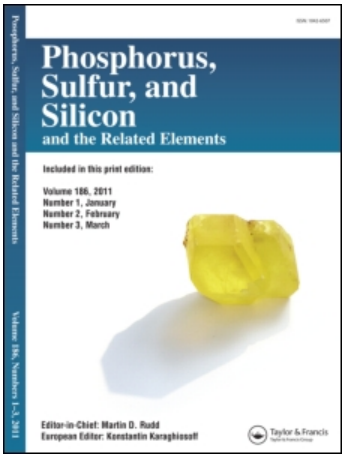

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AROYLISOTHIOCYANATES IN HETEROCYCLIC SYNTHESIS: SYNTHESIS OF NEW BENZIMIDAZOLE DERIVATIVES WITH ANTICIPATED FUNGICIDAL ACTIVITY

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The reactions of aroylisocyanates with 2-cyanomethylbenzimidazole (**1**) lead to the formation of 1:1 adducts (**2a,b,c**) and the corresponding α-aroyl derivatives (**4a,b,c**). The adducts (**2a,b**) could be cyclized affording pyrimido [**3,4–a**] benzimidazole derivatives (**5a–d**). They also afforded (pyrazol-4-yl) benzimidazole derivatives (**7a,b**) when (**2a,b,c**) reacts with hydrazine hydrate. Derivatives (**5c,7a**) could be cyclized to pyrazolo [4′,5′:5,4] pyrimidobenzimidazoles (**8,9**).

Key words: 2-Cyanomethylbenzimidazole; aroylisothiocyanates; pyrimidobenzimidazole; (pyrazol-4-yl) benzimidazole; fungicides.

INTRODUCTION

Benzimidazoles are associated with anthelmentic,[1] antifungal[2] and other pharmacological activities[3–5]; on the other hand, activated nitriles are known as versatile reagents.[6–8] Accordingly, one may well expect the substituted 2-cyanomethylbenzimidazoles to be good precursors for the synthesis of annulated and substituted benzimidazole derivatives with anticipated biological activities.

RESULTS AND DISCUSSION

Thus, it has been found that **1a** reacts with benzoylisothiocyanate to yield a mixture of two compounds which were separated by fractional crystallisation. The product m.p. 234°C having the molecular formula $C_{17}H_{12}N_4OS$ (m/z = 320) was identified as the adduct (**2a**) rather than (**3a**) based on ^1H NMR which revealed aromatic protons only along with D_2O exchangeable protons NH and SH. On the other hand, compound (**4a**) was found to be identical with the reported α-benzoyl-2-cyanomethylbenzimidazole (upon comparison of their melting points and IR spectra).[9] The formation of (**4a**) from the reaction of (**1a**) with benzoylisothiocyanate is assumed to proceed via an intermediate (**3a**) which then rearranges into (**4a**) by losing thiocyanic acid. Similar rearrangements of N-benzoylthiocarbamoylazoles into benzoyl derivatives have been previously reported[10,11] and the mechanism has been discussed.

Similar to the behavior of **1a** towards benzoylisothiocyanate, it also reacted with 2-furanoylisothiocyanate giving a mixture of **2b** and **4b**.

TABLE I

Physical and chemical data for **2a,b,c** and **4a,b,c**

Compd. No.	Yield %	Solvent/ M.p. °C	Molecular formula/ M. Wt.	Analysis % Calc./Found C	H	N	S	MS (%)
2a	60	dioxane	$C_{17}H_{12}N_4OS$	63.74	3.78	17.50	10.01	320(8), 302(2), 261(4),
		234	320.368	63.70	4.29	16.99	9.72	156(8), 105(100), 77(56), 51(18).
2b	55	dioxane	$C_{15}H_{10}N_4O_2S$	58.05	3.25	18.06	10.33	
		210–12	310.324	58.00	3.23	17.82	9.77	
2c	60	dioxane	$C_{19}H_{16}N_4OS$	65.49	4.63	16.08	9.20	348(29), 330(32),
		235–38	348.414	65.0	4.2	15.66	8.70	298(12), 226(17), 186(34), 170(21), 106(100).
4a	20	D.M.F.	$C_{16}H_{11}N_3O$	73.55	4.24	16.08	—	
		over 300	261.27	73.60	4.53	16.50	—	
4b	25	D.M.F.	$C_{14}H_9N_3O_2$	66.93	3.61	16.73	—	251(100), 209(10),
		over 300	251.232	67.00	4.00	16.98	—	196(18), 153(20), 96(24), 72(15).
4c	10	D.M.F.	$C_{18}H_{15}N_3O$	74.72	5.23	14.52	—	
		264–65	289.32	74.38	4.97	14.29	—	

TABLE I (cont.)

