A NEW SYNTHESIS OF PYRIMIDO[4,5-b][1,5]BENZODIAZEPIN-2-ONE AND -2-THIONE DERIVATIVES

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Abstract —— Derivatives of pyrimido[4,5-b][1,5]benzodiazepin-2-one and -2-thione were synthesized by intramolecular cyclization of N-(3-cyano-1H-1,5-benzodiazepin-4-yl)-N'-alkylureas and -N'-phenylthiourea which were obtained by reactions of 4-amino-1H-1,5-benzodiazepine-3-carbonitrile with alkyl isocyanates and phenyl isothiocyanate, respectively.

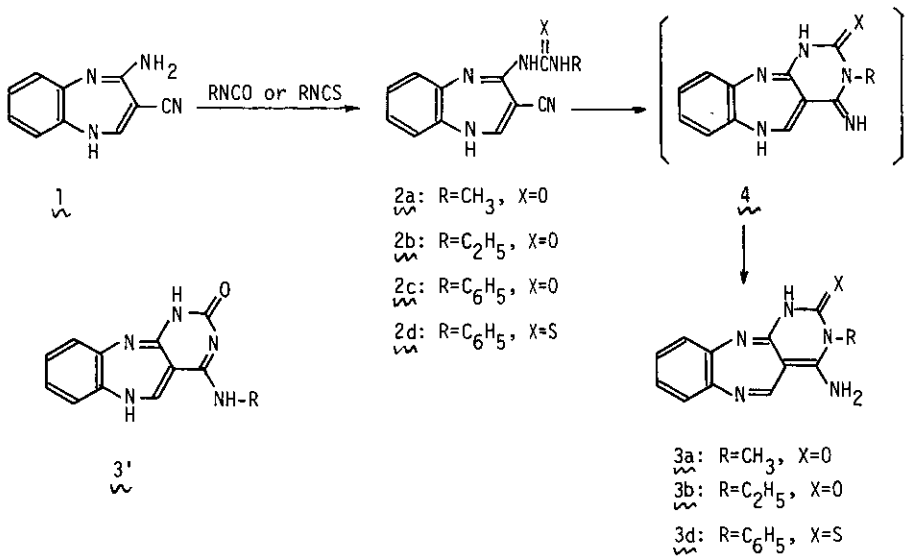
Previously, we reported the ring transformation of 4-amino-1H-1,5-benzodiazepine-3-carbonitrile (1), which involves ring opening in the diazepine nucleus by nucleophilic attack of hydroxylamine[1] and hydrazines[2]. However, our attempt to prepare biologically interesting fused tricyclic systems such as pyrimido[4,5-b]-[1,5]benzodiazepine[3] by condensation of guanidine on the o-aminonitrile moiety of 1 was not successful[4]. On the other hand, we have recently described[5] a new synthetic approach to pyrimido[4,5-b][1,5]benzodiazepin-2-ones via ring transformation of 4-ethoxycarbonylamino-1H-1,5-benzodiazepine-3-carbonitrile with aliphatic primary amines. In continuation of this kind of works, we found that new derivatives of pyrimido[4,5-b][1,5]benzodiazepin-2-one and -2-thione were synthesized via reactions of 1 with alkyl isocyanates and phenyl isothiocyanate.

The preparation of condensed pyrimidines by reacting aromatic o-aminonitriles with phenyl isocyanate or phenyl isothiocyanate is well known[6]. We applied this method to 1. Treatment of 1 with methyl isocyanate in dry tetrahydrofuran at room temperature for 1 h provided orange crystalline precipitates of N-(3-cyano-1H-1,5-

