Synthesis and Reactions of 2-Chloro-3,4-dihydrothienopyrimidines and -quinazolines

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Reaction of 2,4-dichlorothienopyrimidines and -quinazolines **1** with sodium borohydride gave the corresponding 2-chloro-3,4-dihydro derivatives **2**. Some nucleophilic substitutions of **2b** afforded 2-substituted derivatives **3b-7b** and reaction of **2g,h** with ethyl bromoacetate yielded selectively the corresponding 3-substituted compounds **8g,h** which were derived to imidazo[2,1-*b*]quinazolin-2-ones **9g,h**.

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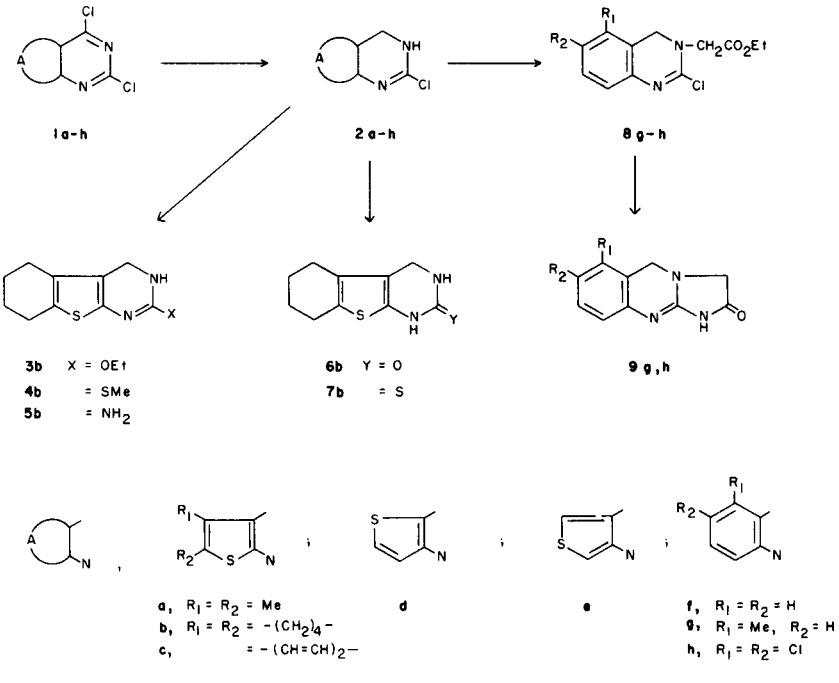
Although the 2-aminothiophene-3-methanol derivatives is a favorable intermediate to synthesize the 3,4-dihydrothieno[2,3-*d*]pyrimidine ring, the preparation may be difficult because of the unstability of the 2-aminothiophene derivatives (1). Only 4-alkyl-3,4-dihydrothieno[2,3-*d*]pyrimidines were prepared by reaction of thieno[2,3-*d*]-pyrimidine with alkyl lithiums (2). To our knowledge, the preparation of 4-unsubstituted 3,4-dihydrothieno[2,3-*d*]-pyrimidine derivatives has not been reported. This paper deals with a facile synthesis and reaction of new and useful 2-chloro-3,4-dihydrothienopyrimidines and -quinazolines.

We have recently reported that reduction of 2-chloro-4-phenylthieno[2,3-*d*]pyrimidine with sodium borohydride gave the corresponding 2-chloro-3,4-dihydro derivative (3). This result shows that selective reduction at position 3 and 4 occurs without affecting the 2-chloro atom. Generally, in the reactions of 2,4-dichloropyrimidine derivatives with some nucleophiles the 4-chlorine atom is more reactive than the 2-chlorine atom. In addition, imidoyl chlorides is reduced with sodium borohydride to give the corresponding amines (4). Thus, we expect that treatment of 2,4-dichloropyrimidine derivatives with sodium borohydride may give the corresponding 2-chloro-3,4-dihydropyrimidine derivatives.

