Synthesis of New Fused Pyrimidines by Isocyanate and Isothiocyanate

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***o*-Aminonitrile or *o*-aminoester compounds were cyclized to fused pyrimidines by reacting with ethyl iso(thio)cyanatoacetate in pyridine, and then were methylated, halogenated and subsequently displaced by the amines studied.**

Key words fused pyrimidine; urethane; displacement reaction; isothiocyanate; isocyanate; *o*-aminonitrile or ester compound

The development of physiologically highly potent fused pyrimidines with interesting antiviral, antibacterial, antimalarial, antiallergic, and radioprotective effects, antihypertensive agents and especially anticancer agents, generated us a great interest in facile and general routes to these molecules in synthetically useful yields.[1—4)]

Aromatic and heteroaromatic compounds bearing an *o*-aminonitrile or *o*-aminoester group are useful substrates for the preparation of various condensed fused pyrimidine heterocyclic systems.[5)] In more recent papers[6—9)] reporting heteroannelations giving access to fused pyrimidines, ethyl *N*-[bis(methylthio)methylene]aminoacetate, called BMMA, is used as a versatile reagent for the preparation of various fused pyrimidine systems (Chart 1).

In 1981, Papadopoulos described the reaction of anthranilonitrile with ethyl isocyanatoacetate, which allowed the preparation of the imidazo[1,2-*c*]quinazoline ring system in a 2- or 3-step procedures.[10)]

We have recently reported the synthesis of quinazoline,[11)] benzothienopyrimidine[11)] and benzofuropyrimidine[9)] systems by the reaction of *o*-aminoester or *o*-aminonitrile compounds with ethyl isothiocyanatoacetate. The present paper follows that line of research by reporting on a new series of fused pyrimidines. Here, we are reporting a simple reaction for the synthesis of fused pyrimidines by the reaction ethyl iso(thio)-cyanatoacetate with *o*-aminonitrile or *o*-aminoester compounds in the presence of pyridine.

Reaction of *o*-aminonitrile compounds with ethyl iso-(thio)cyanatoacetate gave double annelated products, fused pyrimidines **1a**—**d**, in one-pot reactions in 60—70% yield. As the cyclization obviously proceeded *via* thiourea intermediate **1I**, three possible products of the ensuing double-cyclization had to be considered (Chart 2).

The undesired but conceivable products, imidazo derivative **1L** and diazepine derivative **1M** could be ruled out by NMR spectroscopy. In the ^{1}H-NMR spectrum no peaks were found for $-NH_2$ and –OEt groups and in the ^{13}C-NMR spectrum –OEt peaks were also absent, which suggested that the 7-membered diazepine derivative **1M** could be clearly excluded. The method proved to be useful for giving smooth access to tricyclic and tetracyclic heterosystems as depicted by the formulas **1a**—**d**.

Thus, furo[3,2-*e*]imidazo[1,2-*c*]pyrimidine-2(3*H*)-one (**1a**) was synthesized in 72% yield as red needles from furonitrile and ethyl isothiocyanatoacetate in pyridine medium by one-pot reaction. Similarly, **1b** was prepared in 60% yield by a direct condensation of furonitrile with ethyl isocyanatoacetate without isolation of intermediate urea derivative. In a similar manner, imidazo[1,2-*c*]pyrano[4′,3′:4,5]thieno[3,2-*e*]pyrimidine-2(3*H*)-ones (**1c**, **d**) were also obtained frequently from 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carbonitrile (Chart 2).

Methylation of the thioxo group in **1a** with NaOMe and MeI in dry MeOH was carried in the usual manner to afford compound **2** in 76% yield, mp 250 °C (Chart 3). So, further conformation of the structure accorded to compound **1a** was supported by preparation of its methyl derivative **2**. Annelation of such type of angular tricyclic **2** was also established by Sauter *et al.*[6—9)] from *o*-aminonitrile compound with BMMA-reagents.

Compound **3** was prepared in the same manner as compound **1** but obtained bicyclic pyrazolo[3,4-*d*]pyrimidine (**3a**) and imidazo[4,5-*d*]pyrimidine (**3b**, **c**) derivatives. The failure of the formation of pyrazolo[5,4-*e*]imidazo[1,2-*c*]pyrimidine or imidazolo[5,4-*e*]imidazo[1,2-*c*]pyrimidine system, may be due to an electronic effect: the methyl group could be the reason for a +I effect, raising the nucleophilicity and the reactivity of the exocyclic amino function, also a binitrogen atom in the pyrazole and an imidazole ring as well as the steric effect. On the basis of NMR spectra of bicyclic cyclized products, which show ethoxycarbonylmethyl group, it can be concluded that in the formation of compound **3** ethoxycarbonylmethyl group attached at position 5 (in case of pyrazole nucleus) or at position 6 (in case of imidazole nucleus) in pyrimidine ring and participates to give derivatives of pyrazolo[3,4-*d*]pyrimidine (**3a**) and imidazo[4,5-*d*]pyrimidine systems (**3b**, **c**) (Chart 4).