benzodiazepin-4-yl)-N'-methylurea (2a), whose structure was elucidated on the basis of spectral data. In particular, the ^{1}H-NMR spectrum of 2a showed signals at 6.6-7.5 ppm (br, 1H) due to an amino proton and 9.7-10.2 ppm (br, 1H) and 11.77 ppm (br s, 1H) attributable to two amido protons. This observation suggests that methyl isocyanate reacted with the amino group at 4-position of 1, but not with the nitrogen atom in the diazepine nucleus. Similar treatment of 1 with ethyl isocyanate gave N-(3-cyano-1H-1,5-benzodiazepin-4-yl)-N'-ethylurea (2b). Under the same conditions, 1 did not react with phenyl isocyanate. However, when the reaction was carried out on heating in dimethylformamide at 130°C for 1 h, N-(3-cyano-1H-1,5-benzodiazepin-4-yl)-N'-phenylurea (2c) was obtained. On heating with sodium ethoxide in ethanol for 3 h, the compounds 2a,b underwent intramolecular cyclization to afford 3-alkyl-4-aminopyrimido[4,5-b][1,5]benzodiazepin-2(1H, 3H)-ones (3a,b), whereas 2c did not give the expected pyrimido-benzodiazepine because of the decomposition of the starting benzodiazepine. It is worth noting that although the diazepine-3-carbonitriles of type 1 are readily cleaved at C-2 by different nucleophiles[1,2,4,5], the compounds 2a,b did not undergo N_1-C_2 bond cleavage, but smooth ring closure to give 3a,b on treatment with sodium ethoxide. The failure of cyclization of 2c may be explained in terms of low nucleophilicity of the phenylamino group. The structural assignement of 3a,b is based on microanalyses, IR-, mass- and ^{1}H-NMR spectral data. There were no change of the molecular weight between 2a,b and 3a,b. In the IR spectra, 3a,b showed no absorption band at nitrile region. The ^{1}H-NMR spectral data were also compatible with the proposed structures. Particularly, a singlet signal for methyl protons of 3a appears at 3.20 ppm. This finding excluded the structure 3' (R=CH_3) which could arise by the Dimroth type rearrangement[7] of the intermediate imine 4 (R=CH_3, X=O), because 3' (R=CH_3) must give a doublet signal for methyl protons owing to the coupling with NH-proton as observed in the spectrum of 2a. It is the same with 3b which showed a quartet signal (3.87 ppm) for methylene protons of the ethyl group.

Methyl and ethyl isothiocyanates did not react with 1 in dry tetrahydrofuran at room temperature. When the reaction was carried out under reflux, many unidentified products were formed. However, heating of 1 with phenyl isothiocyanate in dry tetrahydrofuran for 3 h gave N-(3-cyano-1H-1,5-benzodiazepin-4-yl)-N'-phenylthiourea (2d) which was converted to 4-amino-3-phenylpyrimido[4,5-b][1,5]benzodiazepin-2(1H, 3H)-thione (3d) on treatment with sodium ethoxide in boiling etha-

nol. Since the chemical shifts of NH-protons of 3d very resembled those of NH-protons of 3a,b, 3d could have an analogous structure to that of 3a,b, but not a rearranged structure of type 3'. It is interesting that the thiourea 2d was readily cyclized to 3d in contrast with the urea 2c which did not undergo intramolecular cyclization.



EXPERIMENTAL

Melting points were determined using a Yamato Scientific stirred liquid apparatus and are uncorrected. Analyses were done by a Perkin Elmer Model 240 elemental analyzer. ^{1}H-NMR spectra were measured with a JEOL C-60H spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were taken on a JEOL-JMS-DX300 spectrometer. IR spectra were recorded on a JASCO A-102 spectrophotometer.

N-(3-Cyano-1H-1,5-benzodiazepin-4-yl)-N'-alkylureas (2a,b).

Methyl isocyanate (0.63 g, 11 mmol) was added to a suspension of 1 (1.84 g, 10 mmol) in dry tetrahydrofuran (10 ml) with stirring at 0°C. The stirring was then continued for 1 h at room temperature. The precipitates were collected by suction filtration and recrystallized from dimethylformamide-water to yield 2a as orange needles. In the same manner, 2b was obtained by using ethyl isocyanate in place of methyl isocyanate.

2a, yield 1.73 g (72%), mp 195-196°C. IR (KBr): ν = 3340, 3270, 2220, 1625 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 2.62 (d, J=5Hz, 3H, CH_3), 6.33-7.33 (m, 4H, Ph), 6.6-7.5 (br, 1H, NH), 7.10 (s, 1H, C2-H), 9.7-10.2 (br, 1H, CONH), 11.77 (br s, 1H, CONH). MS m/z: 184 (M^+-CH_3NCO). Anal. Calcd, for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.53; H, 4.60; N, 29.10.

2b, yield 2.11 g (83%), mp 204-205°C. IR (KBr): ν = 3340, 3270, 2200, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.07 (t, J=7Hz, 3H, CH_3), 3.17 (m, 2H, CH_2), 6.43-7.10 (m, 4H, Ph), 7.13 (s, 1H, C2-H), 6.8-7.6 (br, 1H, NH), 9.5-10.3 (br, 1H, CONH), 12.00 (s, 1H, CONH). MS m/z: 184 (M^+-C_2H_5NCO). Anal. Calcd, for $C_{13}H_{13}N_5O$: C, 61.16; H, 5.13; N, 27.44. Found: C, 61.12; H, 5.03; N, 27.76.

