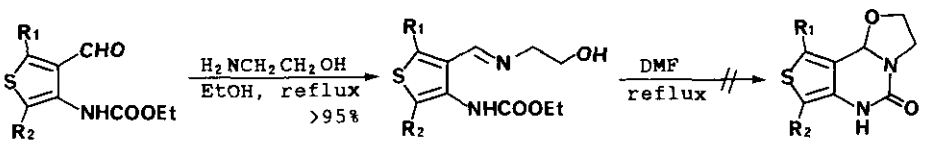


Chart 2

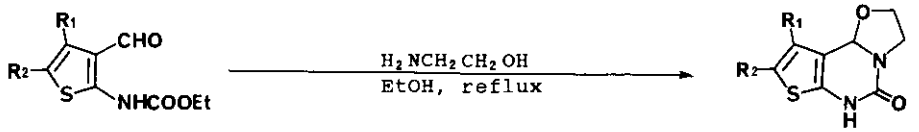
The reaction of 1a[1a] with ethanolamine under refluxing in EtOH gave only 2-hydroxyethylimine derivative (3a)[1a] in excellent yield. The tricyclic analogue (2a) was obtained by refluxing a solution of 3a in DMF. The reactivity of 1a with ethanolamine is similar to that of 4 in the formation of the stable 2-hydroxyethyl-imine. On the other hand, the reactions of other 2-formylthiophene-3-carbamate analogues (1b-d)[1a] with ethanolamine afforded directly angular annelated tricyclic analogues (2b-d) under refluxing in EtOH (Table 1). In 2-formylthiophene-3-carbamate derivatives (1a-d), therefore, it was found that 1a exhibited a different reactivity from the other derivatives (1b-d). The yields of 2b-d from 1b-d were affected by the presence of alkyl-substituents on the thiophene ring. Methyl-substituted derivatives (1c-d) at R_2 gave 2c-d in better yields than an unsubstituted one (2b), and especially 1a did not give 2a under refluxing in EtOH.

Table 1 Investigation of the Reaction Condition for Synthesis of 2 or 3 under Refluxing in EtOH

Starting Material	R_1	R_2	Product	Reaction Time (h)	Yield of isolated 2 or 3 (%)
1a	H	H	3a	7	82
1b	Me	H	2b	4	21
1c	H	Me	2c	2	71
1d	Me	Me	2d	1	87
1e	H	H	3e	7	quant.
1f	Me	H	3f	7	95
1g	H	Et	3g	7	quant.
1h	Me	Me	3h	7	quant.
1i	H	H	2i	3	40
1j	H	Me	2j	1.5	37



1e-h 3e-h 2e-h



1i-j 2i-j

Chart 3

In contrast with the reactions of 1a-d, the reactions of 4-foymylthiophene-3-carbamate derivatives (1e-h)[1a] with ethanolamine gave the Schiff's bases (3e-h) in excellent yields as whole products, regardless of the existence of alkyl-substituents on the thiophene ring (Chart 3). However, attempted ring closures of 3e-h to tricyclic compounds (2e-h) were unsuccessful.

Tricyclic compounds (2i-j) were easily obtained from the reactions of 3-formylthiophene-2-carbamates (1i-j)[1a] with ethanolamine under refluxing in EtOH (Table 1).

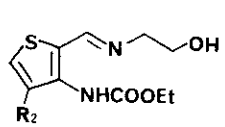
We investigated the utilization of various organic solvents on this reaction (Table 2). It was observed that 1a gave only dehydrated product (3a) at a temperature below 150℃, regardless of the species of organic solvent. Under refluxing at a temperature above 150℃, cyclized product (2a) was formed. Under refluxing in DMF, 2a was obtained in 70% yield, together with a trace amount of 3a.

Table 2 Solvent Effects in the Reaction of 1a with Ethanolamine

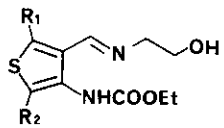
Run	Solvent	Temperature (℃)	Time (h)	Product (Isolated Yield, %)
1	THF	reflux	7	3a (94)
2	EtOH	reflux	7	3a (82)
3	Benzene	reflux	6	3a (91)
4	MIBK[a)]	reflux	6	3a (90) + 2a (trace)
5	Xylene	reflux	7	3a (65) + 2a (trace)
6	DMF	100	6	3a (64)
7	DMF	reflux	6	3a (trace) + 2a (70)

a) 4-Methyl-2-pentanone.

