Synthesis of Fused Pyrimidines with *N*-, *S*-Heterocyclic Moieties by Double-annelation Reaction

A. Z. M. Shaifullah Chowdhury* and Yasuyuki Shibata

Environmental Chemistry Division, National Institute for Environmental Studies, 16-2 Onogawa, Tsukuba, Ibaraki 305-0053, Japan.

Received September 7, 2000

A variety of tri- and tetracyclic hetero systems were obtained by reaction of heteroaromatic *ortho*-aminoesters or *ortho*-aminonitriles with iminothioether, yielding double-annelation of a thiazolo[3,2-*a*]-pyrimidine, pyrimido[2,1-*b*]thiazine, imidazo[1,2-*a*]pyrimidine, and pyrimido[1,2-*a*]pyrimidine moieties in a one-pot process.

J. Heterocyclic Chem., **38**, 743 (2001).

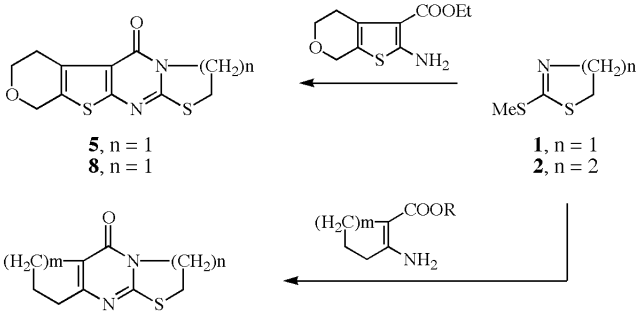
Compounds containing a fused pyrimidine ring represent a broad class of compounds which have received considerable attention over the past years due to their wide range of biological activity. With the development of clinically useful anticancer, antihypertensive agents, antiviral, antibacterial, antiallergic, antimalarial, analgesic and anti-inflammatory drugs, there has recently been remarkable interest in the preparation of annelated pyrimidines [1-5].

In recent papers [6-12] we reported on new hetero-annelations reactions to fused pyrimidines. These were achieved by reacting *ortho*-aminonitriles or *ortho*-aminoesters with *N*-[bis(methylthio)methylene]amino derivatives (BMMA-reagents), leading to mono-annelations or angular double-annelations respectively.

In the present paper we report on the extension of this strategy to related cyclic reagents **(1-4)**, which give access to double-annelated target compounds **(5-22)** with linear structure by one-pot reactions.

A heteroaromatic 2-aminoester, ethyl 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylate reported by Gewald, reacted readily with 2-methylthio-2-thiazoline (**1**) to give novel tetracyclic fusion product **5** as red crystals in 61% yield. The desired tricyclic fusion products **6** and **7** were also obtained from *ortho*-aminoesters of cyclohex-1-ene and cyclopent-1-ene with 1 in a similar manner (Scheme 1).

Scheme 1

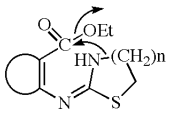


5, n = 1
8, n = 1

1, n = 1
2, n = 2

6, m = 2, n = 1
7, m = 1, n = 1
9, m = 2, n = 2
10, m = 1, n = 2

As these above reactions proceeded smoothly, we change the reagent with the application of 5,6-dihydro-2-methylthio-4*H*-1,3-thiazine (**2**) as a "ring extended" cyclic BMMA-reagent, using it for fusions with *ortho*-aminoesters. Thus, the condensed systems, pyrano-[4'',3'':4',5']thieno[2',3':4,5]pyrimido[2,1-*b*][1,3]thiazine derivative (**8**), cyclohexa[4',3':4,5]pyrimido[2,1-*b*][1,3]-thiazine derivative (**9**), and cyclopenta[4',3':4,5]pyrimido-[2,1-*b*][1,3]thiazine derivative (**10**) were obtained smoothly in the same manner as **5** from *ortho*-aminoesters and **2** as red crystals.