All the 2,4-dichlorothienopyrimidines, such as 5,6-dimethylthieno[2,3-*d*]- **1a** (5), 5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]- **1b** (6), [1]benzothieno[2,3-*d*]- **1c**, thieno[3,2-*d*]- **1d** (7) and thieno[3,4-*d*]pyrimidine **1e** (8), were reacted with sodium borohydride in a solution of chloroform and ethanol at 25°-50° to give expected 2-chloro-3,4-dihydro derivatives **2a-e**. Similar reaction of 2,4-dichloroquinazoline derivatives **1f-h** also easily gave the corresponding 2-chloro-3,4-dihydro derivatives **2f-h**. The structures of the compounds **2** were supported by the data of microanalysis and pmr spectra which showed singlet signal of methylene protons at position 4 at δ 4.5-4.8 as

Scheme I



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shown in Table I. Attempt to similarly reduce other 2,4-dichloropyrimidine derivative, such as 2,4-dichloropyrimidine, 2,4-dichloro-5,6,7,8-tetrahydro[1]benzofuro[2,3-*d*]-pyrimidine, 2,4-dichloropyrrolo[2,3-*d*]pyrimidine and 2,4-dichloropyrido[2,3-*d*]pyrimidine, did not succeed.

2-Chlorine atom of compounds **2** was active against some nucleophiles. Reaction of 2-chloro-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidine **2b** with sodium ethoxide, sodium methanethiolate and ammonia gave 2-ethoxy **3b**, 2-methylthio **4b**, and 2-amino **5b** derivatives, respectively. Heating **2b** in acetic acid afforded 2-(1*H*)-one derivative **6b**. Reaction of **2b** with thiourea followed by treatment with sodium hydroxide gave 2-(1*H*)thione derivative **7b**.

The utility of compounds **2** was demonstrated by a novel synthesis of 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one derivatives **9** which were potent blood platelet aggregation inhibitors (9). Reaction of **2g,h** with ethyl bromoacetate in the presence of excess potassium carbonate gave predominantly corresponding 3-substituted derivatives **8g-h**. Heating **8g,h** in ethanolic ammonia in a sealed tube yielded **9g,h**, respectively, which were identical with the sample prepared by Beverung's method. Similar preparation of 1,2,3,5-tetrahydroimidazo[1,2-*a*]-thieno-[2,3-*d*]-, -[3,2-*d*]-, and -[3,4-*d*]-pyrimidin-2-one derivatives with the same potent inhibiting activity will be reported elsewhere (10).

Table I

2-Chloro-3,4-dihydrothienopyrimidines and -quinazolines

Compound No.	Yield %	M.p. °C	Ir cm^{-1}	Formula	Analysis % Calcd. (Found)	Pmr (a) δ
2a	71	170-172	3150 1580	$C_8H_9ClN_2S$	C 47.87 (47.73) H 4.52 (4.47) N 13.96 (13.88)	1.86 (s, 3H, 5-CH_3) 2.19 (s, 3H, 6-CH_3) 4.54 (s, 2H, 4-CH_2)
2b	74	141-143	3140 1580	$C_{10}H_{11}ClN_2S$	C 52.97 (52.79) H 4.89 (4.80) N 12.36 (12.30)	1.6-1.9 (m, 4H, 6-, 7-CH_2) 2.1-2.45 (m, 2H, 5-CH_2) 2.45-2.8 (m, 2H, 8-CH_2) 4.58 (s, 2H, 4-CH_2)
2c	83	173-177	3160 1590 1570	$C_{10}H_7ClN_2S$	C 53.93 (54.05) H 3.17 (3.32) N 12.58 (12.46)	4.89 (s, 2H, 4-CH_2) 7.1-7.4 (m, 3H, aromatic protons) 7.55-7.8 (m, 1H, 8-CH)
2d	84	138-140	3150 1595 1540	$C_6H_5ClN_2S$	C 41.74 (41.58) H 2.92 (2.98) N 16.23 (16.45)	4.80 (s, 2H, 4-CH_2) 6.69 (s, 1H, 6-CH) 7.31 (s, 1H, 7-CH)
2e	89	130-132	3160 1605 1505	$C_6H_5ClN_2S$	C 41.74 (41.56) H 2.92 (2.99) N 16.23 (16.23)	4.65 (s, 2H, 4-CH_2) 6.72 (s, 1H, 5-CH) 6.95 (s, 1H, 7-CH)
2f	84	97-101	1660	$C_8H_7ClN_2$	C 57.67 (57.58) H 4.24 (4.27) N 16.82 (17.06)	4.77 (s, 2H, 4-CH_2) 6.9-7.4 (m, 4H, aromatic protons)
2g	92	unclear (b)	3150 1620 1580	$C_9H_9ClN_2$	C 59.84 (59.63) H 5.02 (4.99) N 15.51 (15.57)	2.13 (s, 3H, 5-CH_3) 4.70 (s, 2H, 4-CH_2) 6.7-7.4 (m, 3H, aromatic protons)
2h	94	unclear (b)	3270 1620 1595	$C_8H_5Cl_3N_2$	C 40.80 (40.68) H 2.14 (2.21) N 11.90 (11.81)	4.67 (s, 2H, 4-CH_2) 6.80 (d, 1H, 7-CH) 7.26 (d, 1H, 8-CH)

