A FACILE ROUTE TO FUSED HETEROCYCLES WITH AN EXOCYCLIC METHYLENE BY INTRAMOLECULAR NUCLEOPHILIC AMINATIONS TO ACETYLENE

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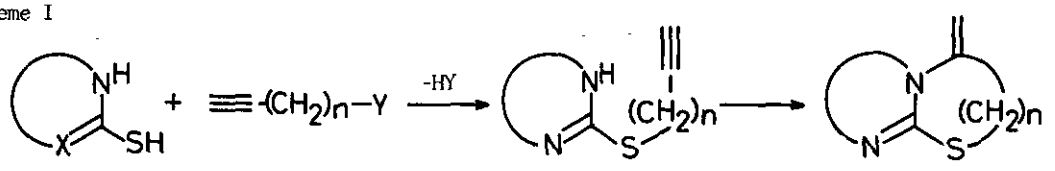
Abstract - The novel method for synthesis of fused heterocycles with an exocyclic methylene was investigated. The terminally acetylene-substituted heterocycles 3a-c and 6a-d were converted to the fused heterocycles with an exocyclic methylene 4a-c and 7a-d by intramolecular nucleophilic amination to acetylene part.

Ambiphilic behavior of acetylene is well-known, and many nucleophilic additions to acetylenes were reported. Amines also interact with acetylenes to give enamines under atmospheric or high pressure. However, application of this reaction to synthesize fused heterocyclic systems seems to be few in the literatures.[1] In this point, we report here the novel synthetic method of fused heterocycles, in which an exocyclic methylene is placed adjacent to the bridgehead nitrogen, utilizing intramolecular attack of ring nitrogen to acetylene in side chain (Scheme I). As shown in Scheme I, mercapto-substituted heterocycles were utilized as the starting materials because of the facile access of the linkage of an acetylenic side chain to the original heterocycles.

Scheme I

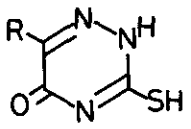


1 : X=N 2 : Y=Br, n=1 3 : n=1 4 : n=1
5 : Y=OTs, n=2 6 : n=2 7 : n=2

Results and Discussion

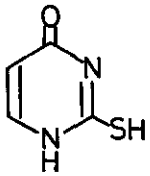
Synthesis of Thiazolidino-fused Heterocycles 4a-c and c'

The terminally acetylene-substituted heterocycles 3a-d were prepared from the corresponding mercapto-substituted heterocycles 1a-d with an equimolar amount of propargyl bromide (2) in ethanol in the presence of sodium hydroxide at room temperature in 56.8-91.5% yield without contamination of N-substitution. The ir spectra of these compounds revealed characteristic acetylenic absorptions

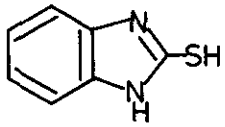


1a : R=H

1b : R=CH_3



1c



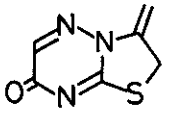
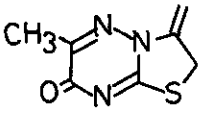
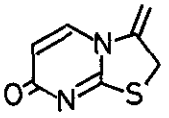
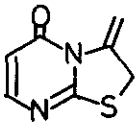
1d

at about 3250 and 2100 cm^{-1} (Table III). The intramolecular aminations of 3a-c in refluxing ethanol with triethylamine (1/2-1/4 equiv.) afforded the corresponding fused heterocycles 4a-c and c' with an exocyclic methylene adjacent to the bridgehead nitrogen in 46.5-83.9% yield (Table I). Triazine derivatives 3a and b gave single products 4a and b, respectively. However, thiouracil derivative 3c afforded a mixture of 4c and c' (3:1), which was separated by silica gel column chromatography. These structures were assigned from their spectroscopic data; the ^1H nmr spectra showed a triplet (J=3 Hz) at δ 4.09-4.29 for methylene protons adjacent to sulfur and two quartets (J= 2-3 Hz) for exocyclic methylene protons (Table I). The difference of the newly formed linking site between 4c and c' became clear from the analysis of the ^1H nmr spectra, because the chemical shift (δ 6.59) of one of the exocyclic methylene protons in 4c' resonated in considerably lower field than that (δ 5.37) of 4c. This deshielding is caused by carbonyl group in the dihydroprimidine ring. Although benzimidazole derivative 3d did not react under these conditions, a mixture of products were obtained by heating in a sealed tube, which could not be separated. The ^1H nmr spectra of this mixture showed the characteristic peak for cyclization product.[2]

