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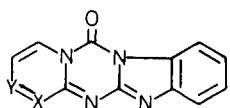
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2-(2,6-Dimethylpyrimidin-4-ylaminobenzimidazole) (VIIa) and 2-(1,3,4-thiadiazol-2-ylamino)benzimidazole (VIIb) underwent a ring-closure reaction with phosgene giving 1,3-dimethyl-12*H*-benzimidazo[1,2-*a*]pyrimido[6,1-*d*][1,3,5]triazin-12-one (IIa) and 5*H*-benzimidazo[1,2-*a*][1,3,4]thiadiazolo[2,3-*d*][1,3,5]triazin-5-one (IIb) two hitherto unknown heterocyclic systems. A convenient synthesis of 2,6-dimethyl-4-aminopyrimidine is described.

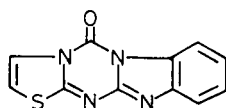
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In our previous papers [1,2] we described the synthesis of a number of new heterocyclic ring systems having a fused triazino[1,2-*a*]benzimidazole system, corresponding to the formulas Ia-d.



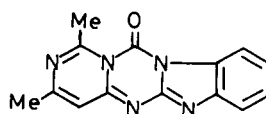
Ia-c

a X = CH Y = CH
b X = N Y = CH
c X = CH Y = N

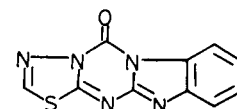


Id

In continuation of our studies on this class of compounds we decided to attempt the synthesis of 1,3-dimethyl-12*H*-benzimidazo[1,2-*a*]pyrimido[6,1-*d*][1,3,5]triazin-12-one (IIa) and 5*H*-benzimidazo[1,2-*a*][1,3,4]thiadiazolo[2,3-*d*][1,3,5]triazin-5-one (IIb).



IIa

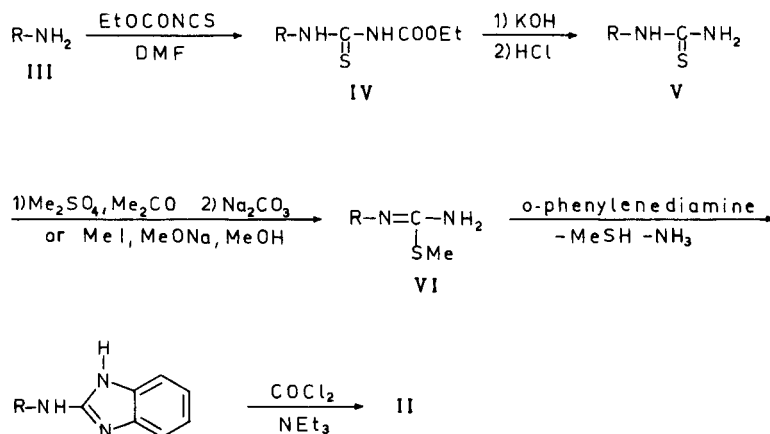


IIb

The synthesis was achieved following the known synthetic route [1,2] described in Scheme 1.

As the starting 4-aminopyrimidine we chose 2,6-dimethyl-4-aminopyrimidine which can be prepared by trimerizing acetonitrile in the presence of bases. With regard to this reaction, several synthetic methods [3-5] resulted unsatisfactory, giving poor yields, or an impure product, or both, we therefore developed a new synthetic method which allows us to obtain pure 2,6-dimethyl-4-aminopyrimidine in 70% yields. Compound IIIa was converted into *N*-ethoxycarbonyl-*N'*-(2,6-dimethylpyrimidin-4-

Scheme 1



a R = 2,6-Dimethylpyrimidin-4-yl

b R = 1,3,4-Thiadiazol-2-yl

yl)thiourea (IVa) on treatment with ethoxycarbonyl isothiocyanate. Alkaline hydrolysis of IVa gave the thiourea Va which was converted into methyl *N'*-(2,6-dimethylpyrimidin-4-yl)carbamimidothioate (VIa) on treatment with dimethyl sulfate and sodium carbonate. Surprisingly methylation of *N*-(1,3,4-thiadiazol-2-yl)thiourea (Vb) with dimethyl sulfate gave only poor yields of methyl *N'*-(1,3,4-thiadiazol-2-yl)carbamimidothioate (VIb) which was however obtained in high yields by performing the methylation with methyl iodide in the presence of sodium methoxide. Methyl carbamimidothioates VIa-b on fusion with *o*-phenylenediamine afforded 2-(heteroarylamino)benzimidazoles VIIa-b respectively. As expected, treatment of VIIa-b with phosgene in the presence of triethylamine gave compounds IIa-b in almost quantitative yields. The ir spectra of IIa-b show CO peaks at about 1750 cm⁻¹ and these values are in agreement with thioureidic carbonyl groups. In the mass spectra of IIa-b apart from the molecular ions [M(IIa)]⁺ *m/z* 265 and [M(IIb)]⁺ *m/z* 243, the fragment ion [Benzimidazole-CO]⁺ *m/z* 144 is detectable and this agrees with the assigned structure.