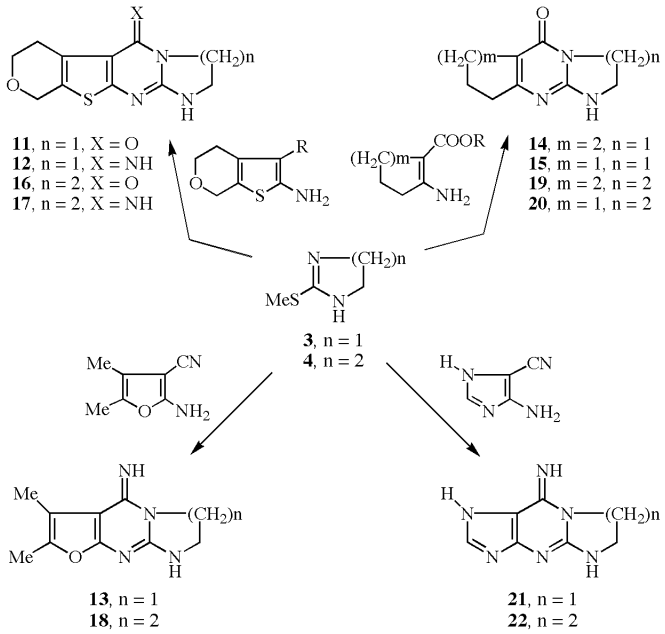
G

The mechanism of the above reactions probably involved an initial nucleophilic addition of the amino group of *ortho*-aminoesters to the electron deficient carbon of the thiazoline **1** or thiazine **2** to form the intermediate **G** by elimination of methyl mercaptane. **G** subsequently carried out a nucleophilic attack of the nitrogen atom of the thiazolo or thiazino moiety to the sp^2 carbon of the carboxylate followed by an elimination of ethanol to give desired products **5-10** *via* an intramolecular cyclization.

As described already for fusions with BMMA-reagent [6-12], various solvents and different reaction conditions were tested to accomplish the desired cyclizations, whereby dry acetic acid at 100° proved to be optimal for approaching the condensed systems. Here, once again, dry acetic acid was found to be a suitable solvent and the reaction was carried out as a one-step synthesis for condensed systems **5-10**.

In addition, to extend of our BMMA method to the readily available 2-methylthio-2-imidazoline (**3**) studying its applicability to a variety of heteroaromatic substrates. Gewald adduct of heteroaromatic *ortho*-aminoester, and *ortho*-aminonitrile, with 2-methylthio-2-imidazoline (**3**) in hexamethylphosphoric triamide (HMPTA) at 160° afforded novel tetracyclic double-annelated products **11** and **12** in good yields (Scheme 2). Similarly, the reaction

Scheme 2



of furonitrile with reagent **3** for 4 hours yielded the novel tricyclic fusion product: furo[2,3-*d*] imidazo[1,2-*a*]pyrimidine derivative (**13**) as colourless crystals. *Via* this method, other imidazo[1,2-*a*]pyrimidine derivatives **14** and **15** were accessible from *ortho*-aminoesters of cyclohex-1-ene and cyclopent-1-ene with **3** in resonable yield. The products **14** and **15** were purified by column–chromatography (eluent $CHCl_3$:MeCOMe, 9:2).

Displacement reactions have been employed to create the middle ring of tricyclic or tetracyclic systems in one-step as described above. So, the concept of creating our desired tricyclic and tetracyclic condensed systems in one-step *via* a double displacement process using 2-methylthio-1,4,5,6-tetrahydropyrimidine (**4**) is demonstrated smoothly. Thus, the reactions of *ortho*-aminoesters or *ortho*-aminonitriles with 2-methylthio-1,4,5,6-tetrahydropyrimidine (**4**) in HMPTA at 160° gave readily: i) the desired tetracyclic fusion products: pyrimido[1,2-*a*]pyrano[4',3':4,5]thieno-[2,3-*d*]pyrimidine derivatives (**16** and **17**); ii) the desired tricyclic fusion products: furo[2,3-*d*]pyrimido[1,2-*a*]-pyrimidine derivative **(18)**, cyclohexa[1,2-*d*]pyrimido[1,2-*a*]pyrimidine **(19)**, and cyclopenta[1,2-*d*]pyrimido[1,2-*a*]pyrimidine **(20)** in overall good yields.

Imidazolo[4,5-*d*]imidazo[1,2-*a*]pyrimidine derivative (**21**) is derived from a new parent system and was prepared from imidazolonitrile and **3** at 150° for 2 hours under nitrogen in neat reaction. Compound **22** was also obtained by neat reaction from imidazolonitrile with **4** in 62% yield.

Various solvents and different reaction conditions were applied to accomplish the desired cyclization products **11-22**. The best results were obtained either in HMPTA at 160° or neat reaction at 150°.

EXPERIMENTAL

Melting points were determined on a Yanaco hot stage apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra were obtained using a JNM - ALPHA 500 (500 MHz) spectrometer. The solvents were deuterated dimethyl sulfoxide and chloroform, respectively. The δ-values are given in ppm and the internal standard was tetramethylsilane. Elemental analyses were performed on an EA 1108 (Fisons Instruments) Elemental Analyzer**.**

2-Amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carbonitrile and ethyl 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylate were prepared according to Gewald procedure [13] in 72% and 65% yields, respectively. 2-Amino-4,5-dimethylfuran-3-carbonitrile is prepared according to the literature procedure [14]. Ethyl 2-amino-1-cyclopentene-1-carboxylate, and methyl 2-amino-1-cyclohexene-1-carboxylate were purchased from Kanto Chemicals. 4-Amino-1*H*-imidazole-5-carbonitrile was purchased from TCI (Tokyo Chemical Industry Co., Ltd.).