Thus, the reaction of 5-amino-2-methylpyrazole-4-carbonitrile and ethyl isothiocyanatoacetate for reflux 1 h in pyridine led to the bicyclic product **3a** in 69% yield. By a similar method treatment of 4-amino-1*H*-imidazole-5-carbonitrile with ethyl isothiocyanatoacetate in pyridine for 1 h furnished 6-ethoxycarbonylmethyl-7-imino-5-thioxo-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*d*]pyrimidine (**3b**) in 66% and

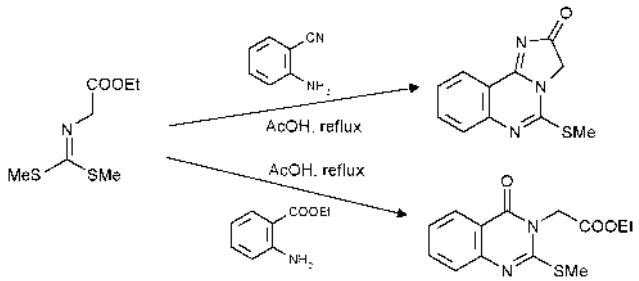

Chart 1. Reaction of *o*-Aminonitrile or *o*-Aminoester Compound with BMMA-Reagent in Acetic Acid

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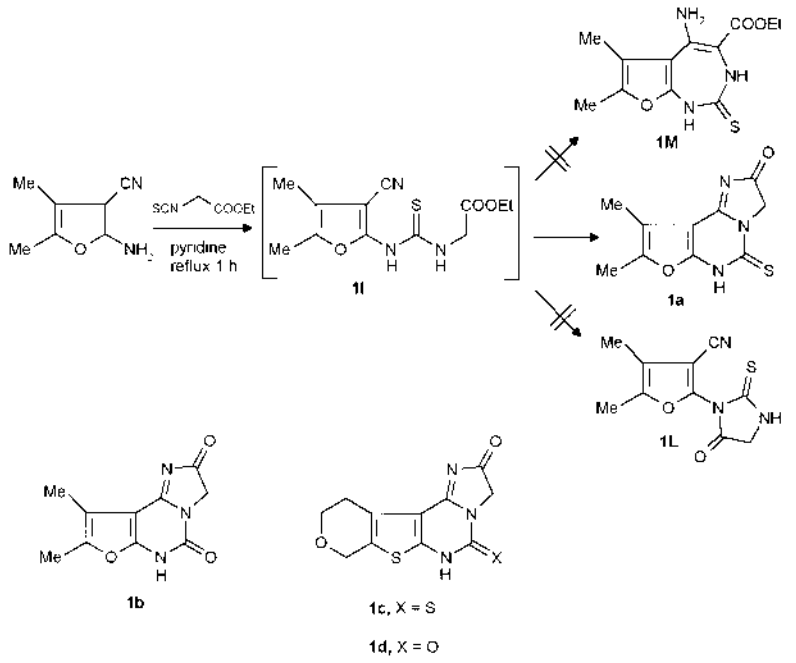

Chart 2. Reactions of *o*-Aminonitrile Compounds with Ethyl Isothiocyanatoacetate or Ethyl Isocyanatoacetate in Pyridine

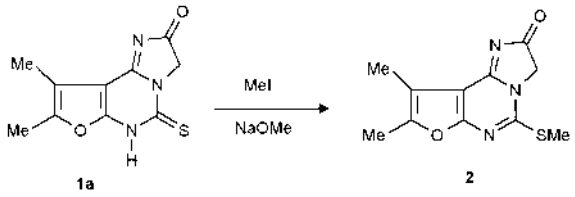

Chart 3. Methylation of Thioxo Compound

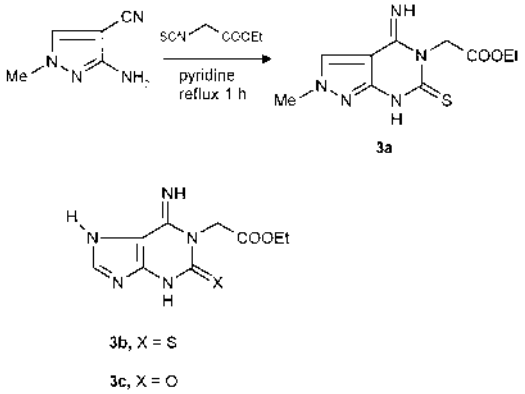

Chart 4. Reactions of Pyrazolonitrile and Imidazolonitrile with Ethyl Isothiocyanatoacetate or Ethyl Isocyanatoacetate in Pyridine

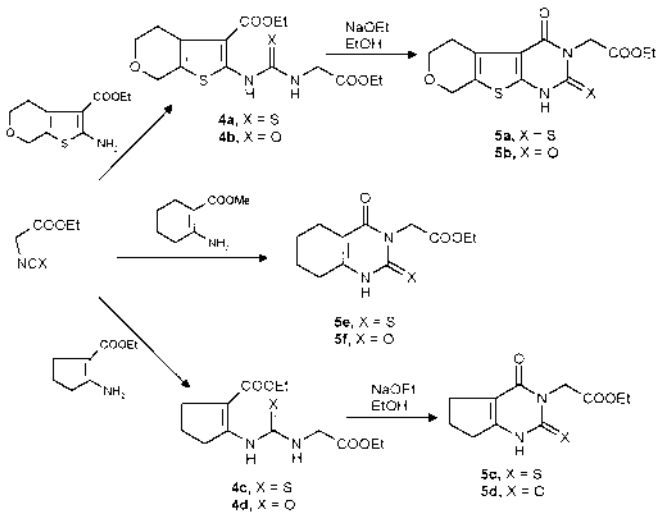

Chart 5. Reactions of *o*-Aminoester Compounds with Ethyl Isothiocyanatoacetate or Ethyl Isocyanatoacetate and Cyclization to Target Products

also furnished 63% of **3c** when ethyl isocyanatoacetate was used.

o-Aminoester compound was treated with ethyl isocyanatoacetate or ethyl isothiocyanatoacetate in pyridine to give the corresponding urea or thiourea derivatives (**4**) (Chart 5) as pale yellow needles in good yield. Treatment of ethyl 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylate with ethyl isothiocyanatoacetate in refluxing pyridine gave the thiourea derivative (**4a**) in 68% of yellow needles. A perusal of resulting urea (**4b**, **d**) and thiourea derivative (**4c**) were similarly readily accessible.