(a) Solvent: DMSO-d_6 for **2d** and **2e**. (b) The compounds did not show the clear melting point because of the unstability under heating.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded with a Hitachi 285 spectrometer. Using a Hitachi Perkin-Elmer R-20B (60 MHz) or a Hitachi R-40 (90 MHz) instrument, pmr spectra were determined in deuterochloroform, unless otherwise stated, with tetramethylsilane as an internal standard. Most of the starting 2,4-dichloropyrimidines **1** are known compounds and were prepared by means of the literature methods.

General Procedure for the Preparation of 2-Chloro-3,4-dihydrothienopyrimidines and -quinazolines (**2**).

Sodium borohydride (200 mmoles) was added portionwise to a solution of **1** (40 mmoles) in chloroform (100 ml.) and ethanol (40 ml.) in ice-bath. The mixture was stirred at 40-50° for 14 hours [in the case of **1c**, **g-h** at 25° for 2 hours]. The solvent was evaporated and the residual solid was washed with water and ethanol to give crude **2** which was recrystallized from chloroform-ethanol.

Results are shown in Table I.

2-Ethoxy-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidine (**3b**).

Compound **2b** (2.27 g., 10 mmoles) was added to a solution of sodium metal (0.23 g., 10 mmoles) in ethanol (30 ml.). The mixture was heated under reflux for 1 hour under nitrogen atmosphere and concentrated *in vacuo*. The residue was mixed with water and extracted with chloroform. The extract was washed with water, dried, and concentrated *in vacuo*. The residue was recrystallized from benzene-hexane to give 1.23 g. (52%) of **3b**, m.p. 111-114°; ir (potassium bromide): 3250, 1570, 1290, 1270 cm^{-1}; pmr: δ 1.26 (t, 3H, CH_3), 1.6-2.0 (m, 4H, 6-,7-CH_2), 2.2-2.5 (m, 2H, 5-CH_2), 2.5-2.7 (m, 2H, 8-CH_2), 4.23 (q, 2H, O-CH_2), 4.53 (s, 2H, 4-CH_2).

Anal. Calcd. for $C_{12}H_{16}N_2OS$: C, 60.98; H, 6.82; N, 11.85. Found: C, 60.65; H, 6.85; N, 12.31.

2-Methylthio-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidine (**4b**).

A mixture of **2b** (5.70 g., 25 mmoles), 20% aqueous sodium methane thiolate solution (25 ml.), tetra(*n*-butyl)ammonium iodide (0.50 g.) and benzene (200 ml.) was heated under reflux for 1 hour under nitrogen atmosphere. After cooling, benzene layer was separated, washed with water, dried, and concentrated *in vacuo*. The residue was recrystallized from benzene-hexane to give 4.90 g. (68%) of **4b**, m.p. 125-126°; ir (potassium bromide): 3150, 2900, 1540, 1520, 1280, 1260, cm^{-1}; pmr: δ 1.6-1.9 (m, 4H, 6,7-CH_2), 2.2-2.4 (m, 2H, 5-CH_2), 2.47 (s, 3H, S-CH_3), 2.6-2.8 (m, 2H, 8-CH_2), 4.52 (s, 2H, 4-CH_2).