Synthesis of Perhydro-1,3-thiazino-fused Heterocycles 7a-d

The starting materials 6a-d were obtained from the reaction of 1a-d and 3-butyn-1-yl tosylate (5) in the presence of sodium hydroxide in refluxing ethanol, in 31.5-41.4% yield. The yields were not optimized. The structures of these compounds 6a-d were confirmed by the ^1H nmr spectra, which showed a doublet of triplet for $\equiv C-CH_2-$ and two triplets for an acetylenic proton and two protons adjacent to sulfur (Table IV). The cyclization of these compounds 6a-c were accomplished by heating in a sealed tube in ethanolic solution of triethylamine (1/4-1/5 equiv.) at 140°C. The structures of these cyclized products 7a-c were established by the ^1H nmr spectra. Thiazinotriazines 7a and b have a multiplet for one of the exocyclic methylene protons and a doublet for the other in the ^1H nmr spectra. A resonance which is assignable to the protons of $-S-CH_2-CH_2-\overset{n}{C}-$ moiety appeared as a multiplet for 4H centered at 3.12(7a), 3.10(7b), and 3.05(7c), respectively (Table II). In contrast, the similar type of cyclization of 6d was not affected under the same conditions, but was accomplished by using sodium hydroxide instead of triethylamine and to give 7d in 21.9% yield. In this cyclization reaction (for 13.5 h) another product 8 was also isolated in 25.8% yield, which is presumably formed by β-elimination of once formed 7d as shown in Scheme II.

Table I. Yields and Physical Data of Thiazolidino-fused Heterocycles 4a-c and c'

compd.	reaction time (h)	yield(%)	mp(°C)	ir(cm^{-1})(KBr)	^1H nmr(δ)($CDCl_3$)
4a 	8.0	46.5	159-161	1560, 1650, 1670 3100	4.23(t, 2H, J=3 Hz) 4.91(q, 1H, J=3 Hz) 5.53(q, 1H, J=3 Hz) 7.63(s, 1H)
4b 	7.0	54.6	188-191	1580, 1650, 3120	2.34(s, 3H) 4.18(t, 2H, J=3 Hz) 4.85(q, 1H, J=3 Hz) 5.53(q, 1H, J=3 Hz)
4c 	6.5	62.9	292-294	1590, 1650, 3100	*4.29(t, 2H, J=3 Hz) 4.94(q, 1H, J=3 Hz) 5.37(q, 1H, J=3 Hz) 6.00(d, 1H, J=8 Hz) 8.25(d, 1H, J=8 Hz)
4c' 	6.5	21.0	121-123	1580, 1670, 3140	4.09(t, 2H, J=2 Hz) 5.19(q, 1H, J=2 Hz) 6.16(d, 1H, J=7 Hz) 6.59(q, 1H, J=2 Hz) 7.62(d, 1H, J=7 Hz)

*DMSO-d_6

Table II. Yields and Physical Data of Perhydro-1,3-thiazino-fused Heterocycles 7a-d

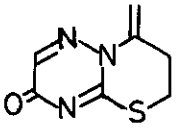
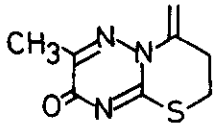
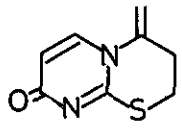
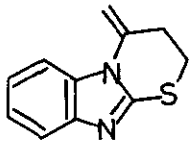
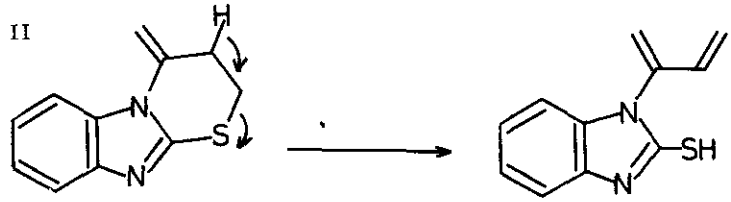
compd.	reaction time (h)	yield(%)	mp(°C)	ir(cm^{-1})(KBr)	^1H nmr(δ)($CDCl_3$)
7a 	33.5	33.2	160-161[a]	1590, 1650, 2950 3000, 3150	3.12(m, 4H) 4.94(m, 1H) 5.64(d, 1H, J=1 Hz) 7.65(s, 1H)
7b 	36.0	38.0	199-200[a]	1550, 1600, 1650 2930, 2970, 3280	2.33(s, 3H) 3.10(m, 4H) 4.90(m, 1H) 5.66(d, 1H, J=1 Hz)