EXPERIMENTAL

Melting points were obtained in open capillary tubes and are uncorrected. The ir spectra were measured on a Perkin-Elmer 283 spectrophotometer for potassium bromide discs. The ¹H-nmr spectra were recorded with a Perkin-Elmer R32 instrument; chemical shifts are reported in ppm (δ) from TMS [6]. The mass spectra were recorded with a Kratos MS 80 instrument.

2,6-Dimethyl-4-aminopyrimidine (IIIa).

A mixture of dry acetonitrile (49.26 g, 1.2 moles) and freshly prepared sodium methoxide (21.6 g, 0.4 mole) was heated at 140° in a sealed tube for 5 hours. The reaction mixture was heated under reduced pressure to remove unreacted acetonitrile, then poured into a mortar and treated with a little water until a thick sludge resulted. The latter was dried at 75° over phosphorus pentoxide in a vacuum desiccator then poured into the flash of a distilling apparatus containing 300 ml of ligroine (bp, 150-190°). On distilling the ligroine compound IIIa codistilled and solidified in the collecting flask. The crystals were collected by filtration, washed with petroleum ether (bp 30-50°), and dried. The yield of pure IIIa was 34.5 g (70%), mp 183-184°; ir: 3320 cm⁻¹; ¹H-nmr (DMSO-d₆): 2.12 (s, 3H, CH₃ (2)), 2.24 (s, 3H, CH₃ (6)), 6.08 (s, 1H, H-5), 6.62 (broad s, 2H, NH₂).

Anal. Calcd. for C₆H₈N₂: C, 58.51; N, 34.12; H, 7.36. Found: C, 58.39; N, 34.00; H, 7.22.

N-Ethoxycarbonyl-*N'*-(2,6-dimethylpyrimidin-4-yl)thiourea (IVa).

Compound IIIa (14.2 g, 115.3 mmoles) was dissolved in as little as possible DMF at 80°. Ethoxycarbonyl isothiocyanate [7] (15.12 g, 115.3 mmoles) was slowly dropped into the above described solution at such a rate that the temperature did not rise above 100°. The reaction mixture was then maintained at 100° for an additional hour. Removal of the solvent left a glass-like residue which crystallized on treatment with a little water. The solid product was collected by filtration and amounted to 20.82 g (71% yield) of IVa, mp 166-167° from acetonitrile; ir: 3120, 1720, 1530 cm⁻¹; ¹H-nmr (DMSO-d₆): 1.21-1.37 (t, 3H, CH₂CH₃), 2.42 (s, 3H, CH₃ (6)), 2.50 (s, 3H, CH₃ (2)), 4.13-4.36 (q, 2H, CH₂), 8.26 (s, 1H, H-5), 11.90 (broad s, 2H, NH).

Anal. Calcd. for C₁₀H₁₄N₄O₂S: C, 47.23; N, 22.03; H, 5.55. Found: C, 47.11; N, 22.10; H, 5.46.

N-(2,6-Dimethylpyrimidin-4-yl)thiourea (Va).

A solution of IVa (17.3 g, 68 mmoles) and potassium hydroxide (19.08 g, 340 mmoles) in water was refluxed for 2 hours then cooled and filtered. Compound Va (7.43 g, 60% yield) was separated out by neutralizing the filtrate with hydrochloric acid, mp 210-212° from acetonitrile; ir: 3320, 3230, 1530 cm⁻¹; ¹H-nmr (DMSO-d₆): 2.32 (s, 3H, CH₃ (6)), 2.48 (s, 3H, CH₃ (2)), 6.82 (s, 1H, H-5), 9.12 (broad s, 1H, NH), 10.45 (broad s, 2H, NH₂).

Anal. Calcd. for C₇H₁₀N₄S: C, 46.13; N, 30.74; H, 5.53. Found: C, 46.25; N, 30.59; H, 5.40.

Methyl *N'*-(2,6-Dimethylpyrimidin-4-yl)carbamimidothioate (VIa).