2-Methylthio-2-thiazoline (**1**) [15,16] and 5,6-dihydro-2-methylthio-4*H*-1,3-thiazine (**2**) [15,17] were prepared by condensation of ethanolamine or propanolamine and CS_2 in water in the presence of excess NaOH followed by methylation with methyl iodide. 2-Methylthio-2-imidazoline (**3**) and 2-methylthio-1,4,5,6-tetrahydro-pyrimidine (**4**) were prepared according to literature procedures [18,19].

General Procedure for the Cyclization Reaction: Synthesis of Compounds **5-10.**

A solution of *ortho*-aminoester (5 mmoles) and iminothioacetal reagent (**1** and **2**, 5 mmole) was heated to reflux temperature in dry acetic acid (6 ml) for an appropriate period of time. After cooling to room temperature, crushed ice was added, and the mixture stirred for 1 hour. The separated product was collected by filtration and crystallized from methanol or ethanol.

2,3,6,9-Tetrahydro-5*H*,7*H*-thiazolo[3,2-*a*]pyrano[4',3':4,5]-thieno[2,3-*d*]pyrimidin-5-one (**5**).

From ethyl 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylate and 2-methylthio-2-thiazoline, reaction time 5 hours, recrystallized from methanol as red crystals, mp 157°, yield 61%; ^1H nmr (deuteriochloroform): δ_H 2.83 (t, 2H, 6-H, J = 5.1 Hz), 3.41 (t, 2H, 2-H, J = 7.0 Hz), 3.87 (t, 2H, 7-H, J = 5.4 Hz), 4.32 (t, 2H, 3-H, J = 7.0 Hz), 4.47 (s, 2H, 9-H); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ_C 26.00 (t, C-6), 26.93 (t, C-2), 48.21 (t, C-3), 64.06 (t, C-7), 64.57 (t, C-9), 118.83 (s, C-5b), 128.38 (s, C-5a), 130.57 (s, C-9a), 157.05 (s, C-10a), 159.60 (s, C-11a), 164.21 (s, C=O).

Anal. Calcd. for $C_{11}H_{10}N_2O_2S_2$: C, 49.60; H, 3.78; N, 10.51. Found: C, 49.51; H, 3.70; N, 10.45.

2,3,6,7,8,9-Hexahydro-5*H*-cyclohexa[1,2-*d*]thiazolo[3,2-*a*]-pyrimidin-5-one (**6**).

From methyl 2-amino-1-cyclohexene-1-carboxylate and 2-methylthio-2-thiazoline, reaction time 20 hours, recrystallized from ethanol as red crystals, mp 130°, yield 64%; ^1H nmr (deuteriochloroform): δ_H 1.64-1.70 (m, 4H, 7-H and 8-H), 2.39 (t, 2H, 6-H), 2.49 (t, 2H, 9-H), 3.38 (t, 2H, 2-H, J = 7.6 Hz), 4.38 (t, 2H, 3-H, J = 7.6 Hz); ^{13}C nmr (deuteriochloroform): δ_C 21.42 (t, C-7), 21.87 (t, C-8), 26.29 (t, C-2), 26.41 (t, C-6), 31.42 (t, C-9), 48.21 (t, C-3), 116.77 (s, C-5a), 148.98 (s, C-9a), 160.18 (s, C-10a), 162.31 (s, C=O).

Anal. Calcd. for $C_{10}H_{12}N_2OS$: C, 57.66; H, 5.80; N, 13.44. Found: C, 57.79; H, 5.66; N 13.28.

2,3,7,8-Tetrahydro-5*H*,6*H*-cyclopenta[1,2-*d*]thiazolo[3,2-*a*]-pyrimidin-5-one (**7**).

From ethyl 2-amino-1-cyclopentene-1-carboxylate and 2-methylthio-2-thiazoline, reaction time 24 hours, recrystallized from ethanol as red crystals, mp 120°, yield 60%; ^{1}H nmr (deuteriochloroform): δ_H 1.91 (m, 2H, 7-H), 2.52 (t, 2H, 6-H), 2.80 (t, 2H, 8-H), 3.43 (t, 2H, 2-H, J = 7.3 Hz), 4.38 (t, 2H, 3-H, J = 7.3 Hz); ^{13}C nmr (deuteriochloroform): δ_C 21.22 (t, C-7), 28.15 (t, C-2), 26.86 (t, C-6), 34.53 (t, C-8), 48.00 (t, C-3), 105.92 (s, C-5a), 155.10 (s, C-8a), 156.31 (s, C-9a), 168.12 (s, C=O).