Table II. (continued)

compd.	reaction time (h)	yield(%)	mp(°C)	ir(cm^{-1})(KBr)	^{1}H nmr(δ)($CDCl_3$)
7c 	19.5	36.0	115-117[b]	1640, 3000, 3100	2.78-3.32(m, 4H) 5.02(d, 1H, J=2 Hz) 5.13(d, 1H, J=2 Hz) 6.06(d, 1H, J=8 Hz) 7.54(d, 1H, J=8 Hz)
7d 	13.5	21.9	oil	1445, 1605, 1650[c]	2.74-3.39(m, 4H) 4.97(m, 1H) 5.39(d, 1H, J=1 Hz) 7.13-7.70(m, 4H)

a EtOH : b silica gel column : c neat

Scheme II



7d 8

Table. III Yields and Physical Data of 2-Propyn-1-ylthio-substituted Heterocycles 3a-d

compd.	reaction time (h)	yield(%)	mp(°C)	ir(cm^{-1})(KBr)	^{1}H nmr(DMSO-d_6)(δ)
3a	2.0	56.8	147-150	1630, 2120, 3240	3.17(t, 1H, J=3 Hz), 4.01(d, 2H, J=3 Hz) 7.67(s, 1H)
3b	9.5	91.5	191-193	1620, 2120, 3250	2.14(s, 3H), 3.21(t, 1H, J=3 Hz) 4.00(d, 2H, J=3 Hz)
3c	1.0	88.8	156-158	1660, 2120, 3210	3.10(t, 1H, J=3 Hz), 4.00(d, 3H, J=3 Hz) 6.19(d, 1H, J=7 Hz), 7.95(d, 1H, J=7 Hz)
3d	1.0	64.5	153-154 (151-152[3])	2130, 3220	3.32(t, 1H, J=3 Hz), 4.30(d, 2H, J=3 Hz) 7.27-7.75(m, 4H)

Table IV. Yields and Physical Data of 3-Butyn-1-ylthio-substituted Heterocycles 6a-d

compd.	reaction time (h)	yield(%)	mp(°C)	ir(cm^{-1})(KBr)	^{1}H nmr(DMSO-d_6)(δ)(*$CDCl_3$)
6a	9.0	36.7	167-169	1562, 1590, 1640 3240, 3270	2.58(dt, 2H, J=2,7 Hz), 2.91(t, 1H, J=2 Hz) 3.27(t, 2H, J=7 Hz), 7.62(s, 1H)
6b	4.0	31.5	180-182	1540, 1590, 3240	2.12(s, 3H), 2.58(dt, 2H, J=3,7 Hz) 2.91(t, 1H, J=3 Hz), 3.24(t, 2H, J=7 Hz)
6c	5.0	33.9	168-171	1540, 1570, 1670 3250	2.59(dt, 2H, J=3,7 Hz), 2.91(t, 1H, J=3 Hz) 3.28(t, 2H, J=7 Hz), 6.12(d, 1H, J=7 Hz) 7.91(d, 1H, J=7 Hz)
6d	15.0	41.4	127-128	1580, 3280	*2.02(t, 1H, J=3 Hz), 2.70(dt, 2H, J=3,7 Hz) 3.46(t, 2H, J=7 Hz), 7.10-7.59(m, 4H)

EXPERIMENTAL

Melting points were measured with a Yanagimoto micro melting-point apparatus and are uncorrected. Microanalyses were performed with a Perkin-Elmer 240 B elemental analyzer and satisfactory elemental analysis data were obtained for all new compounds. The ^{1}H nmr spectra were taken at room temperature with a JEOL C-60-HL spectrometer wiht tetramethylsilane as an internal standard. The ir spectra were taken with a JASCO-A-100 spectrometer.

2-Propyn-1-ylthio-substituted heterocycles 3a-d.

To an ethanolic solution (10 ml) of 1 (1 mmol) and sodium hydroxide (1a and c 2 mmol ; 1b and d 1.2 mmol) was added propargyl bromide (1 mmol) in one portion at room temperature. The solution was stirred for an appropriate period (Table III). After evaporation of the solvent, water (10 ml) was added to the residue and the aqueous solution was acidified with diluted sulfuric acid. Precipitates were collected by filtration, washed with water, and recrystallized from ethanol. Yields and physical data of 3a-d are summarized in Table III.

2,3-Dihydro-3-methylene-7H-thiazolo[3,2-b][1,2,4]triazin-7H-ones (4a and b).