The reaction of methyl 2-amino-1-cyclohexene-1-carboxylate with ethyl isothiocyanatoacetate or ethyl isocyanatoacetate in boiling pyridine for 4 h gave the cyclized products: cyclohexa[1,2-*d*]pyrimidine system (**5e**, **f**) in excellent yield (76—84%), without isolation of the intermediates thiourea or urea derivatives.

Cyclization of urea or thiourea derivatives (**4**) into the thieno[2,3-*d*]pyrimidine or cyclopenta[1,2-*d*]pyrimidine compounds (**5a**—**d**) occurred in EtONa and EtOH with good yield (Chart 5).

Compound **5a** was chlorinated by $POCl_3$ to afford **6**, which was displaced by amines without further purification. Treatment of chloro compound **6** with hydrazine gave 1-amino-

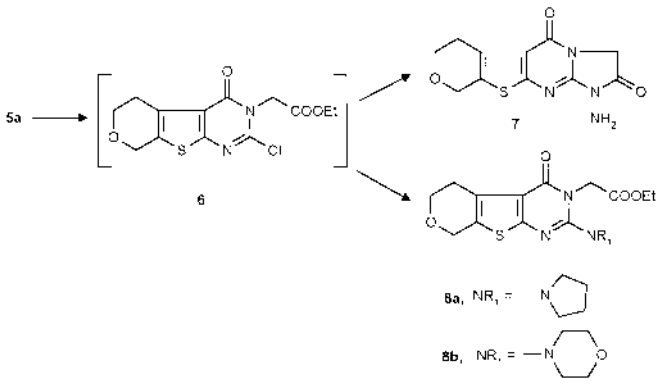

Chart 6. Halogenation of Thioxo Compound and Substitution by Amines

6,7,9-trihydroimidazo[1,2-*a*]pyrano[4′,3′:4,5]thieno[2,3-*d*]-pyrimidine-2,5(1*H*,3*H*)-dione (**7**) in 70% yield, mp 283 °C. The chloro product (**6**) was treated with pyrrolidine in triethylamine at reflux temperature and gave compound **8a** in 64% yield; with morpholine in triethylamine, it gave the morpholino derivative (**8b**) in 62% yield (Chart 6).

Experimental

Melting points were determined on a Yanaco hot stage apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a JNM-ALPHA 500 (500 MHz) spectrometer (internal standard TMS, solvents $CDCl_3$ or DMSO-d_6 respectively, δ-values in ppm) at the National Institute for Environmental Studies, Tsukuba, Japan. Elemental analyses were performed on an EA 1108 (Fisons Instruments) Elemental analyzer.

Ethyl isothiocyanatoacetate was prepared using the method reported by Sauter *et al.*[11] in 1996 as a syrup in 71% yield. 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 obtained according to the Gewald procedure[12] in 72% and 65% yields, respectively. 2-Amino-4,5-dimethylfuran-3-carbonitrile,[13] and 5-amino-2-methylpyrazole-4-carbonitrile[14] were prepared according to the procedures in the literature. Ethyl 2-amino-1-cyclopentene-1-carboxylate, methyl 2-amino-1-cyclohexene-1-carboxylate and ethyl isocyanatoacetate were purchased from Kanto Chemicals. 4-Amino-1*H*-imidazole-5-carbonitrile was purchased from TCI (Tokyo Chemical Industry Co., Ltd.).

8,9-Dimethyl-5-thioxo-5,6-dihydrofuro[3,2-*e*]imidazo[1,2-*c*]pyrimidine-2(3*H*)-one (1a) A solution of 2-amino-4,5-dimethylfuran-3-carbonitrile (0.81 g, 6 mmol) and ethyl isothiocyanatoacetate (0.87 g, 6 mmol) in 8 ml of pyridine was refluxed for 1 h. The reaction mixture was diluted with aqueous ethanol and cooled. The resulting crystals were collected by filtration and recrystallized from ethanol to give **1a** as red needles. Yield: 1.00 g (72%); mp 210 °C. ^{1}H-NMR (DMSO-d_6): δ_H 8.60 (1H, s, NH), 4.35 (2H, s, 3-H), 2.25 (3H, s, 8-Me), 2.10 (3H, s, 9-Me). ^{13}C-NMR (DMSO-d_6): δ_C 172.36 (s, C=O), 170.38 (s, C-6a), 166.10 (s, C=S), 148.65 (s, C-9b), 124.27 (s, C-8), 107.58 (s, C-9a), 95.46 (s, C-9), 53.35 (t, C-3), 14.46 (q, 8-Me), 14.13 (q, 9-Me). *Anal.* Calcd for $C_{10}H_9N_3O_2S$: C, 51.05; H, 3.85, N, 17.86. Found: C, 51.12; H, 3.90; N, 17.80.

8,9-Dimethyl-5-oxo-5,6-dihydrofuro[3,2-*e*]imidazo[1,2-*c*]pyrimidine-2(3*H*)-one (1b) A solution of 2-amino-4,5-dimethylfuran-3-carbonitrile (0.81 g, 6 mmol) and ethyl isocyanatoacetate (0.77 g, 6 mmol) in 8 ml of pyridine was refluxed for 1 h. The reaction mixture was diluted with aqueous ethanol and cooled. The resulting crystals were collected by filtration and recrystallized from ethanol to give **1b** as brown needles. Yield: 0.78 g (60%); mp 219—220 °C. ^{1}H-NMR (DMSO-d_6): δ_H 4.35 (2H, s, 3-H), 2.23 (3H, s, 8-Me), 2.08 (3H, s, 9-Me). ^{13}C-NMR (DMSO-d_6): δ_C 176.95 (s, C=O), 171.10 (s, C-6a), 169.50 (s, C=O), 157.70 (s, C-9b), 125.39 (s, C-8), 112.81 (s, C-9a), 95.47 (s, C-9), 56.00 (t, C-3), 14.53 (q, 8-Me), 14.21 (q, 9-Me). *Anal.* Calcd for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.13; N, 19.16. Found: C, 54.84; H, 3.99; N, 19.04.