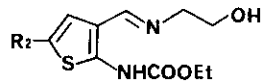
Table 3 Uv Spectral Data for 2-Hydroxyethylimino Dervatives (3 and 5)



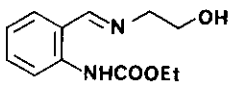
3a,c



3e,h



3j

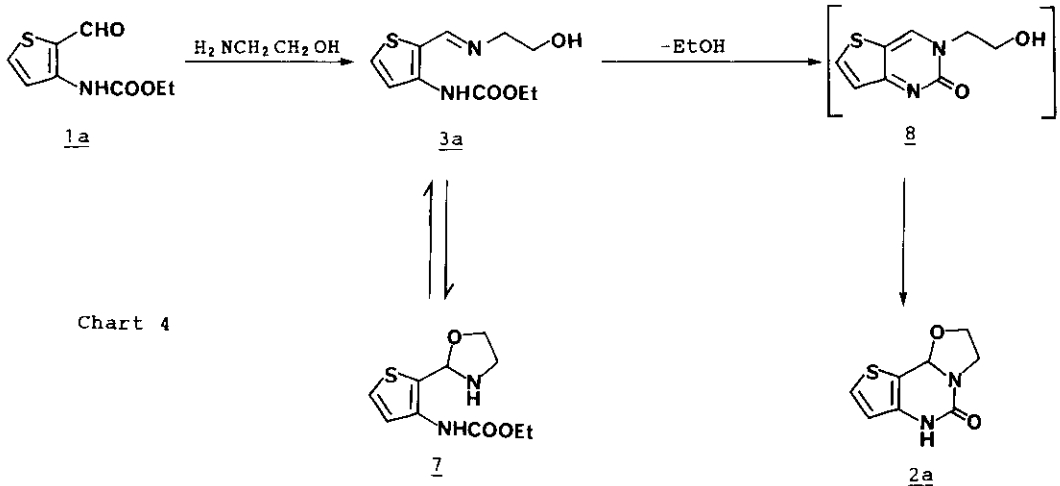


5

Compd. No.	R_1	R_2	Uv λ (MeOH), nm (ε)
3a[a)]		H	232 (5800), 280 (12900), 299 (12400)
3c[a)]		Me	285 (6800)
3e[a)]	H	H	230 (30000), 234 (29200), 248 (sh,13900)
3h[a)]	Me	Me	229 (20000), 257 (11400)
3j[a)]		Me	237 (23100), 252 (12000), 320 (5700)
5			226 (44900), 232 (46500), 260 (12000), 268 (9600) 314 (4400)

a) Ref 1a.

In order to obtain mechanistic information concerning the different reactivities between 3a-d,i-j and 3e-h, ultraviolet (uv) spectra of 3a,c,e,h,j[4] and 5 were measured, as shown in Table 3. The maximum absorptions of 2-iminothiophene-3-carbamate derivatives (3a and 3c), 3-iminothiophene-2-carbamate derivative (3j), and benzene analogue (5) appeared at a higher wavelength than those of 4-imino-thiophene-3-carbamate derivatives (3e and 3h) in the uv spectra, because the imine



1a 3a 8

Chart 4

7 2a

group could conjugate with the carbamate group in 3a-d, 3i-j, and 5. The hard cyclization of 2e-h from 3e-h is supposed to be related to non-conjugation between the carbamate group and the imine group.

In speculating on a possible mechanistic pathway to 2, we proposed that 8 might be involved as a labile intermediate, regardless of the existence of the tautomer (7) of 3a. From this mechanism, the possibility of ring closure of 3e-h might be excluded by the absence of formation of an intermediate like 8 from 3e-h (Chart 4).

Gastric antisecretory activity of these angular annelated tricyclic compounds (2a-d,i-j) will be reported elsewhere.

EXPERIMENTAL

All melting points are uncorrected. Infrared (Ir) spectra were measured on a JASCO A-102 spectrophotometer. Nuclear magnetic resonance (Nmr) spectra were recorded with a Varian T-60A (60MHz) or EM-390 (90MHz) spectrometer and the chemical shifts are expressed in ppm from tetramethylsilane as an internal standard. Uv spectra were recorded on a Shimadzu UV-3100 spectrophotometer. Mass spectra (Ms) were obtained with a JEOL JMS-01SG or JMS-G300 mass spectrometer. Merck silica gel (Kieselgel 60 Art.7734) was employed for column chromatography.