Dimethyl sulphate (4.8 g, 38 mmoles) was dropped into a saturated solution of Va (6.92 g, 38 mmoles) in DMF and the resulting solution heated at 50° for 4 hours. Removal of the solvent left a residue which was suspended in water. The above described suspension was treated with dilute sodium carbonate until the pH was 9 then extracted with five 15 ml-portion of chloroform. Evaporation of the dried chloroform solution left crude VIa (4.1 g, 55% yield, mp 128-129° from ligroine (bp 90-100°); ir: 3250 cm⁻¹; ¹H-nmr (DMSO-d₆): 2.28 (s, 3H, SCH₃), 2.40 (s, 3H, CH₃ (6)), 2.44 (s, 3H, CH₃ (2)), 6.53 (s, 1H, H-5), 8.95 (broad s, 2H, NH₂).

Anal. Calcd. for C₈H₁₂N₄S: C, 48.96; N, 28.54; H, 6.16. Found: C, 48.81; N, 28.70; H, 6.20.

2-(2,6-Dimethylpyrimidin-4-ylamino)benzimidazole (VIIa).

A mixture of VIa (3.34 g, 17 mmoles) and *o*-phenylenediamine (1.84 g, 17 mmoles) was heated at 160° for 80 minutes. The reaction mixture was treated with a little hot ethanol and filtered. The collected product amounted to 1.42 g (39% yield) of VIIa, mp 281-282° from DMF/ethanol; ir: 3260, 1460 cm⁻¹.

Anal. Calcd. for C₁₃H₁₃N₅: C, 65.25; N, 29.27; H, 5.48. Found: C, 65.32; N, 29.12; H, 5.35.

N-(1,3,4-Thiadiazol-2-yl)thiourea (Vb).

This compound was prepared starting from IIIb *via* IVb according to the method reported in the literature [8].

Methyl *N'*-(1,3,4-Thiadiazol-2-yl)carbamimidothioate (VIb).

Compound Vb (5.13 g, 32 mmoles) was added to 50 ml of methanol in which had been dissolved 0.74 g (32 mmoles) of sodium. Methyl iodide (4.54 g, 32 mmoles) was slowly added to the above described solution maintaining the temperature at 0-5° and the resulting mixture was allowed to react at room temperature for 24 hours. Removal of the solvent left a viscous oil which solidified on treatment with water. Compound VIb (4.8 g, 86% yield) was collected by filtration, mp 118-119° from ligroine (bp 90-100°); ir: 3350 cm⁻¹; ¹H-nmr (DMSO-d₆): 2.46 (s, 3H, SCH₃), 8.93 (broad s, 2H, NH₂), 9.08 (s, 1H, H-5).

Anal. Calcd. for C₄H₆N₄S₂: C, 27.57; N, 32.15; H, 3.47. Found: C, 27.45; N, 32.20; H, 3.35.

2-(1,3,4-Thiadiazol-2-ylamino)benzimidazole (VIIb).

A mixture of VIb (4 g, 23 mmoles) and *o*-phenylenediamine (2.5 g, 23 mmoles) was heated at 160° for 100 minutes. The glass-like residue was treated under stirring with a little ethyl acetate and the resulting solid product collected by filtration, which amounted to 1.6 g (32% yield) of VIIb, mp 225-226° from DMF/water; ir: 3240 cm⁻¹.

Anal. Calcd. for C₉H₇N₅S: C, 49.76; N, 32.24; H, 3.25. Found: C, 49.85; N, 32.30; H, 3.15.

1,3-Dimethyl-12*H*-Benzimidazo[1,2-*a*]pyrimido[6,1-*d*][1,3,5]triazin-12-one (IIa) and 5*H*-Benzimidazo[1,2-*a*][1,3,4]thiadiazolo[2,3-*d*][1,3,5]triazin-5-one (IIb).

General Procedure.

A solution of phosgene in toluene was slowly dropped into a well-stirred suspension of VII and triethylamine in dry toluene (molar ratio phosgene:VII:triethylamine = 1:1:2) maintaining the temperature below 5°. The reaction mixture was allowed to react at room temperature for 2 hours then filtered. The collected solid product was washed with ether, then with water, and dried. The yields of IIa-b were almost quantitative.

Compound IIa.

This compound had mp 257-258° from DMF/water; ir: 1750 cm⁻¹; ms: (70 eV) (M)⁺ m/z 265, (Benzimidazole-CO)⁺ m/z 144.

Anal. Calcd. for C₁₄H₁₁N₃O: C, 63.39; N, 24.60; H, 4.18. Found: C, 63.30; N, 24.50; H, 4.22.

Compound IIb.

This compound had mp 250-251° from DMF/water; ir: 1760 cm⁻¹; ms: (70 eV) (M)⁺ m/z 243, (Benzimidazole-CO)⁺ m/z 144.

Anal. Calcd. for C₁₀H₈N₂OS: C, 49.38; N, 28.79; H, 2.07. Found: C, 49.45; N, 28.75; H, 2.00.

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