Synthesis of Some 2-(Heteroarylamino)benzimidazoles and Their Cyclization with Phosgene

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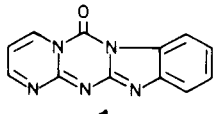
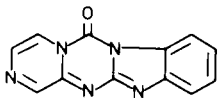
2-(Benzimidazol-2-ylamino)pyridine (**4a**), 2-(benzimidazol-2-ylamino)pyrazine (**4b**), and 2-(benzimidazol-2-ylamino)thiazole (**4c**) underwent a ring-closure reaction on treatment with phosgene affording 6*H*-pyrimido[1′,2′:5,4][1,3,5]triazino[1,2-*a*]benzimidazol-6-one (**1a**), 6*H*-pyrazino[1′,2′:5,4][1,3,5]triazino[1,2-*a*]benzimidazol-6-one (**1b**), and 5*H*-thiazolo[2′,3′:4,5][1,3,5]triazino[1,2-*a*]benzimidazol-5-one (**1c**) respectively. The structure of these hitherto unknown heterocyclic systems was confirmed by their ir and mass spectra.

J. Heterocyclic Chem., **22**, 1147 (1985).

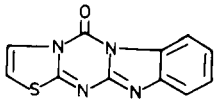
Continuing our studies concerning the synthesis of new heterocyclic systems having fused imidazole or benzimidazole rings [1] [2] [3], we decided to attempt the synthesis of 6*H*-pyrimido[1′,2′:5,4][1,3,5]triazino[1,2-*a*]benzimidazol-6-one (**1a**), 6*H*-pyrazino[1′,2′:5,4][1,3,5]triazino[1,2-*a*]benzimidazol-6-one (**1b**), and 5*H*-thiazolo[2′,3′:4,5][1,3,5]triazino[1,2-*a*]benzimidazol-5-one (**1c**).



1a



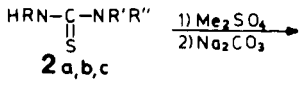
1b



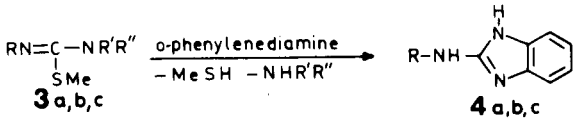
1c

The first step consists of the synthesis of 2-(heteroarylamino)benzimidazoles **4a-c** (Scheme 1 below).

Scheme 1



2a,b,c

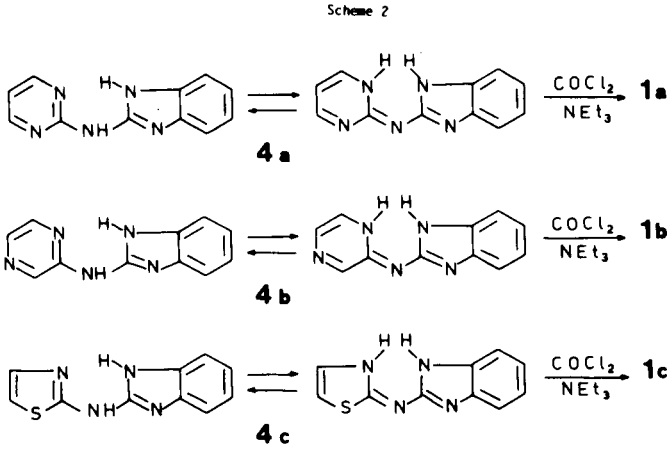


3a,b,c **4a,b,c**

a	R = 2-Pyrimidinyl	R′ = R″ = H
b	R = Pyrazinyl	R′ = R″ = H
c	R = 2-Thiazolyl	R′ = R″ = Et

The second step consists of the cyclization of **4a-c** with phosgene (Scheme 2 below).

Scheme 2



On the synthesis some remarks can be made: the conversion of thioureas **2a-c** into the corresponding methyl carbamimidothioates **3a-c** occurred in satisfactory yields by treating thioureas **2a-c** (in acetone or DMF solution) with dimethylsulfate: the methyl sulfate salts of **3a-c** obtained were converted into the free bases on treatment with aqueous sodium carbonate. Compounds **3a-c** on fusion with *o*-phenylenediamine according to Deck and Dains [4] gave 2-(heteroarylamino)benzimidazoles **4a-c**. The yields of **4a** and **4b** were satisfactory, whereas compound **4c** was obtained in low yields; this fact is probably related to the impossibility of obtaining **3c** in pure form. Attempts to improve the yields of **4c** were unsuccessful. The Reaction between 2-(heteroarylamino)benzimidazoles **4a-c** and phosgene in each case occurred very easily, in the presence of triethylamine, and the cyclization products **1a-c** were obtained in almost quantitative yields. Evidence for the assigned structures was provided by ir and mass spectra of **1a-c**. In fact the ir spectra show CO peaks at about 1750 cm^{-1}. These values are in agreement with the presence of an ureidic carbonyl group. In the mass spectra of **1a-c**, besides the molecular ions, some fragment ions are detectable, which confirm the assigned structures. The frag-

ment ion [Benzimidazole + CO]$^+$ m/z 144 is detectable in the mass spectra of **1a** and **1c**, while the fragment ion [Benzene + NCO]$^+$ m/z 118 is detectable in the mass spectra of **1a** and **1b**.

EXPERIMENTAL

Melting points were obtained in open capillary tubes and are uncorrected. The ir and mass spectra were recorded with a Perkin-Elmer 283 spectrophotometer and a Kratos MS 80 instrument respectively.

Methyl *N'*-(2-Pyrimidinyl)carbamimidothioate (**3a**).