Anal. Calcd. for $C_9H_{10}N_2OS$: C, 55.64; H, 5.18; N, 14.41. Found: C, 55.53; H, 5.05; N 14.26.

2,3,4,7,8,10-Hexahydro-6*H*-pyrano[4",3":4',5']thieno[2',3':4,5]-pyrimido[2,1-*b*][1,3]thiazin-6-one (**8**).

From ethyl 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylate and 5,6-dihydro-2-methylthio-4*H*-1,3-thiazine, reaction time 7 hours, recrystallized from methanol as red crystals, mp 140°, yield 58%; ^{1}H nmr (deuteriochloroform): δ_H 2.30 (m, 2H, 3-H), 2.90 (t, 2H, 7-H, J = 5.1 Hz), 3.20 (t, 2H, 2-H, J = 7.0 Hz), 3.92 (t, 2H, 8-H, J = 5.4 Hz), 4.20 (t, 2H, 4-H, J = 6.5 Hz), 4.59 (s, 2H, 10-H); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ_C 22.93 (t, C-3), 26.04 (t, C-7), 27.73 (t, C-2), 40.88 (t, C-4), 64.17 (t, C-8), 64.84 (t, C-10), 118.86 (s, C-6b), 127.80 (s, C-6a), 130.65 (s, C-10a), 154.19 (s, C-11a), 157.68 (s, C-12a), 161.94 (s, C=O).

Anal. Calcd. for $C_{12}H_{12}N_2O_2S_2$: C, 51.40; H, 4.31; N, 9.99. Found: C, 51.26; H, 4.23; N 10.04.

3,4,7,8,9,10-Hexahydro-2*H*,6*H*-cyclohexa[4',3':4,5]pyrimido[2,1-*b*]-[1,3]thiazin-6-one (**9**).

From methyl 2-amino-1-cyclohexene-1-carboxylate and 5,6-dihydro-2-methylthio-4*H*-1,3-thiazine, reaction time 20 hours, recrystallized from ethanol as red crystals, mp 106-107°, yield 59%; ^{1}H nmr (deuteriochloroform): δ_H 1.64-1.72 (m, 4H, 8-H and 9-H), 2.30 (m, 2H, 3-H), 2.39 (t, 2H, 7-H), 2.50 (t, 2H, 10-H), 3.20 (t, 2H, 2-H, J = 7.5 Hz), 4.10 (t, 2H, 4-H, J = 6.5 Hz); ^{13}C nmr (deuteriochloroform): δ_C 22.25 (t, C-8), 22.80 (t, C-9), 22.84 (t, C-3), 26.64 (t, C-7), 27.80 (t, C-2), 31.79 (t, C-10), 40.78 (t, C-4), 115.24 (s, C-6a), 148.72 (s, C-10a), 157.98 (s, C-11a), 161.78 (s, C=O).

Anal. Calcd. for $C_{11}H_{14}N_2OS$: C, 59.43; H, 6.34; N, 12.59. Found: C, 59.48; H, 6.36; N 12.47.

2,3,4,7,8,9-Hexahydro-6*H*-cyclopenta[4',3':4,5]pyrimido[2,1-*b*]-[1,3]thiazin-6-one (**10**).

From ethyl 2-amino-1-cyclopentene-1-carboxylate and 5,6-dihydro-2-methylthio-4*H*-1,3-thiazine, reaction time 24 hours, recrystallized from ethanol as red crystals, mp 96-97°, yield 56%; ^{1}H nmr (deuteriochloroform) : δ_H 1.94 (m, 2H, 8-H), 2.40 (m, 2H, 3-H), 2.60 (t, 2H, 7-H), 2.82 (t, 2H, 9-H), 3.20 (t, 2H, 2-H, J = 7.3 Hz), 4.20 (t, 2H, 4-H, J = 6.5 Hz); ^{13}C nmr (deuteriochloroform): δ_C 21.68 (t, C-8), 23.04 (t, C-3), 27.80 (t, C-2), 26.91 (t, C-7), 34.55 (t, C-9), 41.00 (t, C-4), 105.90 (s, C-6a), 155.85 (s, C-9a), 156.04 (s, C-10a), 166.70 (s, C=O).

Anal. Calcd. for $C_{10}H_{12}N_2OS$: C, 57.66; H, 5.80; N, 13.44. Found: C, 57.55; H, 5.89; N 13.36.

General Procedure for the Cyclization Reaction: Synthesis of Compounds **11**-**20**.

A solution of *ortho*-aminoester or *ortho*-aminonitrile (4 mmoles) and appropriate reagent (**3** and **4**, 6 mmoles) in hexamethylphosphoric triamide (HMPTA, 5 ml) was heated to 160° for an appropriate period of time. After cooling to room temperature, crushed ice (70g) was added and the mixture stirred for 1 hour. The resulting crystals were collected by filtration and were purified by recrystallization from an appropriate solvent.

