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 papers6—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) benzothienopyrimidine11) and benzofuropyrimidine9) 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 1H-NMR spectrum no peaks were found for –NH2 and –OEt groups and in the 13C-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-c]imidazo[1,2-c]pyrimidine-2(3H)-one (1a) was synthesized in 72% yield as red needles from furoonitrile and ethyl isothiocyanatoacetate in pyridine medium by one-pot reaction. Similarly, 1b was prepared in 60% yield by a direct condensation of furoonitrile 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-c]pyrimidine-2(3H)-ones (1c, d) were also obtained frequently from 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carbonitrile (Chart 2).

Methylation of the thiox group in 1a with NaOMe and Mel 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. Annellation of such type of angular tricyclic 2 was also established by Sauter et al.5—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-c]imidazo[1,2-c]pyrimidine or imidazo[5,4-c]imidazo[1,2-c]pyrimidine system, may be due to an electronic effect: the methyl group could be the reason for a +1 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-methylpyrazolo[4,5-d]pyrimidine 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-1H-imidazo[5,4-c]benzotriptyl with ethyl isothiocyanatoacetate in pyridine for 1 h furnished 6-ethoxycarbonylmethyl-7-imino-5-thioxo-4,5,6,7-tetrahydro-1H-imidazo[4,5-d]pyrimidine (3b) in 66% and

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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-5H-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 POCl₃ to afford 6, which was displaced by amines without further purification. Treatment of chloro compound 6 with hydrazine gave 1-amino-
6,7,9-trihydroimidazo[1,2-a]pyrano[4',3',4,5]thieno[2,3-d]-pyrimidine-2,5(1H,3H)-dione (7) in 70% yield. mp 283°C. The chloro product (6) was treated with pyridine 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. 1H- and 13C-NMR spectra were recorded on a JNM-ALPHA 500 (500 MHz) spectrometer (internal standard TMS, solvents CDCl3, or DMSO-d6 respectively, δ-values in ppm) for 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.15 in 1996 as a syrup in 71% yield. 2-Amino-4,7-dihydro-5H-thieno[3,2-c]pyrano-3-carbonitrile and ethyl 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyrano-3-carbonitrile and ethyl isothiocyanatoacetate, reaction time 4h, recrystallized from ethanol to give 1d as red needles. Yield: 54%; mp 190°C (dec.).

**1H-NMR** (DMSO-d6): δH 4.68 (2H, s, 8-H), 4.36 (2H, s, 3-H), 3.90 (2H, t, 10-H), 2.82 (2H, t, 11-H). 13C-NMR (DMSO-d6): δC 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), 115.11 (s, C-11a), 64.39 (t, C-8), 63.59 (t, C-10), 52.61 (t, C-5), 25.37 (t, C-11). Anal. Calcd for C11H9N3O3S: 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-5H-imidazo[1,2-c]pyrano[4',3',4,5]-thieno[3,2-c]pyrimidine-2(3H)-one (1d): The title compound was prepared in the same manner as 1b from 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carbonitrile and ethyl isothiocyanatoacetate, reaction time 4h, recrystallized from ethanol to give 1e as red needles. Yield: 63%; mp 270°C (dec.).

**Chart 6. Halogenation of Thiorex Compound and Substitution by Amines**

**8.9-Dimethyl-5-thioxo-5,6-dihydropyrido[3,2-][3,4-][pyrimidine-2(3H)]-one (1a)** A solution of 2-amino-4,5-dimethylfur-3-carbonitrile (0.87 g, 6mmol) and ethyl iso(thiocyanato)acetate (0.87 g, 6mmol) in 8 ml of pyridine was refluxed for 1h. 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. 1H-NMR (DMSO-d6): δH 8.60 (1H, s, NH), 3.45 (2H, s, 2-H), 2.45 (3H, s, Me). Anal. Calcd for C8H11N2O2S: C, 45.33; H, 5.88; N, 16.84. Found: C, 45.07; H, 5.92; N, 16.88.