Dimethyl sulfate (7.8 g, 61.6 mmoles) was slowly dropped into a saturated solution of *N*-(2-pyrimidinyl)thiourea (**2a**) [5] (9.5 g, 61.6 mmoles) in DMF. The resulting solution was then heated at 60-65° for three hours. Removal of the solvent left a residue which was treated with cold water and filtered. On treatment of the filtrate with dilute sodium carbonate until the *p*H was 9.5, **3a** (7.9 g, 80% yield) separated, mp 160-161° from ethanol; ir (potassium bromide): 3285 cm^{-1}.

Anal. Calcd. for $C_6H_6N_4S$: C, 42.84; N, 33.31; H, 4.79. Found: C, 42.77; N, 33.36; H, 4.70.

Methyl *N'*-(Pyrazinyl)carbamimidothioate (**3b**).

This compound was prepared starting from **2b** [6] following the procedure described for **3a**. The yield was 75%, mp 126-127° from ethanol; ir (potassium bromide): 3250 cm^{-1}.

Anal. Calcd. for $C_6H_6N_4S$: C, 42.84; N, 33.31; H, 4.79. Found: C, 42.75; N, 33.32; H, 4.82.

2-(Benzimidazol-2-ylamino)pyrimidine (**4a**).

A mixture of **3a** (5.05 g, 30 mmoles) and *o*-phenylenediamine (3.24 g, 30 mmoles) was heated at 160° for 50 minutes. The residue was treated with a little hot ethanol and filtered. The collected crude **4a** amounted to 5.4 g (85% yield), mp 284-285° from DMF; ir (potassium bromide): 3300 cm^{-1}.

Anal. Calcd. for $C_{11}H_9N_5$: C, 62.55; N, 33.15; H, 4.29. Found: C, 62.50; N, 33.18; H, 4.23.

(Benzimidazol-2-ylamino)pyrazine (**4b**).

A mixture of **3b** (3.9 g, 23 mmoles) and *o*-phenylenediamine (2.5 g, 23 mmoles) was heated at 165° for 70 minutes. The residue was recrystallized from DMF. The yield of pure **4b** was 3.5 g (71% yield), mp 287-288°; ir (potassium bromide): 3320 cm^{-1}.

Anal. Calcd. for $C_{11}H_9N_5$: C, 62.55; N, 33.15; H, 4.29. Found: C, 62.57; N, 33.09; H, 4.34.

2-(Benzimidazol-2-ylamino)thiazole (**4c**).

Dimethyl sulfate (9.33 g, 74 mmoles) was slowly dropped into a solution of **2c** [7] (15.9 g, 74 mmoles) in acetone, and the resulting solution refluxed for three hours. Removal of the solvent left a residue which was dissolved in water. The above described solution was treated with dilute sodium carbonate until the *p*H was 9.5, then extracted with chloroform. Evaporation of the chloroform solution left crude methyl *N,N*-diethyl-*N'*-(2-thiazolyl)carbamimidothioate (**3c**) (16 g, 95% yield) as a viscous syrup which did not crystallize after standing for several days. Attempts to purify this compound were unsuccessful. A mixture of crude **3c** (16 g, 70 mmoles) and *o*-phenylenediamine (7.56 g, 70 mmoles) was heated at 160° for 70 minutes. The residue was treated, under stirring, with a little ethanol/water (1:1), and filtered. The collected crude **4c** amounted to 4 g (25% yield based on **2c**), mp 252-253° from DMF/ethanol; ir (potassium bromide): 3280 cm^{-1}.

Anal. Calcd. for $C_{10}H_8NS$: C, 55.54; N, 25.91; H, 3.73. Found: C, 55.49; N, 25.97; H, 3.71.

In other runs different temperatures and reaction periods were employed but the yields could not be improved.

Cylization of 2-(Heteroarylamino)benzimidazoles **4a-c** with Phosgene. General Procedure.

A solution of phosgene in toluene was slowly dropped into a well-stirred suspension of **4** and triethylamine (molar *ratio* phosgene:**4**:triethylamine = 1:1:2) in toluene, maintaining the temperature at 0°. The resulting mixture was allowed to react at room temperature for six hours, then filtered. The collected solid was washed with ether, then with water, and dried. Compounds **1a-c** were obtained in almost quantitative yields.

Compound **1a**.

This compound had mp 259-260° from DMF; ir (potassium bromide): 1755 cm^{-1}; ms: (60 eV) [M]$^+$ m/z 237, [M-CN]$^+$ m/z 211, [M-CON]$^+$ m/z 195, [Benzimidazole + CO]$^+$ m/z 144, [Benzene + NCO]$^+$ m/z 118.

Anal. Calcd. for $C_{12}H_7N_5O$: C, 60.76; N, 29.52; H, 2.97. Found: C, 60.68; N, 29.54; H, 3.00.

Compound **1b**.

This compound had mp 256-257° from DMF; ir (potassium bromide): 1750 cm^{-1}; ms: (60 eV) [M]$^+$ m/z 237, [M-CN]$^+$ m/z 211, [Benzene + NCO]$^+$ m/z 118.

Anal. Calcd. for $C_{12}H_7N_5O$: C, 60.76; N, 29.52; H, 2.97. Found: C, 60.70; N, 29.59; H, 3.01.

Compound **1c**.

This compound had mp 243-244° from DMF/ethanol; ir (potassium bromide): 1740 cm^{-1}; ms: (60 eV) [M]$^+$ m/z 242, [M-CO]$^+$ m/z 214, [Benzimidazole + CO]$^+$ m/z 144, [Benzene + N]$^+$ m/z 90, [CH=CH-S]$^+$ m/z 58.

Anal. Calcd. for $C_{11}H_6N_4OS$: C, 54.48; N, 23.10; H, 2.49. Found: C, 54.39; N, 23.11; H, 2.52.

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