1,2,3,6,7,9-Hexahydro-5*H*-imidazo[1,2-*a*]pyrano[4',3':4,5]thieno-[2,3-*d*]pyrimidin-5-one (**11**).

From ethyl 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylate and 2-methylthio-2-imidazoline, reaction time 5 hours, recrystallized from methanol as red crystals, mp 170° (decomposed), yield 70%; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ_H 2.64 (t, 2H, 6-H, J = 4.9 Hz), 3.62 (t, 2H, 2-H, J = 6.5 Hz), 3.76 (t, 2H, 7-H, J = 5.4 Hz), 4.12 (t, 2H, 3-H, J = 6.5 Hz), 4.58 (s, 2H, 9-H), 9.94 (s, 1H, NH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ_C 27.27 (t, C-6), 42.03 (t, C-2), 47.01 (t, C-3), 63.81 (t, C-7), 64.13 (t, C-9), 113.41 (s, C-5b), 127.55 (s, C-5a), 129.19 (s, C-9a), 155.85 (s, C-10a), 156.71 (s, C-11a), 164.79 (s, C=O).

Anal. Calcd. for $C_{11}H_{11}N_3O_2S$: C, 52.99; H, 4.44; N, 16.85. Found: C, 52.84; H, 4.32; N, 16.71.

1,2,3,6,7,9-Hexahydro-5*H*-imidazo[1,2-*a*]pyrano[4',3':4,5]-thieno[2,3-*d*]pyrimidin-5-imine (**12**).

From 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carbonitrile and 2-methylthio-2-imidazoline, reaction time 10 hours, recrystallized from methanol as red crystals, mp >300°, yield 60%; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ_H 2.98 (t, 2H, 6-H, J = 4.9 Hz), 3.58 (t, 2H, 2-H, J = 6.5 Hz), 3.75 (t, 2H, 7-H, J = 5.4 Hz), 3.92 (t, 2H, 3-H, J = 6.5 Hz), 4.56 (s, 2H, 9-H), 8.55 (s, 1H, NH), 9.86 (s, 1H, NH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ_C 26.76 (t, C-6), 42.21 (t, C-2), 44.01 (t, C-3), 64.08 (t, C-7), 64.23 (t, C-9), 114.24 (s, C-5b), 127.64 (s, C-5a), 129.42 (s, C-9a), 154.97 (s, C--10a), 156.31 (s, C-11a), 162.25 (s, C-5).

Anal. Calcd. for $C_{11}H_{12}N_4OS$: C, 53.20; H, 4.87; N, 22.56. Found: C, 53.07; H, 4.78; N 22.37.

6,7-Dimethyl-2,3-dihydro-1*H*,5*H*-furo[2,3-*d*]imidazo[1,2-*a*]-pyrimidin-5-imine (**13**).

From 2-amino-4,5-dimethylfuran-3-carbonitrile and 2-methylthio-2-imidazoline, reaction time 4 hours, recrystallized from methanol as colourless crystals, mp 210°, yield 59%; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ_H 2.08 (s, 3H, 6-Me), 2.27 (s, 3H, 7-Me), 3.34 (t, 2H, 2-H, J = 6.4 Hz), 3.72 (t, 2H, 3-H, J = 6.4 Hz), 7.41 (s, 1H, NH), 8.85 (s, 1H, NH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ_C 14.21 (q, 6-Me), 14.53 (q, 7-Me), 45.14 (t, C-2), 51.02 (t, C-3), 95.46 (s, C-6), 118.17 (s, C-5a), 124.20 (s, C-7), 146.79 (s, C-8a), 157.70 (s, C-9a), 162.10 (s, C-5).

Anal. Calcd. for $C_{10}H_{12}N_4O$: C, 58.80; H, 5.92; N, 27.43. Found: C, 58.92; H, 5.89; N, 27.58.

2,3,6,7,8,9-Hexahydro-1*H*,5*H*-cyclohexa[1,2-*d*]imidazo[1,2-*a*]-pyrimidin-5-one (**14**).

From methyl 2-amino-1-cyclohexene-1-carboxylate and 2-methylthio-2-imidazoline, reaction time 12 hours, purified by column chromatography (silica gel, chloroform/acetone 9:2) to give **14** as colourless crystals, mp 225°, yield 58%; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ_H 1.62-1.72 (m, 4H, 7-H and 8-H), 2.35

(t, 2H, 6-H), 2.49 (t, 2H, 9-H), 3.60 (t, 2H, 2-H, J = 6.7 Hz), 3.90 (t, 2H, 3-H, J = 6.7 Hz), 8.53 (s, 1H, NH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ_C 21.45 (t, C-7), 21.90 (t, C-8), 26.70 (t, C-6), 31.49 (t, C-9), 40.08 (t, C-2 and C-3), 125.54 (s, C-5a), 146.60 (s, C-9a), 156.90 (s, C-10a), 166.15 (s, C=O).