5-Thioxo-6,8,10,11-tetrahydro-5*H*-imidazo[1,2-*c*]pyrano[4′,3′ : 4,5]-thieno[3,2-*e*]pyrimidine-2(3*H*)-one (**1c**): The title compound was prepared in the same manner as **1a** from 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carbonitrile and ethyl isothiocyanatoacetate, reaction time 4 h, recrystallized from ethanol to give **1c** as red needles. Yield: 63%; mp 270 °C (dec.). ^{1}H-NMR (DMSO-d_6): δ_H 4.68 (2H, s, 8-H), 4.36 (2H, s, 3-H), 3.90 (2H, t, 10-H), 2.82 (2H, t, 11-H). ^{13}C-NMR (DMSO-d_6): δ_C 181.55 (s, C=O), 167.48 (s, C=S), 161.83 (s, C-11c), 159.14 (s, C-6a), 128.24 (s, C-7a), 126.91 (s, C-11b), 111.51 (s, C-11a), 64.39 (t, C-8), 63.59 (t, C-10), 52.61 (t, C-3), 25.37 (t, C-11). *Anal.* Calcd for $C_{11}H_9N_3O_2S_2$: C, 47.29; H, 3.24; N, 15.04. Found: C, 47.40; H, 3.31; N, 14.94.

5-Oxo-6,8,10,11-tetrahydro-5*H*-imidazo[1,2-*c*]pyrano[4′,3′ : 4,5]-thieno[3,2-*e*]pyrimidine-2(3*H*)-one (**1d**): The title compound was prepared in the same manner as **1b** from 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carbonitrile and ethyl isocyanatoacetate, reaction time 4 h, recrystallized from ethanol to give **1d** as red needles. Yield: 54%; mp 190 °C (dec.). ^{1}H-NMR (DMSO-d_6): δ_H 4.55 (2H, s, 8-H), 4.36 (2H, s, 3-H), 3.92 (2H, t, 10-H), 3.30 (2H, t, 11-H). ^{13}C-NMR (DMSO-d_6): δ_C 182.46 (s, C=O), 170.02 (s, C=O), 156.41 (s, C-11c), 147.33 (s, C-6a), 128.83 (s, C-7a), 125.86 (s, C-11b), 113.16 (s, C-11a), 63.69 (t, C-8), 63.63 (t, C-10), 47.94 (t, C-3), 24.01 (t, C-11). *Anal.* Calcd for $C_{11}H_9N_3O_3S$: C, 50.18; H, 3.44; N, 15.96. Found: C, 50.32; H, 3.53; N, 15.84.

8,9-Dimethyl-5-methylthiofuro[3,2-*e*]imidazo[1,2-*c*]pyrimidine-2(3*H*)-one (2) To a solution of thioxo compound (**1a**) (2.35 g, 10 mmol) and NaOMe (0.53 g, 10 mmol) in dry methanol (35 ml) was added MeI (1.42 g, 10 mmol). The reaction mixture was refluxed under nitrogen for 2 h. The mixture was then cooled in water to give a solid, which was collected and recrystallized from ethanol to afford compound **2** as brown needles. Yield: 1.89 g (76%), mp 250 °C. ^{1}H-NMR (DMSO-d_6): δ_H 4.35 (2H, s, 3-H), 2.70 (3H, s, SMe), 2.20 (3H, s, 8-Me), 2.10 (3H, s, 9-Me). ^{13}C-NMR (DMSO-d_6): δ_C 182.77 (s, C=O), 169.10 (s, C-6a), 164.22 (s, C-5), 150.00 (s, C-9b), 120.20 (s, C-8), 110.38 (s, C-9a), 94.30 (s, C-8), 49.76 (t, C-3), 14.82 (q, 8-Me), 14.30 (q, 9-Me), 14.14 (q, SMe). *Anal.* Calcd for $C_{11}H_{11}N_3O_2S$: C, 52.99; H, 4.44; N, 16.85. Found: C, 53.10; H, 4.32; N, 16.73.

5-Ethoxycarbonylmethyl-4-imino-2-methyl-6-thioxo-4,5,67-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidine (3a) A solution of 5-amino-2-methylpyrazole-4-carbonitrile (73 g, 6 mmol) and ethyl isothiocyanatoacetate (0.87 g, 6 mmol) in 8 ml of pyridine was refluxed for 1 h. The reaction mixture was diluted with aqueous ethanol and cooled. The resulting crystals were collected by filtration and recrystallized from ethanol–DMF (10 : 1) to give **3a** as yellow needles. Yield: 1.10 g (69%); mp >300 °C. ^{1}H-NMR (DMSO-d_6): δ_H 12.50 (1H, s, NH), 9.00 (1H, s, NH), 8.20 (1H, s, 3-H), 4.30 (2H, s, CH_2), 4.10 (2H, q, OCH_2), 3.80 (3H, s, N-Me), 1.20 (3H, t, Me). ^{13}C-NMR (DMSO-d_6): δ_C 181.47 (s, C=S), 169.50 (s, C=O), 155.83 (s, C-4), 151.43 (s, C-7a), 127.38 (s, C-3), 97.60 (s, C-3a), 60.66 (t, OCH_2), 41.48 (t, CH_2), 39.49 (q, N–Me), 14.07 (q, Me). *Anal.* Calcd for $C_{10}H_{13}N_5O_2S$: C, 44.93; H, 4.90; N, 26.19. Found: C, 45.01; H, 4.94; N, 26.09.