N-(3-Cyano-1H-1,5-benzodiazepin-4-yl)-N'-phenylurea (2c).

A mixture of 1 (1.0 g, 5.4 mmol) and phenyl isocyanate (0.64 g, 5.4 mmol) in dry dimethylformamide (15 ml) was heated at 130°C for 1 h. After cooling, the precipitates were collected by filtration, washed with ethanol and recrystallized from dimethylformamide to yield 1.24 g (76%) of 2c as red leaflets, mp 184-187°C. IR (KBr): ν = 3340, 3280, 2220, 1640 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 6.30-8.00 (m, 11H, Ph, C2-H and NH), 9.50 (s, 1H, CONH), 11.70 (s, 1H, CONH). MS m/z: 184 (M^+-PhNCO). Anal. Calcd, for $C_{17}H_{13}N_5O$: C, 67.32; H, 4.32; N, 23.09. Found: C, 67.05, H, 4.44; N, 22.81.

N-(3-Cyano-1H-1,5-benzodiazepin-4-yl)-N'-phenylthiourea (2d).

A mixture of 1 (1.84 g, 10 mmol) and phenyl isothiocyanate (2.03 g, 15 mmol) in dry tetrahydrofuran (50 ml) was refluxed for 3 h. The reaction mixture was concentrated under reduced pressure to give a residue which was treated with benzene. The precipitates were collected by filtration and recrystallized from methanol to yield 2.0 g (63%) of 2d as red crystals, mp 176-177°C. IR (KBr): ν = 3400, 3180, 2200, 1640 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 6.30-8.03 (m, 11H, Ph, C2-H and NH), 9.50 (br s, 1H, CSNH), 11.50 (br s, 1H, CSNH). MS m/z: 184 (M^+-PhNCS). Anal. Calcd, for $C_{17}H_{13}N_5S$: C, 63.93; H, 4.10; N, 21.93. Found: C, 64.21; H, 4.35; N, 21.84 (dried over P_2O_5 at 120°C for 48 h).

3-Alkyl-4-aminopyrimido[4,5-b][1,5]benzodiazepin-2(1H, 3H)-ones (3a,b) and 4-Amino-3-phenylpyrimido[4,5-b][1,5]benzodiazepin-2(1H, 3H)-thione (3d).

An ethanolic sodium ethoxide solution (46 mg of sodium and 10 ml of anhydrous

ethanol) of compound 2a, 2b or 2d (2 mmol) was refluxed for 3 h. After removal of the solvent, the residue was treated with ice water to yield a crystalline solid which was collected and recrystallized from ethanol-water (3a,b) or dimethylformamide-water (3d).

3a, yield 0.30 g (62%), mp 268-271°C. IR (KBr): ν = 3370, 3150, 1680, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 3.20 (s, 3H, CH_3), 6.60-7.00 (m, 4H, Ph), 7.47 (s, 1H, C5-H), 7.60 (br s, 2H, NH_2), 8.15 (br s, 1H, NH). MS m/z: 241 (M^+). Anal. Calcd, for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.49, H, 4.51; N, 29.21.

3b, yield 0.31 g (61%), mp 258-259°C. IR (KBr): ν = 3350, 3150, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.07 (t, J=7Hz, 3H, CH_3), 3.87 (q, J=7Hz, 2H, CH_2), 6.77-7.00 (m, 4H, Ph), 7.53 (s, 1H, C5-H), 7.63 (s, 2H, NH_2), 8.23 (s, 1H, NH). MS m/z: 255 (M^+). Anal. Calcd, for $C_{13}H_{13}N_5O$: C, 61.16; H, 5.13; N, 27.44. Found: C, 60.81; H, 5.19; N, 27.70.

3d, yield 0.45 (71%), mp 231-234°C. IR (KBr): ν = 3400, 1610, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 6.60-7.73 (m, 11H, Ph and NH_2), 7.47 (s, 1H, C5-H), 8.87 (br s, 1H, NH). MS m/z: 319 (M^+). Anal. Calcd, for $C_{17}H_{13}N_5S \cdot H_2O$: C, 60.52; H, 4.48; N, 20.76. Found: C, 60.40; H, 4.12; N, 20.75 (dried over P_2O_5 at 120°C for 48 h).

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