Anal. Calcd. for $C_{10}H_{13}N_3O$: C, 62.80; H, 6.85; N, 21.97. Found: C, 62.93; H, 6.79; N, 21.80.

1,2,3,6,7,8-Hexahydro-5*H*-cyclopenta[1,2-*d*]imidazo[1,2-*a*]-pyrimidin-5-one (**15**).

From ethyl 2-amino-1-cyclopentene-1-carboxylate and 2-methylthio-2-imidazoline, reaction time 12 hours, purified by column chromatography (silica gel, chloroform/acetone 9:2) to give **15** as colourless crystals, mp 240°, yield 52%; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ_H 1.89 (m, 2H, 7-H), 2.52 (t, 2H, 6-H), 2.79 (t, 2H, 8-H), 3.59 (t, 2H, 2-H, J = 6.5 Hz), 4.01 (t, 2H, 3-H, J = 6.5 Hz), 9.08 (s, 1H, NH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ_C 21.64 (t, C-7), 26.90 (t, C-6), 34.59 (t, C-8), 42.80 (t, C-2), 42.84 (t, C-3), 108.01 (s, C-5a), 148.75 (s, C-8a), 156.20 (s, C-9a), 168.12 (s, C=O).

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.25; N, 23.71. Found: C, 60.83; H, 6.14; N, 23.85.

2,3,4,7,8,10-Hexahydro-1*H*,6*H*-pyrimido[1,2-*a*]pyrano-[4',3':4,5]thieno[2,3-*d*]pyrimidin-6-one (**16**).

From ethyl 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylate and 2-methylthio-1,4,5,6-tetrahydropyrimidine, reaction time 5 hours, recrystallized from methanol as yellow crystals, mp 250°, yield 72%; ^{1}H nmr (deuteriochloroform): δ_H 2.07 (m, 2H, 3-H), 2.99 (t, 2H, 7-H, J = 4.9 Hz), 3.50 (t, 2H, 2-H, J = 5.8 Hz), 3.94 (t, 2H, 4-H, J = 5.8 Hz), 4.01 (t, 2H, 8-H, J = 4.9 Hz), 4.66 (s, 2H, 10-H), 7.81 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ_C 20.58 (t, C-3), 26.21 (t, C-7), 38.87 (t, C-2), 39.37 (t, C-4), 64.57 (t, C-8), 64.97 (t, C-10), 113.40 (s, C-6b), 123.92 (s, C-6a), 128.69 (s, C-10a), 150.14 (s, C-11a), 157.35 (s, C-12a), 165.86 (s, C=O).

Anal. Calcd. for $C_{12}H_{13}N_3O_2S$: C, 54.73; H, 4.97; N, 15.95. Found: C, 54.81; H, 4.89; N, 15.81.

2,3,4,7,8,10-Hexahydro-1*H*,6*H*-pyrimido[1,2-*a*]pyrano-[4',3':4,5]thieno[2,3-*d*]pyrimidin-6-imine (**17**).

From 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carbonitrile and 2-methylthio-1,4,5,6-tetrahydropyrimidine, reaction time 4 hours, recrystallized from methanol as brown crystals, mp 294-295°°, yield 63%; ^{1}H nmr (deuteriochloroform) : δ_H 2.08 (m, 2H, 3-H), 2.98 (t, 2H, 7-H, J = 4.9 Hz), 3.50 (t, 2H, 2-H, J = 5.8 Hz), 3.95 (t, 2H, 4-H, J = 5.8 Hz), 4.05 (t, 2H, 8-H, J = 5.4 Hz), 4.67 (s, 2H, 10-H), 6.70 (s, 1H, NH), 7.50 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ_C 20.79 (t, C-3), 27.18 (t, C-7), 38.90 (t, C-2), 39.83 (t, C-4), 64.62 (t, C-8), 64.92 (t, C-10), 113.16 (s, C-6b), 123.41 (s, C-6a), 127.37 (s, C-10a), 150.02 (s, C-11a), 156.28 (s, C-12a), 160.63 (s, C-6).

Anal. Calcd. for $C_{12}H_{14}N_4OS$: C, 54.94; H, 5.37; N, 21.35. Found: C, 54.82; H, 5.46; N, 21.51.

7,8-Dimethyl-1,2,3,4-tetrahydro-6*H*-furo[2,3-*d*]pyrimido[1,2-*a*]-pyrimidin-6-imine (**18**).