6-Ethoxycarbonylmethyl-7-imino-5-thioxo-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*d*]pyrimidine (**3b**): Compound **3b** was obtained in 66% yield using a procedure similar to that which afforded **3a** from 4-amino-1*H*-imidazole-5-carbonitrile and ethyl isothiocyanatoacetate, reaction time 1 h, recrystallized from ethanol to give as pale yellow needles. Yield: 66%; mp >300 °C. ^{1}H-NMR (DMSO-d_6): δ_H 9.67 (1H, s, NH), 8.81 (1H, s, NH), 8.30 (1H, s, NH), 7.97 (1H, s, 2-H), 4.44 (2H, s, CH_2), 4.10 (2H, q, OCH_2), 1.21 (3H, t, Me). ^{13}C-NMR (DMSO-d_6): δ_C 175.83 (s, C=S), 167.08 (s, C=O), 151.33 (s, C-7), 149.40 (s, C-3a), 144.58 (s, C-2), 136.27 (s, C-7a), 60.86 (t, OCH_2), 40.09 (t, CH_2), 14.00 (q, Me). *Anal.* Calcd for $C_9H_{11}N_5O_2S$: C, 42.67; H, 4.37; N, 27.64. Found: C, 42.57; H, 4.40; N, 27.73.

6-Ethoxycarbonylmethyl-7-imino-5-oxo-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*d*]pyrimidine (**3c**): The title compound **3c** was prepared using the same procedure as **3a** from 4-amino-1*H*-imidazole-5-carbonitrile and ethyl isocyanatoacetate, reaction time 2 h, recrystallized from ethanol to give **3c** as yellow needles. Yield: 63%; mp >300 °C. ^{1}H-NMR (DMSO-d_6): δ_H 9.37 (1H, s, NH), 8.97 (1H, s, NH), 8.20 (H, s, NH), 7.99 (1H, s, 2-H), 4.50 (2H, s, CH_2), 4.11 (2H, q, OCH_2), 1.20 (3H, t, Me). ^{13}C-NMR (DMSO-d_6): δ_C 176.29 (s, C=O), 169.22 (s, C=O), 150 (s, C-7), 149.34 (s, C-3a), 144.06 (s, C-2), 135.93 (s, C-7a), 60.83 (t, OCH_2), 41.73 (t, CH_2), 14.05 (q, Me). *Anal.* Calcd for $C_9H_{11}N_5O_3$: C, 45.56; H, 4.67; N, 29.52. Found: C, 45.68; H, 4.80; N, 29.61.

Ethyl 2-[3-Ethoxycarbonylmethylthioureido]-4,7-dihydro-5*H*-thieno-[2,3-*c*]pyran-3-carboxylate (4a) A solution of ethyl 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylate (1.81 g, 8 mmol) and ethyl isothiocyanatoacetate (1.16 g, 8 mmol) in 12 ml of pyridine was refluxed for 1 h. The reaction mixture was diluted with aqueous ethanol and cooled. The resulting crystals were collected by filtration and recrystallized from ethanol to give **4a** as yellow needles. Yield: 2.01 g (68%); mp 180—181 °C. ^{1}H-NMR ($CDCl_3$): δ_H 8.65 (1H, s, NH), 7.69 (1H, s, NH), 4.60 (2H, s, 7-H), 4.34 (2H, s, CH_2), 4.26—4.22 (4H, q, OCH_2), 3.87 (2H, t, 5-H), 2.79 (2H, t, 4-H), 1.45—1.13 (6H, t, 2Me). ^{13}C-NMR (DMSO-d_6): δ_C 177.67 (s. C=S),

169.76 (s, C=O), 166.19 (s, C=O), 151.69 (s, C-2), 136.59 (s, C-7a), 128.01 (s, C-3), 123.91 (s, C-3a), 64.54 (t, C-7), 64.25 (t, C-5), 61.83 (t, OCH_2), 60.98 (t, OCH_2), 46.99 (t, CH_2), 26.92 (t, C-4), 14.32 (q, Me), 14.01 (q, Me). *Anal.* Calcd for $C_{15}H_{20}N_2O_5S_2$: C, 48.36; H, 5.41; N, 7.52. Found: C, 48.31; H, 5.46; N, 7.39.

Ethyl 2-[3-Ethoxycarbonylmethylureido]-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylate (4b) A solution of ethyl 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylate (1.81 g, 8 mmol) and ethyl isocyanatoacetate (1.03 g, 8 mmol) in 12 ml of pyridine was refluxed for 1 h. The reaction mixture was diluted with aqueous ethanol and cooled. The resulting crystals were collected by filtration and recrystallized from ethanol to afford **4b** as pale yellow needles. Yield: 1.73 g (61%); mp 196 °C. ^{1}H-NMR ($CDCl_3$): δ_H 9.10 (1H, s, NH), 7.87 (1H, t, NH), 4.60 (2H, s, 7-H), 4.35 (2H, s, CH_2), 4.25—4.19 (4H, q, OCH_2), 3.82 (2H, t, 5-H), 2.78 (2H, t, 4-H), 1.42—1.14 (6H, t, 2Me). ^{13}C-NMR (DMSO-d_6): δ_C 169.19 (s, C=O), 167.32 (s, C=O), 159.78 (s, C=O), 152.13 (s, C-2), 137.32 (s, C-7a), 129.07 (s, C-3), 122.61 (s, C-3a), 64.51 (t, C-7), 64.22 (t, C-5), 61.90 (t, OCH_2), 61.08 (t, OCH_2), 46.51 (t, CH_2), 26.75 (t, C-4), 14.30 (q, Me), 14.07 (q, Me). *Anal.* Calcd for $C_{15}H_{20}N_2O_6S$: C, 50.54; H, 5.65; N, 7.85. Found: C, 50.43; H, 5.73; N, 7.78.