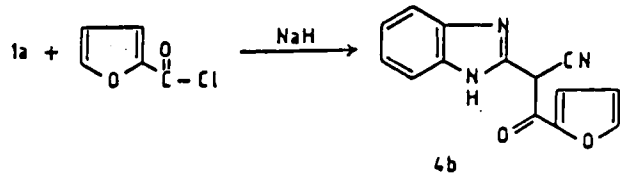
Physical and chemical data for **5a–d** and **7a,b**

Compd. No.	Yield %	Solvent/ M.p. °C	Molecular formula/ M. Wt.	Analysis % Calc./Found C	H	N	S	MS (%)
5a	70	toluene	$C_{18}H_{12}N_4S$	68.33	3.82	17.71	10.13	
		284–86	316.37	68.4	3.9	17.40	9.72	
5b	60	dioxane	$C_{19}H_{14}N_4S$	69.07	4.27	16.96	9.70	330(100), 297(58),
		over 300	330.39	68.70	4.00	16.58	9.60	198(23), 156(3), 104(12), 90(45), 77(11), 63(6).
5c	75	dioxane-toluene	$C_{16}H_{10}N_4OS$	62.73	3.29	18.29	10.47	306(100), 272(22),
		195–196	306.33	62.91	3.40	17.93	9.85	215(9), 185(8), 178(14), 152(6), 98(19), 67(17).
5d	60	dioxane	$C_{17}H_{12}N_4OS$	63.73	3.78	17.49	10.01	
		over 300	320.36	63.45	3.61	16.98	9.82	
7a	70	D.M.F.	$C_{10}H_{10}N_6$	56.06	4.70	39.23	—	214(100), 183(21),
		over 300	214.23	55.90	4.90	38.72		158(11), 118(12), 92(9), 77(6).
7b	60	dioxane	$C_{12}H_{14}N_6$	59.48	5.82	34.69	—	
		232–234	242.28	59.70	5.80	34.35		

TABLE II

Compound No.	IR (cm^{-1})	^1H NMR (ppm)
2a	3200-2900 (NH and SH), 2200 (CN), 1650 (CO)	7.3–8.1 (m, 9H, C_6H_5 and benzimidazole, protons), 10.8 (br, s, 1H, NH), 14.8 (br, s, 1H, SH).
2b	3200-2900 (NH and SH), 2200 (CN), 1655 (CO)	
2c	3200-2800 (NH and SH), 2200 (CN), 1670 (CO)	2.3 (s, 6H, $2CH_3$), 7.4–8.0 (m, 7H, C_6H_5 and benzimidazole protons), 10.5 (s, br, 1H, NH) 12.1 (s, 1H, SH)
4b	3200 (NH), 2220 (CN), 1620 (hydrogen bonded (CO)	3.6 (s, 1H, CH—CN), 6.5 (q, 1H, furan H-4), 7.2 (m, 3H, benzimidazole H-5, H-6 and furan H-3), 7.6 (m, 2H, benzimidazole H-4 and H-7), 7.8 (q, 1H, furan H-5).
4c	3200 (NH), 2220 (CN), 1630 (hydrogen bonded CO)	
5a	2220 (CN)	2.9 (s, 3H, S—CH_3), 6.8 (q, 1H, benzimidazole H-7), 7.1 (m, 2H, benzimidazole H-5 and H-6) 7.6 (q, 1H, benzimidazole H-4), 7.9 (m, 5H, C_6H_5).
5b	2220 (CN)	1.5 (t, 3H, CH_3), 3.5 (q, 2H, CH_2), 7.2 (q, 2H, benzimidazole H-5 and H-6), 7.5 (t, 2H, benzimidazole H-4 and H-7), 7.9 (m, 5H, C_6H_5).
5c	2215 (CN)	2.8 (s, 3H, SCH_3), 7.1 (q, 1H, furan H-4), 7.4–7.9 (m, 5H, benzimidazole and furan H-3, H-5 protons), 8.3 (q, 1H, benzimidazole H-7).
5d	2215 (CN)	
7a	3390 (NH_2), 3300 (NH_2)	7.0 (m, 2H, benzimidazole H-5 and H-6), 7.4 (m, 2H, benzimidazole H-4 and H-7).
7b	3410, 3300 (NH_2), 3220-2800 (NH) 1615 (C=N)	2.3 (s, 6H, $2CH_3$), 7.3 (d, 2H, benzimidazole H-4, 7), 4.4 (s, 1H), 5.6 (br s, 2H), 6.3 (s, 1H), 7.5 (br s, 1H) all are (D_2O) exchangeable signals attributed to NH and NH_2 protons).
8	br 3450-2900 (NH), 1610 (C=N)	7.1 (m, 3H, phenyl H-3, H-4 and H-5), 7.6 (m, 4H, benzimidazole, H-5, H-6 and phenyl H-2, H-6), 8.1 (m, 2H, benzimidazole H-4, H-7), 11.5 (s, 1H, NH), 12.5 (s, 1H, NH).
9	3400, 3300 (NHCO, NH) 1650 (CO)	2.0 (s, 3H, acetyl CH_3), 3.1 (s, 3H, pyrimido CH_3), 7.0–7.7 (m, 3H, benzimidazole H-4, H-5 and H-6), 8.1 (q, 1H, benzimidazole H-7), 12.1 (s, 1H, NH).