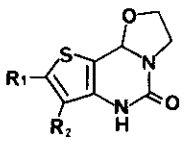
Ethyl N-(4,5-Dimethyl-2-formyl-3-thienyl)carbamate (1d)

Methyl 4,5-dimethyl-3-ethoxycarbonylaminothiophene-2-carboxylate[1b] (15.00 g, 58.3 mmol) was added portionwise to a suspension of lithium aluminum hydride (LAH, 2.88 g, 75.9 mmol) in dry ethyl ether (220 ml) at 0 ℃ during 10 min under a nitrogen atmosphere, and the whole was stirred for 20 min at the same temperature. After saturated NH_4Cl solution was carefully added to the reaction mixture, the precipitate was filtered through celite, and the filtrate was washed with water, dried over $MgSO_4$, and filtered. To the filtrate was added activated manganese(Ⅳ) oxide (MnO_2, 120 g), and the resulting reaction mixture was stirred at room temperature for 3 h. The insoluble material was filtered off, the filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel using ethyl acetate (AcOEt)-hexane (1:3) as an eluent. Recrystallization from AcOEt-hexane gave 1d (7.87 g, 59 %) as colorless needles. mp 104-105 ℃. Anal. Calcd for $C_{10}H_{13}NO_3S$: C,52.85; H,5.77; N,6.16; S,14.11. Found: C,52.80; H,5.67; N,6.12; S,14.03. Ir (KBr): 1730, 1700, 1645cm^{-1}. Nmr ($CDCl_3$) δ ppm: 1.30 (3H,t,J=7.2Hz), 2.06 and 2.40 (each 3H,s), 4.21 (2H,q,J=7.2Hz), 7.67-8.20 (1H,br), 9.74 (1H,s). Ms (*m/z*): 227(M^+).

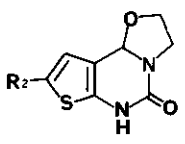
Ethyl N-(3-Formyl-2-thienyl)carbamate (1i)

The same procedure as described for 1d was applied to methyl 2-ethoxycarbonylaminothiophene-3-carbaxylate[1b] (1.002 g, 4.37 mmol), using LAH (252 mg, 6.64 mmol) as a reducing agent and pyridinium dichromate (1.61 g, 4.28 mmol) as an oxidizing agent. Recrystallization from AcOEt-hexane afforded 1i (76 mg, 9 %) as colorless needles. mp 42-44 ℃. Anal. Calcd for $C_8H_9NO_3S$: C,48.23; H,4.55; N,7.03; S,16.09. *Found: C,47.94; H,4.49; N,6.98; S,15.79.* Ir (KBr): 1730, 1640cm^{-1}. Nmr ($CDCl_3$) δ ppm: 1.34 (3H,t,J=7.0Hz), 4.31 (2H,q,J=7.0Hz), 6.69 and 7.11 (each 1H, d,J=6.0Hz), 9.82 (1H,s). Ms (*m/z*): 199(M^+).

Table 4 2,3,6,9b-Tetrahydro-5H-oxazolo[3,2-c]thieno[2,3-e]-, and [3,2-e]-pyrimidin-5-one Derivatives (2a-d,i-j)



2a-d



2i-j

Compd. No.	R_1	R_2	Yield (%)	Mp(℃)	Recryst. solvent	Formula	Analysis (%) Calcd (found) C	H	N	S
2a	H	H	71	228-230 (decomp)	DMF-MeOH	$C_8H_8N_2O_2S$	48.97 (48.83	4.11 4.05	14.28 14.25	16.34 16.21)
2b	Me	H	21	206-208 (decomp)	DMF-EtOH	$C_9H_{10}N_2O_2S$	51.41 (51.44	4.79 4.89	13.32 13.26	15.25 15.20)
2c	H	Me	71	248-252 (decomp)	DMF-MeOH	$C_9H_{10}N_2O_2S$	51.41 (51.48	4.79 4.72	13.32 13.38	15.25 15.08)
2d	Me	Me	87	209-211 (decomp)	DMF-MeOH	$C_{10}H_{12}N_2O_2S$	53.55 (53.52	5.39 5.54	12.49 12.26	14.29 14.20)
2i		H	40	205-206	DMF -acetone	$C_8H_8N_2O_2S$	48.97 (49.09	4.11 4.30	14.28 14.27	16.34 16.33)
2j		Me	37	230-232	MeOH	$C_9H_{10}N_2O_2S$	51.41 (51.17	4.79 4.85	13.32 13.16	15.25 15.04)