Ethyl 2-[3-Ethoxycarbonylmethylthioureido]cyclopentene-1-carboxylate (4c) A solution of ethyl 2-amino-1-cyclopentene-1-carboxylate (0.93 g, 6 mmol) and ethyl isothiocyanatoacetate (0.87 g, 6 mmol) in 8 ml of pyridine was refluxed for 2 h. The reaction mixture was diluted with aqueous ethanol and cooled. The resulting crystals were collected by filtration and recrystallized from ethanol to give **4c** as pale yellow needles. Yield: 1.36 g (76%); mp 138—139 °C. ^{1}H-NMR ($CDCl_3$): δ_H 9.89 (1H, s, NH), 8.06 (1H, s, NH), 4.35 (2H, s, CH_2), 4.22—4.14 (4H, q, OCH_2), 3.06 (2H, t, 5-H), 2.55 (2H, t, 3-H), 1.86 (2H, m, 4-H), 1.24—1.19 (6H, t, 2Me). ^{13}C-NMR ($CDCl_3$): δ_C 176.24 (s, C=S), 166.63 (s, C=O), 157.96 (s, C=O), 147.50 (s, C-1), 109.91 (s, C-2), 61.51 (t, OCH_2), 61.12 (t, OCH_2), 47.98 (t, CH_2), 34.54 (t, C-5), 28.83 (t, C-3), 20.82 (t, C-4), 14.01 (q, Me), 13.95 (q, Me). *Anal.* Calcd. for $C_{13}H_{20}N_2O_4S$: C, 51.98; H, 6.71; N, 9.32. Found: C, 52.09; H, 6.59; N, 9.30.

Ethyl 2-[3-Ethoxycarbonylmethylureido]cyclopentene-1-carboxylate (4d) The title compound was obtained in the same manner as **4c** from ethyl 2-amino-1-cyclopentene-1-carboxylate and ethyl isocyanatoacetate, reaction time 2 h, recrystallized from ethanol to give **4d** as pale yellow needles. Yield: 58%; mp 150—151 °C. ^{1}H-NMR ($CDCl_3$): δ_H 9.46 (1H, s, NH), 8.82 (1H, s, NH), 4.35 (2H, s, CH_2), 4.25—4.18 (4H, q, OCH_2), 3.14 (2H, t, 5-H), 2.54 (2H, t, 3-H), 1.80 (2H, m, 4-H), 1.25—1.20 (6H, t, 2Me). ^{13}C-NMR ($CDCl_3$): δ_C 169.17 (s, C=O), 166.63 (s, C=O), 157.02 (s, C=O), 147.23 (s, C-1), 108.56 (s, C-2), 61.45 (t, OCH_2), 61.21 (t, OCH_2), 46.63 (t, CH_2), 36.02 (t, C-5), 27.96 (t, C-3), 21.92 (t, C-4), 14.12 (q, Me), 13.22 (q, Me). *Anal.* Calcd for $C_{13}H_{20}N_2O_5$: C, 54.91; H, 7.09; N, 9.85. Found: C, 55.02; H, 6.98; N, 9.94.

3-Ethoxycarbonylmethyl-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydrocyclohexa[1,2-*d*]pyrimidine (5e) A solution of methyl 2-amino-1-cyclohexene-1-carboxylate (0.93 g, 6 mmol) and ethyl isothiocyanatoacetate (0.87 g, 6 mmol) in 8 ml of pyridine was refluxed for 4 h. The reaction mixture was diluted with aqueous ethanol and cooled. The resulting crystals were collected by filtration and recrystallized from ethanol to give **5e** as white needles. Yield: 1.26 g (84%); mp 187—188 °C. ^{1}H-NMR ($CDCl_3$): δ_H 10.34 (1H, s, NH), 4.59 (2H, s, CH_2), 4.19—4.13 (2H, q, OCH_2), 2.31—2.29 (4H, t, 5-H, 8-H), 1.72—1.63 (4H, m, 6-H, 7-H), 1.23—1.13 (3H, t, Me). ^{13}C-NMR (DMSO-d_6): δ_C 170.76 (s, C=S), 167.15 (s, C=O), 154.56 (s, C=O), 147.50 (s, C-8a), 109.91 (s, C-4a), 61.51 (t, OCH_2), 41.25 (t, CH_2), 26.04 (t, C-8), 21.43 (t, C-5), 21.11 (t, C-7), 20.94 (t, C-6), 13.95 (q, Me). *Anal.* Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.72; H, 6.01; N, 10.44. Found: C, 53.66; H, 5.89; N, 10.32.

3-Ethoxycarbonylmethyl-2,4-dioxo-1,2,3,4,5,6,7,8-octahydrocyclohexa-[1,2-*d*]pyrimidine (**5f**): This compound was prepared in the same manner as **5e** from methyl 2-amino-1-cyclohexene-1-carboxylate acid and ethyl isocyanatoacetate, reaction time 4 h to give **5f** as pale yellow needles. Yield: 76%; mp 203—204 °C ^{1}H-NMR ($CDCl_3$): δ_H 8.56 (1H, s, NH), 4.50 (2H, s, CH_2), 4.22—4.15 (2H, q, OCH_2), 2.32—2.28 (4H, t, 5-H, 8-H), 1.70—1.64 (4H, m, 6-H, 7-H), 1.21—1.14 (3H, t, Me). ^{13}C-NMR (DMSO-d_6): δ_C 167.94 (s, C=O), 162.94 (s, C=O), 152.23 (s, C=O), 147.29 (s, C-8a), 107.53 (s, C-4a), 61.46 (t, OCH_2), 41.30 (t, CH_2), 26.00 (t, C-8), 21.67 (t, C-5), 21.50 (t, C-7), 20.62 (t, C-6), 13.86 (q, Me). *Anal.* Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.05; H, 6.45; N, 11.17.