**8.9-Dimethyl-5-oxo-5,6-dihydropyrido[3,2-][3,4-][pyrimidine-2(3H)]-one (1b)** A solution of 2-amino-4,5-dimethylfuran-3-carbonitrile (0.81 g, 6mmol) and ethyl iso(thiocyanato)acetate (0.77 g, 6mmol) in 8 ml of pyridine was refluxed for 1h. 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. 1H-NMR (DMSO-d6): δH 4.35 (2H, s, 3-H), 2.23 (3H, s, Me), 2.08 (3H, s, Me). 13C-NMR (DMSO-d6): δC 177.65 (s, C = O), 171.10 (s, C-6a), 169.50 (s, C = O), 157.70 (s, C-9b), 125.39 (s, C-8), 122.81 (s, C-9a), 95.47 (s, C-9), 56.00 (t, C-3), 14.53 (q, Me), 14.21 (q, Me). Anal. Calcd for C10H7N2O2S: C, 51.05; H, 3.85; N, 16.84. Found: C, 50.98; H, 4.02; N, 16.88.

5-Thio-6,8,10,11-tetrahydro-5H-imidazo[1,2-c][2,3-][pyran-3-carbonitrile and ethyl isothiocyanatoacetate, reaction time 4h, recrystallized from ethanol to give 1e as red needles. Yield: 63%; mp 270°C (dec.).
169.76 (s, C-5), 166.19 (s, C-6), 157.23 (s, C-O), 151.21 (s, C-Na), 135.70 (s, C-8a), 129.87 (s, C-4a), 114.24 (s, C-6b), 64.3 (s, C-6), 60.70 (t, OCH3), 46.01 (t, CH3), 25.96 (t, C-5), 13.80 (q, Me). Anal. Calc. for C19H19NO3S: C, 51.50; H, 5.54; N, 5.11. Found: C, 52.08; H, 5.62; N, 11.10.

Ethyl 2-(3-Ethoxycarbonylmethylthioureido)cyclopentene-1-carboxylate (4e) A solution of ethyl 2-amino-1-cyclopentene-1-carboxylate (0.93 g, 6 mmol) and ethyl isothiocyanatoacetate, reaction time 4 h to give 4e as yellow needles. Yield: 66%; mp 246–247 °C. 1H-NMR (CDCl3): δ 6.40 (2H, s, 8-H), 4.30 (2H, CH2), 3.96 (2H, t-H, 6-δ), 2.75 (2H, t-H, 5), 1.30–1.10 (6H, t-Me, 2Me). 13C-NMR (DMSO-d6): δ 169.42 (s, C-O), 166.19 (s, C-O), 157.23 (s, C-O), 151.21 (s, C-Na), 135.70 (s, C-8a), 129.87 (s, C-4a), 114.24 (s, C-6b), 64.3 (s, C-6), 60.70 (t, OCH3), 46.01 (t, CH3), 25.96 (t, C-5), 13.80 (q, Me). Anal. Calc. for C19H19NO3S: C, 51.50; H, 5.54; N, 5.11. Found: C, 52.08; H, 5.62; N, 11.10.

Ethyl 2-[3-Ethoxycarbonylmethylthioureido]cyclopentene-1-carboxylate (5a) 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 afford 4a as pale yellow needles. Yield: 136 g (76%); mp 203–204 °C. 1H-NMR (CDCl3): δ 1.73 (g, 1H, s, NH), 7.87 (t, H, 7), 4.60 (2H, s, 7H, 6-H), 4.35 (2H, CH2), 4.25–4.19 (4H, q, OCH2), 3.82 (2H, t-H, 5), 2.78 (2H, t-H, 4), 1.42–1.41 (6H, t-Me, 2H). 13C-NMR (DMSO-d6): δ 169.19 (s, C-O), 157.50 (s, C-O), 153.12 (s, C-2), 135.17 (s, C-3), 128.70 (s, C-4), 122.61 (s, C-3a), 64.51 (t, C-7), 64.22 (t, C-5), 61.90 (t, OCH3), 61.08 (t, OCH3), 46.51 (t, CH2), 26.75 (t, C-4), 14.30 (q, Me), 14.07 (g, Me). Anal. Calc. for C19H19NO3S: C, 50.54; H, 6.56; N, 7.78. Found: C, 52.09; H, 6.59; N, 9.30.