The structure of compounds **2b** and **4b** have been established from their analytical data, IR spectra, ^1H NMR and mass spectroscopy (cf. Tables I, II). The α-furoyl-2-cyanomethylbenzimidazole **4b** could also be obtained by the reaction of **1a** with furoyl chloride in presence of NaH. 5,6-Dimethyl-2-cyanomethylbenzimidazole **1b** also reacted with benzoylisothiocyanate in the same manner affording products **2c** and **4c**.



In contrast to the recently reported pyrimido [**4,3–b**] benzothiazole (II)[12] which was obtained from the cyclization of the 1:1 adducts (I) when boiled under reflux in dioxane, cyclization of the 1:1 adducts **2a,b** failed under the same condition. However, compound **2a** could be cyclized into a product which was formulated as **5a** on treatment with methyl iodide in dimethyl sulphoxide in the presence of an equimolecular amount of sodium hydride. Thus the ^1H NMR of product **5a** showed beside the absence of any D_2O exchangeable signals and the presence of a $S.CH_3$ group as a singlet located at δ 2.9 ppm, a proton pattern for the benzimidazole ring as a quartet signal integrated to one proton located at δ 6.8 ppm, a multiplet signal integrated to two protons located at δ 7.1 ppm and a quartet signal located at δ 7.6 ppm integrated to one proton; these along with the phenyl protons signals which appeared as multiplet at δ 7.9 ppm.

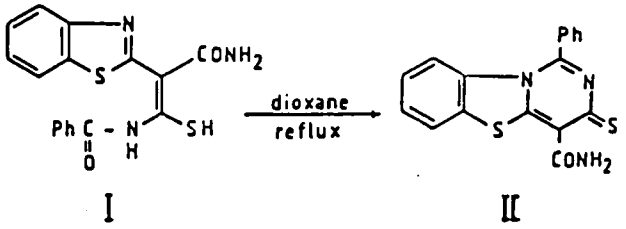
The IR spectrum revealed also the absence of any absorbance due to OH,SH and benzimidazole ring NH groups.

Under the same conditions utilized for the cyclization of **5a**, compound **2b** could also be cyclized into **5c** on treatment with methyl iodide. Analytical and spectral data are in agreement with the given structure of the new furyl derivative (cf. Tables I, II).