Anal. Calcd. for $C_{11}H_{14}N_2S_2$: C, 55.42; H, 5.92; N, 11.75. Found: C, 55.52; H, 5.50; N, 11.67.

2-Amino-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidine Hydrochloride (**5b**).

A solution of **2b** (6.30 g., 28 mmoles) in 10% ammonia-ethanol solution (50 ml.) was heated at 110° for 37 hours in a sealed tube under nitrogen atmosphere. After cooling, an insoluble material was filtered off and the filtrate was concentrated to one-third volume *in vacuo*. The crystal separated was collected by filtration, washed with ethanol. The crude product was recrystallized from methanol to give 4.31 g. (63%) of **5b**, m.p. 267-270° dec.; ir (potassium bromide): 3280, 3030, 1670, 1620, 1580 cm^{-1}; pmr (DMSO-d_6): δ 1.6-1.9 (m, 4H, 6-, 7-CH_2), 2.2-2.5 (m, 2H, 5-CH_2), 2.5-2.75 (m, 2H, 8-CH_2), 4.41 (s, 2H, 4-CH_2).

Anal. Calcd. for $C_{10}H_{14}ClN_3S$: C, 49.28; H, 5.79; N, 17.24. Found: C, 48.98; H, 6.05; N, 17.59.

3,4,5,6,7,8-Hexahydro[1]benzothieno[2,3-*d*]pyrimidin-2-(1*H*)one (**6b**).

A solution of **2b** (4.40 g., 19.4 mmoles) in acetic acid (50 ml.) was heated under reflux for 1 hour and concentrated *in vacuo*. The residue was washed with methanol and recrystallized from acetic acid to give 2.99 g. (74%) of **6b**, m.p. 259-261° dec.; ir (potassium bromide): 3230, 3100, 1680 cm^{-1}; pmr (DMSO-d_6): δ 1.6-1.9 (m, 4H, 6-,7-CH_2), 2.2-2.45 (m, 2H, 5-CH_2), 2.45-2.65 (m, 2H, 8-CH_2), 4.18 (d, J = 1.5 Hz, 2H, 4-CH_2), 6.68 (br, 1H, 3-NH), 9.05 (br, 1H, 1-NH).

Anal. Calcd. for $C_{10}H_{12}N_2OS$: C, 57.67; H, 5.81; N, 13.45. Found: C, 57.37; H, 5.72; N, 13.09.

3,4,5,6,7,8-Hexahydro[1]benzothieno[2,3-*d*]pyrimidine-2-(1*H*)thione (**7b**).

A mixture of **2b** (0.68 g., 3 mmoles) and thiourea (0.25 g., 3.3 mmoles) in ethanol (30 ml.) was heated under reflux for 16 hours under nitrogen atmosphere and then 8% sodium hydroxide solution (10 ml.) was added to the mixture. The mixture was successively heated under reflux for 2 hours under nitrogen atmosphere. After cooling, the mixture was acidified with 10% hydrochloric acid and concentrated to half-volume *in vacuo*. The residue was extracted with chloroform. The extract was washed with water, dried, and concentrated *in vacuo*. The residue was recrystallized from chloroform-ethanol to give 0.27 g, (40%) of **7b**, m.p. 214-216°; ir (potassium bromide): 3200-2800, 1510, 1200, cm^{-1}; pmr (DMSO-d_6): δ 1.6-1.9 (m, 4H, 6-,7-CH_2), 2.2-2.4 (m, 2H, 5-CH_2), 2.45-2.7 (m, 2H, 8-CH_2), 4.25 (d, J = 2 Hz, 2H, 4-CH_2), 8.40 (br, 1H, 3-NH), 10.56 (br, 1H, 1-NH).