A mixture of 3 (1 mmol), triethylamine (0.5 mmol), and ethanol (10 ml) was refluxed for an appropriate period (Table I). After evaporation of the solvent, the resulting product was recrystallized from ethanol to give 4a (77 mg) and 4b (99 mg), respectively.

2,3-Dihydro-3-methylene-5(7)H-thiazolo[2,3-b]-5(7)-pyrimidinone (4c and c').

A mixture of 3c (2 mmol), triethylamine (0.25 mmol), and ethanol (20 ml) was refluxed for 6.5 h and the solvent was evaporated. To the resulting solid was added dichloromethane (10 ml) and insoluble solid was collected and recrystallized from ethanol to give 4c (209 mg). Evaporation of dichloromethane solution gave crude 4c' which was further purified by column chromatography (silica gel/ CH_2Cl_2 : EtOH=10 : 1) to give 4c' (70 mg).

3-Butyn-1-ylthio-substituted heterocycles 6a-d.

To a mixture of 1 (1 mmol) and sodium hydroxide (1a-c 2 mmol ; 1d 1 mmol) in ethanol (10 ml) was added 3-butyn-1-yl tosylate[4] (1a 1.5 mmol ; 1b 1.2 mmol ; 1c 2.0 mmol ; 1d 1.0 mmol) in one portion. After refluxing of the mixture for an appropriate period (Table IV), the solvent of the mixture was evaporated and water (5 ml) was added to the residue. Following work up was employed:

for 6a-c; the resulting aqueous mixture was extracted with dichloromethane to remove by-products and an aqueous layer was acidified with diluted sulfuric acid to give a pure 6a-c. An analytical sample was obtained by recrystallization from ethanol.

for 6d; the resulting aqueous mixture was acidified with diluted sulfuric acid and stirred for a while. The formed insoluble material was removed by filtration. Careful addition of aqueous sodium hydroxide to the filtrate to ph 8-9 gave 6d. An analytical sample was obtained by recrystallization from ethanol.

Yields and physical data of 6a-d are summarized in Table IV.

8-Methylene-7,8-dihydro-3H,6H-[1,3]thiazino[3,2-b][1,2,4]triazin-3-ones (7a and b) and 4-methylene-3,4-dihydro-2H,8H-[1,3]thiazino[3,2-a]pyrimidin-8-one (7c).

An ethanolic solution (5 ml) of 6 (1 mmol) and triethylamine (6a-b 0.25 mmol ; 6c 0.2 mmol) was heated in a sealed tube at 140°C for an appropriate period (Table II). The solvent was evaporated to give crude 7a-c, which was purified as listed in Table II.

4-Methylene-3,4-dihydro-2H-[1,3]thiazino[3,2-a]benzimidazole (7d).

The ethanolic solution (5 ml) of 6d (151 mg) and sodium hydroxide (31 mg) was heated in a sealed tube at 140°C for 13.5 h and the solvent was evaporated. The resulting mixture was acidified with diluted sulfuric acid, extracted with dichloromethane, and dried over anhydrous magnesium sulfate. After evaporation, the products were separated and purified by preparative TLC (silica gel/CH_2Cl_2) to give 7d (33 mg) and 8 (39 mg).

8 : mp 123-125°C ; ir(cm^{-1})(KBr) 1450, 1475, 1500, 1600, 1640 ; ^1H nmr($CDCl_3$) δ 4.85(d, 1H, J=17 Hz), 5.25(d, 1H, J=11 Hz), 5.51(s, 1H), 5.87(s, 1H), 6.60(dd, 1H, J=11, 17 Hz), 7.19(m, 4H)

REFERENCES AND NOTES

1. I. Iwai and T. Hiraoka, Chem. Pharm. Bull., 1964, 12, 813.
2. Cyclized product assigned to 3-methylene-2,3-dihydro-thiazolo[3,2-a]benzimidazole (4d) was detected in the ^1H nmr spectra of the reaction mixture which was obtained from the reaction of 3d (176 mg) and triethylamine (95 mg) in ethanol (5 ml) in a sealed tube at 140°C for 29 h, but not separated. The ^1H nmr spectra for 4d are at δ 4.48(t, J=2 Hz), 4.81(q, J=2 Hz), 5.26(q, J=2 Hz), and 7.05-7.80(m).
3. K. K. Balasubramanian and B. Venugopalan, Tetrahedron Lett., 1974, 31, 2643.
4. G. Eglinton and C. Whiting, J. Chem. Soc., 1950, 3650.

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