General Procedure for the Cyclization of Urea and Thiourea Derivatives: Synthesis of Compounds 5a—d A solution of the corresponding urea or thiourea derivative (2 mmol) and NaOEt (2 mmol) in 10 ml of absolute ethanol (10 ml) was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the obtained solid was recrystallized from ethanol to give needles.

3-Ethoxycarbonylmethyl-4-oxo-2-thioxo-1,3,4,5,6,8-hexahydro-2*H*-pyrano[4′,3′ : 4,5]thieno[2,3-*d*]pyrimidine (**5a**): This compound was obtained from thiourea derivative (**4a**) as yellow needles. Yield: 74%; mp 226—227 °C. ^{1}H-NMR ($CDCl_3$): δ_H 7.44 (1H, s, NH), 4.60 (2H, s, 8-H), 4.35 (2H, s, CH_2), 4.25 (2H, q, OCH_2), 3.88 (2H, t, 6-H), 2.80 (2H, t, 5-H), 1.33—1.30 (3H, t, Me), 1.27—1.26 (3H, t, Me). ^{13}C-NMR (DMSO-d_6): δ_C 170.76 (s, C=S), 166.79 (s, C=O), 156.19 (s, C=O), 150.43 (s, C-9a), 136.56 (s, C-8a), 128.59 (s, C-4a), 112.40 (s, C-4b), 64.97 (t, C-8), 64.53 (t, C-6), 60.99 (t, OCH_2), 46.10 (t, CH_2), 26.94 (t, C-5), 14.15 (q, Me). *Anal.* Calcd for $C_{13}H_{14}N_2O_4S_2$: C, 47.83; H, 4.32; N, 8.58. Found: C, 47.92; H, 4.22; N, 8.47.

3-Ethoxycarbonylmethyl-2,4-dioxo-1,3,4,5,6,8-hexahydropyrano-2*H*-[4′,3′ : 4,5]thieno[2,3-*d*]pyrimidine (**5b**): This compound was obtained from urea derivative (**4b**) as yellow needles. Yield: 66%; mp 246—247 °C. ^{1}H-NMR ($CDCl_3$): δ_H 4.60 (2H, s, 8-H), 4.30 (2H, s, CH_2), 4.27—4.20 (2H, q, OCH_2), 3.96 (2H, t, 6-H), 2.75 (2H, t, 5-H), 1.30—1.10 (6H, t, 2Me). ^{13}C-NMR (DMSO-d_6): δ_C 169.42 (s, C=O), 166.19 (s, C=O), 157.23 (s, C=O), 151.21 (s, C-9a), 135.70 (s, C-8a), 129.87 (s, C-4a), 114.24 (s, C-4b), 64.63 (t, C-8), 64.29 (t, C-6), 60.70 (t, OCH_2), 46.01 (t, CH_2), 25.96 (t, C-5), 13.80 (q, Me). *Anal.* Calcd for $C_{13}H_{14}N_2O_5S$: C, 50.31; H, 4.54; N, 9.02. Found: C, 50.42; H, 4.59; N, 8.89.

3-Ethoxycarbonylmethyl-4-oxo-2-thioxo-1,3,4,5,6,7-hexahydro-2*H*-cyclopenta[1,2-*d*]pyrimidine (**5c**): This compound was obtained from thiourea derivative (**4c**) as yellow needles. Yield: 73%; mp 197—199 °C. ^{1}H-NMR ($CDCl_3$): δ_H 11.20 (1H, s, NH), 4.74 (2H, s, CH_2), 4.20 (2H, q, OCH_2), 3.08 (2H, s, 7-H), 2.52 (2H, t, 5-H), 1.95 (2H, m, 6-H), 1.20 (3H, t, Me). ^{13}C-NMR (DMSO-d_6): δ_C 172.60 (s, C=S), 166.90 (s, C=O), 159.53 (s, C=O), 155.85 (s, C-7a), 108.45 (s, C-4a), 60.68 (t, OCH_2), 47.83 (t, CH_2), 34.78 (t, C-7), 28.94 (t, C-5), 25.91 (t, C-6), 14.01 (q, Me). *Anal.* Calcd. for $C_{11}H_{14}N_2O_3S$: C, 51.95; H, 5.54; N, 11.01. Found: C, 52.08: H, 5.62; N, 11.10.

3-Ethoxycarbonylmethyl-2,4-dioxo-1,3,4,5,6,8-hexahydro-2*H*-cyclopenta[1,2-*d*]pyrimidine (**5d**): This compound was obtained from urea derivative (**4d**) as yellow needles. Yield: 68%; mp 218—219 °C. ^{1}H-NMR ($CDCl_3$): δ_H 8.45 (1H, s, NH), 5.12 (2H, s, CH_2), 4.73 (2H, q, OCH_2), 3.12 (2H, t, 7-H), 2.51 (2H, t, 5-H), 1.82 (2H, m , 6-H), 1.10 (3H, t, Me). ^{13}C-NMR (DMSO-d_6): δ_C 169.70 (s, C=O), 162.16 (s, C=O), 159.45 (s, C=O), 158.19 (s, C-7a), 103.87 (s, C-4a), 60.11 (t, OCH_2), 46.00 (t, CH_2), 34.51 (t, C-7), 27.17 (t, C-5), 21.21 (t, C-6), 14.15 (q, Me). *Anal.* Calcd for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.75. Found: C, 55.54; H, 5.98; N, 11.77.