From 2-amino-4,5-dimethylfuran-3-carbonitrile and 2-methylthio-1,4,5,6-tetrahydropyrimidine, reaction time 4 hours, recrystallized from methanol as red crystals, mp 275°°, yield 60%; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ_H 1.91 (m, 2H, 3-H), 2.03 (s, 3H, 7-Me)., 2.20 (s, 3H, 8-Me), 3.43 (t, 2H, 2-H, J = 5.8 Hz), 4.01 (t, 2H, 4-H, J = 5.8 Hz), 7.30 (s, 1H, NH), 8.72 (s, 1H, NH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ_C 14.20 (q, 7-Me), 14.65 (q, 8-Me), 20.77 (t, C-3), 39.21 (t, C-2), 40.43 (t, C-4), 95.94 (s, C-7), 110.29 (s, C-6a), 141.61 (s, C--8), 150.79 (s, C-9a), 157.72 (s, C-10a), 162.17 (s, C-6).

Anal. Calcd. for $C_{11}H_{14}N_4O$: C, 60.53; H, 6.46; N, 25.67. Found: C, 60.41; H, 6.51; N, 25.47

1,2,3,4,7,8,9,10-Octahydro-6*H*-cyclohexa[1,2-*d*]pyrimido[1,2-*a*]-pyrimidin-6-one (**19**).

From methyl 2-amino-1-cyclohexene-1-carboxylate 2-methylthio-1,4,5,6-tetrahydropyrimidine, reaction time 8 hours, purified by column chromatography (silica gel, chloroform/acetone 9:2) to give **19** as colourless crystals, mp 237-238°°, yield 60%; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ_H 1.62-1.74 (m, 4H, 8-H and 9-H), 1.90 (m, 2H, 3-H), 2.30 (t, 2H, 7-H), 2.52 (t, 2H, 10-H), 3.70 (t, 2H, 2-H, J = 6.0 Hz), 3.80 (t, 2H, 4-H, J = 6.0 Hz), 7.80 (s, 1H, NH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ_C 21.42 (t, C-8), 21.82 (t, C-9), 22.70 (t, C-3), 26.63 (t, C-7), 31.40 (t, C-10), 38.40 (t, C-2), 38.47 (t, C-4), 124.39 (s, C-6a), 146.96 (s, C-10a), 157.12 (s, C-11a), 165.01 (s, C=O).

Anal. Calcd. for $C_{11}H_{15}N_3O$: C, 64.36; H, 7.36; N, 20.47. Found: C, 64.23; H, 7.27; N, 20.61

2,3,4,7,8,9-Hexahydro-1*H*,6*H*-cyclopenta[1,2-*d*]pyrimido[1,2-*a*]-pyrimidin-6-one (**20**).

From ethyl 2-amino-1-cyclopentene-1-carboxylate and 2-methylthio-1,4,5,6-tetrahydropyrimidine, reaction time 10 hours, purified by column chromatography (silica gel, chloroform/acetone 9:2) as colourless crystals, mp 256-257°°, yield 57%; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ_H 1.83 (m, 2H, 8-H), 1.90 (m, 2H, 3-H), 2.48 (t, 2H, 7-H), 2.76 (t, 2H, 9-H), 3.40 (t, 2H, 2-H, J = 6.0 Hz), 3.90 (t, 2H, 4-H, J = 6.0 Hz), 7.70 (s, 1H, NH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ_C 21.60 (t, C-8), 22.90 (t, C-3), 26.87 (t, C-7), 34.50 (t, C-9), 38.40 (t, C-2), 38.50 (t, C-3), 107.90 (s, C-6a), 148.62 (s, C-9a), 157.45 (s, C-10a), 164.80 (s, C=O).

Anal. Calcd. for $C_{10}H_{13}N_3O$: C, 62.80; H, 6.85; N, 21.97. Found: C, 62.63; H, 6.76; N, 21.78.

1,5,6,7-Tetrahydro-9*H*-imidazolo[4,5-*d*]imidazo[1,2-*a*]pyrimidin-9-imine (**21**).

A mixture of 4-amino-1*H*-imidazole-5-carbonitrile (1.17g, 9 mmole) and 2-methylthio-2-imidazoline (1.38g, 12 mmole) was heated to 150° under nitrogen for 2 hours. The solid mass was chromatographed on silica gel (chloroform/acetone 9:2) to give **21** as light yellow crystals, mp 241-242°, 0.80g (42%); ^{1}H nmr (deuteriochloroform): δ_H 3.60 (t, 2H, 6-H, J = 6.5 Hz), 3.90 (t, 2H, 7-H, J = 6.5 Hz), 7.50 (s, 1H, NH), 7.70 (s, 1H, NH), 8.15 (d, 1H, 2-H), 8.30 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ_C 51.01 (t, C-6), 53.06 (t, C-7), 139.14 (s, C-9a), 147.54 (d, C-2), 149.45 (s, C-3a), 155.10 (s, C-4a), 160.41 (s, C-9).