Anal. Calcd. for $C_{10}H_{12}N_2S_2$: C, 53.54; H, 5.39; N, 12.49. Found: C, 53.36; H, 5.77; N, 12.38.

Ethyl 2-Chloro-5-methyl-3,4-dihydroquinazoline-3-acetate (**8g**).

A mixture of **2g** (2.00 g., 11 mmoles), ethyl bromoacetate (2.00 g., 12 mmoles) and powdered potassium carbonate (4.50 g.) in methyl ethyl ketone (50 ml.) was heated under reflux for 3 hours with vigorous stirring. After cooling, a precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was recrystallized from ether-petroleum ether to give 2.15 g. (73%) of **8g**, m.p. 81-82°; ir (potassium bromide): 1740, 1605, 1570 cm^{-1} pmr: δ 1.25 (t, 3H, CH_3), 2.10 (s, 3H, 5-CH_3), 4.20 (s, 2H, CH_2), 4.25 (q, 2H, O-CH_2), 4.70 (s, 2H, 4-CH_2), 6.80-7.2 (m, 3H, aromatic protons).

Anal. Calcd. for $C_{13}H_{15}ClN_2O_2$: C, 58.54; H, 5.67; N, 10.50. Found: C, 58.58; H, 5.72; N, 10.42.

Ethyl 2,5,6-Trichloro-3,4-dihydroquinazoline-3-acetate (8h).

Following the procedure similar to preparation of **8g**, **8h** was obtained in 76% yield, m.p. 115-116° (from ether); ir (potassium bromide): 1750, 1605, 1585 cm^{-1}; pmr: δ 1.31 (t, 3H, CH_3), 4.26 (s, 2H, CH_2), 4.28 (q, 2H, O-CH_2), 4.77 (s, 2H, 4-CH_2), 6.93 (d, J = 9 Hz, 1H, 7-CH), 7.30 (d, J = 9 Hz, 1H, 8-CH).

Anal. Calcd. for $C_{12}H_{11}Cl_3N_2O_2$: C, 44.81; H, 3.45; N, 8.71. Found: C, 44.60; H, 3.34; N, 8.48.

6-Methyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one Hydrochloride (**9g**).

A solution of **8g** (2.00 g., 7.5 mmoles) in 10% ethanolic ammonia solution (15 ml.) was heated at 120° for 16 hours in a sealed tube. After cooling, a precipitate was collected by filtration, washed with water, and dissolved in 10% methanolic hydrogen chloride solution (20 ml.). The solution was concentrated *in vacuo* and the residue was crystallized from methanol-ether to give 1.38 g. (72%) of **9g**, m.p. 260° dec. [lit. (9a) m.p. > 250°]; ir (potassium bromide): 1800, 1690, 1605, 1590 cm^{-1}; pmr (DMSO-d_6): δ 2.20 (s, 3H, 6-CH_3), 4.32 (s, 2H, 3-CH_2), 4.70 (s, 2H, 5-CH_2), 7.0-7.35 (m, 3H, aromatic protons).

Anal. Calcd. for $C_{11}H_{12}ClN_3O{\cdot}H_2O$: C, 51.67; H, 5.52; N, 16.43. Found: C, 51.90; H, 5.41; N, 16.41.

6,7-Dichloro-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one Hydrochloride (**9h**).

Following the procedure similar to preparation of **9g**, **9h** was obtained in 78% yield, m.p. > 280° [lit. (9b), m.p. > 250°]; ir (potassium bromide): 1805, 1680, 1575 cm^{-1}; pmr (trifluoroacetic acid): δ 4.62 (s, 2H, 3-CH_2), 5.00 (s, 2H, 5-CH_2), 7.27 (d, J = 9 Hz, 1H, 7-CH), 7.67 (d, J = 9 Hz, 1H, 8-CH).

Anal. Calcd. for $C_{10}H_8Cl_3N_3O{\cdot}0.5H_2O$: C, 39.82; H, 3.01; N, 13.93. Found: C, 39.50; H, 3.08; N, 13.88.

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