Table 5 Spectral Data for 2a-d,i-j

Compd. No.	Ir (KBr) ν (cm^{-1})	Nmr (DMSO-d_6) δ (ppm), J (Hz)
2a	1640	3.48-3.85 (2H,m), 3.93-4.16 (2H,m), 4.96 (1H,br s), 7.04 and 8.46 (each 1H,d,J=5.7), 8.96 (1H,s)
2b	1640	2.57 (3H,s), 3.56-3.80 (2H,m), 3.87-4.06 (2H,m), 4.93 (1H,br s), 6.79 (1H,s), 8.73 (1H,s)
2c	1640	2.17 (3H,d,J=1.5), 3.60-3.87 (2H,m), 3.93-4.23 (2H,m), 4.83-5.10 (1H,br), 8.07 (1H,d,J=1.5), 8.88 (1H,s)
2d	1640, 1605	2.06 and 2.47 (each 3H,s), 3.57-3.87 (2H,m), 3.90-4.19 (2H,m), 4.75-5.20 (1H,br), 8.70 (1H,s)
2i	1639, 1611	3.57-3.85 (2H,m), 3.95-4.13 (2H,m), 4.99 (1H,br s), 7.15 and 7.29 (each 1H,d,J=6.0), 8.76 (1H,s)
2j	1644, 1606	2.40 (3H,d,J=1.2), 3.58-3.81 (2H,m), 3.90-4.10 (2H,m), 4.93 (1H,br s), 6.80 (1H,d,J=1.2), 8.51 (1H,s)

Ethyl N-[2-(2-Hydroxyethyl)iminomethylphenyl]carbamate (5)

A solution of 4[3] (273 mg, 1.41 mmol) and ethanolamine (0.43 ml, 7.11 mmol) in EtOH (4 ml) was refluxed for 6 h and then the solvent was evaporated in vacuo. After the addition of water to the residue, the mixture was extracted with AcOEt, and a residue obtained from the extracts was recrystallized from CH_2Cl_2-hexane to give 5 (294 mg, 88 %) as colorless needles. mp 87-88 ℃. Anal. Calcd for $C_{12}H_{16}N_2O_3$: C,61.00; H,6.83; N,11.86. Found: C,61.07; H,6.63; N,11.57. Ir (KBr): 1697, 1642cm^{-1}. Nmr ($CDCl_3$) δ ppm: 1.30 (3H,t,J=7.0Hz), 3.64-4.03 (4H,m), 4.19 (2H,q, J=7.0Hz), 6.90-7.50 (3H,m), 8.31-8.47 (2H,m), 2.30 and 11.14 (each 1H,br s). Ms (m/z): 236(M^+).

2,3,6,10b-Tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (6)

A solution of 5 (216 mg, 0.91 mmol) in DMF (8 ml) was refluxed for 8 h, and then the solvent was evaporated to dryness. After the addition of AcOEt to the residue, the precipitate was collected by filtration, washed with AcOEt, and recrystallized from DMF-AcOEt to give 6 (83 mg, 48 %) as colorless needles. mp 194-196 ℃. Anal. Calcd for $C_{10}H_{10}N_2O_2$: C,63.15; H,5.30; N,14.73. Found: C,63.09; H,5.37; N,14.77. Ir (KBr): 1671, 1600cm^{-1}. Nmr (DMSO-d_6) δ ppm: 3.18-4.27 (4H,m), 5.65 (1H,s), 6.85-7.43 (4H,m), 9.82 (1H,br s). Ms (m/z): 190(M^+).

The compound (2a) was similarly prepared. Other data for 2a are listed in Tables 4 and 5.

7,8-Dimethyl-2,3,6,9b-tetrahydro-5H-oxazolo[3,2-c]thieno[2,3-e]pyrimidin-5-one (2d) (General Procedure)

A solution of 1d (5.00 g, 22.0 mmol) and ethanolamine (6.6 ml, 109 mmol) in EtOH (40 ml) was refluxed for 1 h (Table 1). A residue obtained by evaporation of the solvent was recrystallized from DMF-MeOH to afford 2d (4.31 g, 87 %) as yellow prisms. Ms (m/z): 224(M^+). Other data are listed in Tables 4 and 5.

REFERENCES AND NOTES

1) a) Part 4: M. Sugiyama, T. Sakamoto, K. Tabata, and H. Fukumi, Chem. Pharm. Bull., accepted; b) Part 1: M. Sugiyama, T. Sakamoto, K. Tabata, K. Endo, K. Ito, M. Kobayashi, and H. Fukumi, ibid., accepted.

2) D. H. Reid "Organic Compounds of Sulphur, Selenium, and Tellurium. Vol. 2," ed. by S. Gronowitz, John Wright and Sons Ltd., London, 1973, pp. 483-485 and references cited therein.

3) M. Davis, E. Homfeld, and K. S. L. Srivastava, J. Chem. Soc. Perkin Trans. 1, 1973, 1863.

4) The Schiff's base (3j) was prepared from 1j with ethanolamine by using Molecular Sieves 4A as a dehydrating agent. See ref. 1a.

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