1-Amino-6,9-dihydro-7*H*-imidazo[1,2-*a*]pyrano[4′,3′ : 4,5]thieno[2,3-*d*]pyrimidine-2,5(1*H*,3*H*)-dione (7) A suspension of the thioxo product (**5a**) (4.89 g, 15 mmol) in $POCl_3$ (100 ml) was refluxed at 120 °C for 18 h. Excess $POCl_3$ was distilled off under vacuum. Ether (100 ml) was added and the mixture stirred for 2 h. The solid **6** was collected by filtration and washed with ether to give brown needles. Yield: 3.84 g (78%), mp 122 °C (air sensitive).

A solution of the above solid **6** (0.32 g, 1 mmol) and hydrazine hydrate (0.05 g, 1.5 mmol) in triethylamine (5 ml) was refluxed for 2 h. The solvent was evaporated *in vacuo.* The obtained solid was recrystallized from ethanol and ethyl acetate (3 : 1) to give **7** as white needles. Yield: 0.18 g (70%), mp 283 °C. ^{1}H-NMR ($CDCl_3$): δ_H 5.20 (2H, s, NH_2), 4.58 (2H, s, 9-H), 4.40 (2H, s, 3-H), 3.82 (2H, t, 7-H), 2.74 (2H, t, 6-H). ^{13}C-NMR (DMSO-d_6): δ_C 167.90 (s, C=O), 162.44 (s, C=O), 157.10 (s, C-11a), 156.22 (s, C-10a), 130.68 (s, C-9a), 127.40 (s, C-5a), 116.17 (s, C-5b), 64.39 (t, C-9), 64.05 (t, C-7), 45.96 (t, C-3), 26.45 (t, C-6). *Anal.* Calcd for $C_{11}H_{10}N_4O_3S$: C, 47.47; H, 3.62; N, 20.13. Found: C, 47.56; H, 3.65; N, 20.06.

3-Ethoxycarbonylmethyl-4-oxo-2-(1-pyrrolidinyl)-3,4,5,8-tetrahydro-6*H*-pyrano[4′,3′ : 4,5]thieno[2,3-*d*]pyrimidine (8a) A solution of the chloro product (**6**) (0.32 g, 1 mmol) and pyrrolidine (0.09 g, 1.5 mmol) in triethylamine (5 ml) was refluxed for 2 h. The solvent was evaporated *in vacuo.* The obtained solid was recrystallized from ethanol and ethyl acetate (3 : 1) to give **8a** as white needles. Yield: 0.22 g (64%), mp 189 °C. ^{1}H-NMR ($CDCl_3$): δ_H 4.62 (2H, s, 8-H), 4.32 (2H, s, CH_2), 4.30 (2H, q, CH_2O), 3.50—3.30 (4H, t, –H_2C–N–CH_2–), 3.85 (2H, t, 6-H), 2.90 (2H, t, 5-H), 1.95—1.75 (4H, m, –CH_2–CH_2–), 1.33—1.30 (3H, t, Me). ^{13}C-NMR (DMSO-d_6): δ_C 168.63 (s, C=O), 163.87 (s, C=O), 159.96 (s, C-2), 151.56 (s, C-9a), 133.32 (s, C-8a), 126.48 (s, C-4a), 113.24 (s, C-4b), 64.92 (t, C-8), 64.51 (t, C-6), 61.66 (t, OCH_2), 50.60 (t, –H_2C–N–CH_2–), 47.20 (t, CH_2), 26.54 (t, C-5), 14.20 (q, Me). *Anal.* Calcd for $C_{17}H_{21}N_3O_4S$: C, 56.17; H, 5.82; N, 11.56. Found: C, 56.12; H, 5.86; N, 11.67.

3-Ethoxycarbonylmethyl-2-(4-morpholinyl)-4-oxo-3,4,5,8-tetrahydro-6*H*-pyrano[4′,3′ : 4,5]thieno[2,3-*d*]pyrimidine (8b) A solution of the chloro product (**6**) (0.32 g, 1 mmol) and morpholine (0.13 g, 1.5 mmol) in triethylamine (5 ml) was refluxed for 2 h. The solvent was evaporated *in vacuo.* The obtained solid was recrystallized from ethanol and ethyl acetate (3 : 1) to give **8b** as white needles. Yield: 0.23 g (62%), mp 152 °C. ^{1}H-NMR ($CDCl_3$): δ_H 4.60 (2H, s, 8-H), 4.32 (2H, s, CH_2), 4.30 (2H, q, CH_2O), 3.85 (2H, t, 6-H), 3.80 (4H, t, –CH_2OCH_2–), 3.10 (4H, t, –H_2C–N–CH_2–), 2.81 (2H, t, 5-H), 1.33—1.30 (3H, t, Me). ^{13}C-NMR ($CDCl_3$): δ_C 168.63 (s, C=O), 163.87 (s, C=O), 159.96 (s, C-2), 151.56 (s, C-9a), 133.32 (s, C-8a), 126.48 (s, C-4a), 113.24 (s, C-4b), 66.14 (t, –CH_2OCH_2–), 64.78 (t, C-8), 64.58 (t, C-6), 61.66 (t, OCH_2), 50.49 (t, –H_2C–N–CH_2–), 26.54 (t, C-5), 14.20 (q, Me). *Anal.* Calcd for $C_{17}H_{21}N_3O_5S$: C, 53.81; H, 5.58; N, 11.07. Found: C, 53.75; H, 5.63; N, 10.97.

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