Ethyl 2-[3-Ethoxycarbonylmethylthioureido]cyclopentene-1-carboxylate (5b) The title compound was obtained in the same manner as 4e from ethyl 2-amino-1-cyclopentene-1-carboxylate and ethyl isothiocyanatoacetate, reaction time 2 h, recrystallized from ethanol to give 5a as pale yellow needles. Yield: 58%; mp 150–151 °C. 1H-NMR (CDCl3): δ 2.51 (t, H, 6), 2.47 (t, H, 4), 4.06 (2H, s, 7H, 6-H), 4.03 (2H, CH2), 3.95 (2H, t-H, 5), 2.78 (2H, t-H, 4), 1.82 (2H, m-H, 2-H), 1.42 (6H, t-Me, 2H). 13C-NMR (DMSO-d6): δ 167.32 (s, C-O), 157.02 (s, C-O), 156.13 (s, C-O), 150.72 (s, C-O), 149.04 (t, Me), 13.95 (q, Me). Anal. Calc. for C19H19NO3S: C, 51.98; H, 6.71; N, 9.32. Found: C, 52.09; H, 6.59; N, 9.30.

Ethyl 2-[3-Ethoxycarbonylmethylthioureido]cyclopentene-1-carboxylate (5c) A suspension of the thioxo product (0.32 g, 1 mmol) and pyrrolidine (0.09 g, 1.5 mmol) in triethylamine (5 ml) was refluxed for 2 h. The obtained solid was collected by filtration and washed with ether to give white brown needles. Yield: 3.84% (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 obtained solid was recrystallized from ethanol and ethyl acetate (3:1) to give 7a as white needles. Yield: 0.18 g (70%), mp 283 °C. 1H-NMR (CDCl3): δ 5.20 (2H, s, NH2), 4.58 (2H, s, 9-δ), 4.40 (2H, 3-H, 8), 3.82 (2H, t-H, 7-H), 2.74 (2H, t-H, 6), 1.39 (1H, Me, 5-H). 13C-NMR (DMSO-d6): δ 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. Calc. for C21H23N3O4S: C, 47.47; H, 3.62; N, 20.13. Found: C, 47.56; H, 3.65; N, 20.06.

Ethyl 2-[3-Ethoxycarbonylmethylthioureido]cyclopentene-1-carboxylate (5d) A solution of the chloro product (0.63 g, 1 mmol) and pyridine (0.09 g, 1.5 mmol) in triethylamine (5 ml) was refluxed for 2 h. The obtained solid was recrystallized from ethanol and ethyl acetate (3:1) to give 8a as white needles. Yield: 0.02 g (64%), mp 189 °C. 1H-NMR (CDCl3): δ 4.62 (2H, s, 8-H), 4.32 (2H, CH3), 4.20 (2H, CH2O), 3.50–3.30 (4H, t-H, 5H-C–CH2–), 3.85 (2H, t-H, 6-H), 2.90 (2H, t-H, 5-H), 1.95–1.75 (5H, t-H, 3–H, 4–H). 13C-NMR (DMSO-d6): δ 168.63 (s, C-O), 163.87 (s, C-O), 159.96 (s, C-2), 151.56 (s, C-3a), 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, OCH3), 50.60 (t, H–N–CH–H–), 47.20 (t, CH2), 26.54 (t, C-7), 14.20 (q, Me). Anal. Calc. for C19H19NO3S: 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-6H-pyran[4',3':5,6]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. 1H-NMR (CDCl3): δH 4.60 (2H, s, 8-H), 4.32 (2H, s, CH2), 4.30 (2H, q, CH2O), 3.85 (2H, t, 6-H), 3.80 (4H, t, –CH2OCH2–), 3.10 (4H, t, –H2C–N–CH2–), 2.81 (2H, t, 5-H), 1.33—1.30 (3H, t, Me). 13C-NMR (CDCl3): δC 168.63 (s, C-5O), 163.87 (s, C-5O), 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, –CH2OCH2–), 64.78 (t, C-8), 64.58 (t, C-6), 61.66 (t, OCH2), 50.49 (t, –H2C–N–CH2–), 26.54 (t, C-5), 14.20 (q, Me). Anal. Caled for C17H21N3O5S: C, 53.81; H, 5.58; N, 11.07. Found: C, 53.75; H, 5.63; N, 10.97.

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References and Notes