Anal. Calcd. for $C_7H_8N_6$: C, 47.72; H, 4.57; N, 47.70. Found: C, 47.56; H, 4.48; N 47.43.

5,6,7,8-Tetrahydro-1*H*,10*H*-imidazolo[4,5-*d*]pyrimido[1,2-*a*]-pyrimidin-10-imine (**22**).

A mixture of 4-amino-1*H*-imidazole-5-carbonitrile (1.17g, 9 mmoles) and 2-methylthio-1,4,5,6-tetrahydropyrimidine (1.56g, 12 mmoles) was heated to 150° under nitrogen for 2 hours. The solid mass was recrystallized from water-ethanol to give **22** as yellow crystals, mp 250-251°, 1.15g (56%); ^{1}H nmr (deuterio-

chloroform): δ_H 1.90 (m, 2H, 7-H), 3.30 (t, 2H, 6-H, J = 5.5 Hz), 4.05 (t, 2H, 8-H, J = 5.5 Hz), 7.30 (s, 1H, NH), 7.44 (s, 1H, NH), 8.13 (d, 1H, 2-H), 8.24 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ_C 21.17 (t, C-7), 39.02 (t, C-6), 40.72 (t, C-8), 138.40 (s, C-10a), 147.12 (d, C-2), 149.36 (s, C-3a), 155.02 (s, C-4a), 158.25 (s, C-10).

Anal. Calcd. for $C_8H_{10}N_6$: C, 50.51; H, 5.29; N, 44.18. Found: C, 50.38; H, 5.21; N, 43.96.

Acknowledgements.

The authors wish to express their gratitude to the Japan Science Technology Agency (JST), for their financial support.

REFERENCES AND NOTES

* To whom correspondence should be made E.mail: a.chowdhury@nies.go.jp.

[1] J. V. Ram, H. K. Pandey and A. J. Vlietink, *J. Heterocyclic Chem*., **18**, 1277 (1981).

[2] A. Albert, Advances in Heterocyclic Chemistry, Vol. **39**, ed. A. R. Katritzky, Academic Press, New York, NY, 1986, p 117.

[3] C. Petrie, B. H. Cottam, A. P. Mckernam, R. K. Robins and R. G. Revankar, *J. Med. Chem.*, **28**, 1010 (1985).

[4] A. Santagati, M. Santagati and M. Modica, *Heterocycles*, **36**, 1315 (1993).

[5] J. Chern, P. Tao, M. Yen, G. Lu, C. Shiau, Y. Lai, S. Chien and C. Chan, *J. Med. Chem*., **36**, 2196 (1990).

[6] F. Sauter, J. Fröhlich and A. Z. M. S. Chowdhury, *Sci. Pharm*., **64**, 647 (1996).

[7] F. Sauter, J. Fröhlich, A. Z. M. S. Chowdhury and C. Hametner, *Monatsh. Chem*., **128**, 503 (1997).

[8] J. Fröhlich, F. Sauter, A. Z. M. S. Chowdhury and C. Hametner, *Sci. Pharm.*, **65**, 83 (1997).

[9] A. Z. M. S. Chowdhury, *J. Bangladesh Acad. Sci*., **23**, 59 (1999).

[10] A. Z. M. S. Chowdhury, and M. M. H. Bhuiyan, *J. Bangladesh Acad. Sci.*, **24**, 63 (2000).

[11] A. Z. M. S. Chowdhury and Y. Shibata, *Heterocycles*, **55**, 115 (2001).

[12] A. Z. M. S. Chowdhury, M. S. Rahman, M. M. H. Bhuiyan and L. Yasmin, *Pakistan J. Sci. Ind. Res.*, (in press).

[13] K. Gewald, E. Schinke, and H. Bottcher, *Chem. Ber.*, **94,** 99 (1966).

[14] J. Prousek, A. Jurasek and J. Kovac, *Collect. Czech. Chem. Commun.*, **49**, 1581 (1980).

[15] J. E. Jansen, US Patent, 2,293,465 (1942); *Chem. Abstr.*, **37**, 1300 (1943).

[16] A. K. Bose, J. L. Fahey and M. S. Manhas, *J. Heterocyclic Chem.*, **10**, 791 (1973).

[17] J. L. Fahey, B. C. Lange, J. M. Van der Veen, G. R. Young and A. K. Bose, *J. Chem. Soc. Perkin 1*, 1117 (1977).

[18] C. F. H. Allen, C. O. Edens and J. VanAllan, Org. Syn. Coll. Vol. **3**, 394 (1955).

[19] A. M. Dave, K. N. Bhatt, N. K. Undavia and P. B. Trivedi, *J. Indian Chem. Soc.*, **75**, 296 (1988)**.**