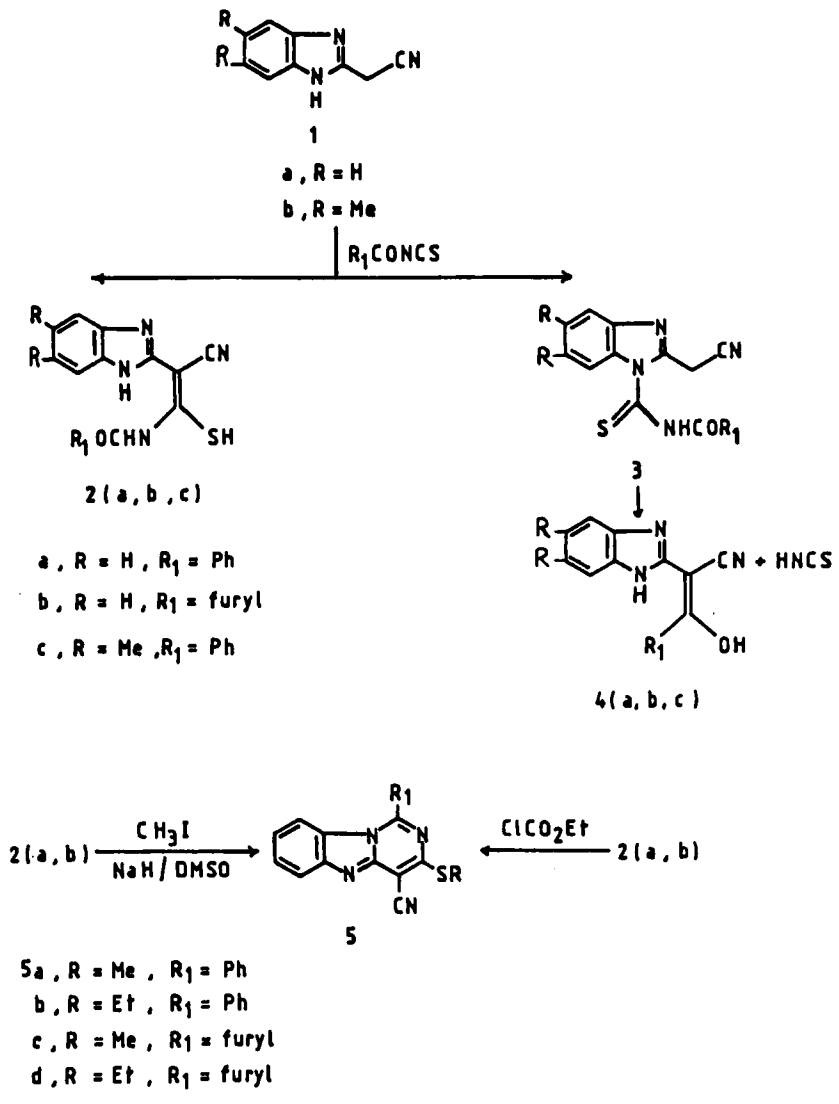
It is assumed that the S-alkylation is essential for the cyclization of adducts **2a,b** which gave the pyrimidobenzimidazole derivatives **5a,c** whereas conducting the reaction in the presence of sodium hydride only without methyl iodide afforded the starting material recovered unchanged. Although the thiosodium salt formed might be expected to act in the same way as the alkyl group, the fact that it separates out as soon as it is formed eliminates it from the reaction course.

In accordance with this view the cyclization of compounds **2a,b** was also achieved by their reaction with ethyl chloroformate in dry dioxane. The newly synthesized pyrimidobenzimidazole derivatives **5b,d** were obtained in good yields. The suggested structures **5b,d** were proven through their analytical, spectral and chemical behavior (cf. Tables I, II).

It is of interest to synthesize 2-substituted heterocyclic benzimidazoles utilizing the adducts **2a–c** since two derivatives of this class of compounds are already marketed under the name of Thiabendazole[13] (anthelmentic and fungicide) and Fuberidazole[14] (fungicide).



I II



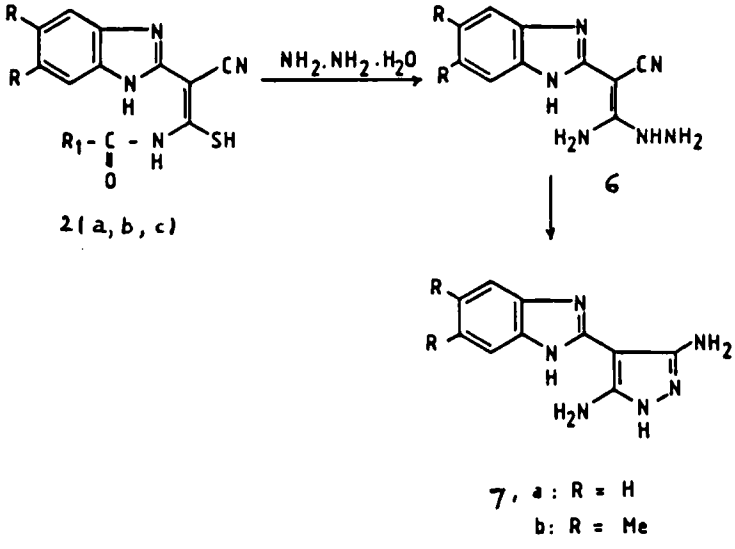
Scheme I

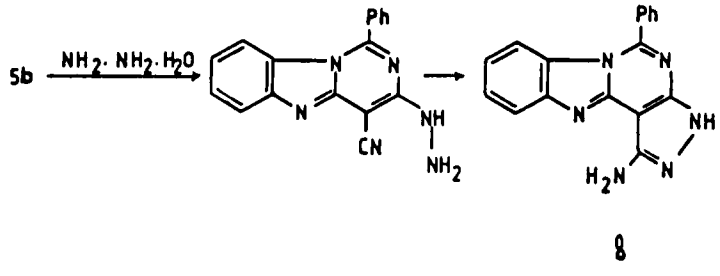
Since under dry conditions, compound **2a,b** underwent a condensation reaction involving the benzimidazole ring NH to give the pyrimidobenzimidazole derivatives **5a–d**, it is assumed that applying aqueous conditions might retard such a reaction and enhance reaction in other directions.

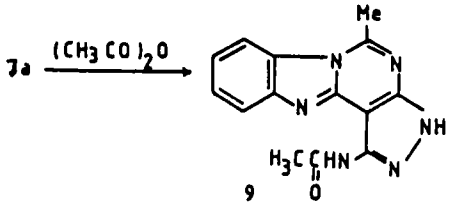
Thus when the adduct **2a** reacted with hydrazine hydrate in ethanol, a product with a molecular formula $C_{10}H_{10}N_6$ (m/z 214) was obtained. Structure (**7a**) was suggested for this product based on its spectral data (cf. Tables I, II). The formation of (**7a**) from **2a** is assumed to proceed via hydrolysis of the benzoyl group and replacement of the SH group both with hydrazine hydrate, to give the intermediate (**6**) which cyclized involving the cyano group affording the final isolable 2-(3,5-diaminopyrazol-4-yl) benzimidazole. In accordance with this view, compound (**7a**)

was also the only product obtained when adduct **2b** reacted with hydrazine hydrate under the same condition.

An analogous result was obtained on applying the same reaction to the adduct **2c** and accordingly the 2-(3,5-diaminopyrazol-4-yl)-5,6-dimethylbenzimidazole (**7b**) was obtained in good yield. Structure (**7b**) was established from its analytical and spectral data (cf. Tables I, II).







Scheme II

Since structure activity relationships have attracted the attention of many authors, we found it interesting to attempt the synthesis of fused benzimidazoles containing both the pyrimido and pyrazoloe moieties to compare their biological activities with that of the above mentioned pyrimido and pyrazolobenzimidazole derivatives (**5**) and (**7**). Thus when compound **5b** was treated with hydrazine hydrate in refluxing ethanol, the obtained product showed absence of CN absorbance in its IR spectrum and absence of ethyl protons in its ^{1}H NMR spectrum. These data along with the analytical ones can be interpreted for structure (**8**). It is suggested that product (**8**) could be formed through replacement of the SCH_2CH_3 group by an $NHNH_2$ group and subsequent cyclization involving the CN group to give the final isolable product.

Another approach to prepare the aimed fused pyrazolopyrimidobenzimidazole was achieved by refluxing the 3,5-diaminopyrazole derivative (**7a**) in acetic anhydride to give a product to which structure (**9**) was suggested. The ^{1}H NMR of compound (**9**) showed a singlet at δ 2.0 ppm assigned to the N-acetyl methyl group and another singlet integrated to three protons located at δ 3.1 ppm attributable to the pyrimido methyl group. These along with the aromatics of the benzimidazole moiety and the lower field NH protons signals at δ 10.0 and 12.1 ppm are consistent with the structure (**9**).

Preliminary fungicidal tests showed that compounds **2a** as a representative example, exhibits remarkable activity against F. manilifarum, P. oxalicum and A. niger. Further work is in progress and will be published elsewhere.

EXPERIMENTAL

All mp's were uncorrected. The IR spectra were recorded in KBr with a Pye-Unicam sp-1000 spectrometer. The ^{1}H NMR spectra were run on a Varian spectrometer at 60 MHz and/or 90 MHz, using TMS as an internal reference. The mass spectra were recorded at 709 ev with a Varian MAT 311 A mass spectrometer. Elemental analyses were performed by the Central Service Laboratory in the National Research Centre.

*3-Aroylamino-3-mercapto-2-(benzimidazol-2-yl or 5,6-dimethylbenzimidazol-2-yl) acrylonitrile (**2a–c**) and 2-(α-aroylcyanomethyl) benzimidazole or 5,6-dimethylbenzimidazole (**4a–c**)*

General Procedure. A solution of (**1a,b**) (0.01 mole) in dry dioxane (30 ml) was treated each with aroylisothiocyanate (aroyl = benzoyl, furoyl) (0.01 mole) (prepared according to reported methods).[15,16] The reaction mixture was stirred at room temperature for 4–5 hours, followed by TLC (ether/toluene 4:1) which determined that all the starting material had reacted. The solution was then poured onto water, the resulting solid was filtered off and washed thoroughly with water. It was found to be a mixture of **2** and **4** in each case which was separated by fractional crystallisation (cf. Table I).

*1-Aryl-3-methylmercapto-4-cyanopyrimido [3,4–a] benzimidazole (**5a,b**)*

General Procedure. A solution of (**2a,b**) (0.01 mole) in dry dimethyl sulphoxide (20 ml) was treated with sodium hydride (0.01 mole, 0.24 g) and stirred for 2 hours till no more salt was precipitated. Methyl iodide (0.01 mole, 1.42 g in 5 ml dry dimethyl sulphoxide) was then added dropwise in a period of 15 minutes, and the mixture was then stirred for 4 hours. The solution was then poured onto water, the resulting solid product was filtered off, washed with water and crystallised from the proper solvent (cf. Table I).

*1-Aryl-3-ethylmercapto-4-cyanopyrimido [3,4–a] benzimidazole (**5b,d**)*

General Procedure. (**2a,b**) (0.01 mole) was boiled under reflux with an equimolecular amount of ethyl chloroformate (1.1 g) in dry dioxane (30 ml) in the presence of triethylamine (0.5 ml); the starting material was consumed in the reaction after 8 hours as predicted by TLC (ether/toluene 4:1). The solution was concentrated and left to cool. The solid formed was filtered off, washed thoroughly with water and then crystallised from the appropriate solvent (cf. Table I).

*2-(3,5-Diaminopyrazol-4-yl) benzimidazole or 5,6-dimethylbenzimidazole (**7a,b**)*

General Procedure. **2a,b,c** (0.01 mole) was refluxed each with hydrazine hydrate 99% (0.03 mole, 1 g) in ethanol (20 ml) for 4 hours. The reaction mixture was then concentrated, cooled and the precipitate formed was filtered off and crystallised from the appropriate solvent.

*10-Phenyl-3-aminopyrazolo-1H-[4',5':5,4] pyrimido [1,6-a] benzimidazole (**8**).* (**5c**) (0.01 mole, 3.3 g) was boiled under reflux with hydrazine hydrate 99% (0.02 mole, 0.64 g) in dioxane (30 ml). After 2 hours the colour of the solution turned to deep yellow with the formation of a precipitate. The reaction mixture was filtered while hot, and the solid product was crystallised from dimethyl formamide affording 1.9 g (63% yield) of yellow crystals, m.p. over 300°C.

Anal. Calcd. For $C_{17}H_{12}N_6$ (300.32): C, 67.98; H, 4.02: N, 27.98%.
Found. C, 67.3; H, 4.2; N, 27.4%.

*10-Methyl-3-acetamidopyrazolo-1H-[4',5':5,4] pyrimido [1,6-a] benzimidazole (**9**).* (**7a**) (0.01 mole, 2.14 g) was boiled under reflux in (20 ml) acetic anhydride under dry conditions for 4 hours. Afterward, the solution was cooled and poured onto water where a brown solid product separated out. The precipitate obtained was crystallised from dimethyl formamide to give 1.68 g (60% yield) of yellowish brown crystals m.p. over 300°C.

Anal. Calcd. For $C_{14}H_{12}N_6O$ (280.29): C, 59.98: H, 4.31: N, 29.98%.
Found. C, 59.4; H, 4.2; N, 29.4%.

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