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Studies with polyfunctionally substituted heterocycles: synthetic approaches to azinylcarbonitrile

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Summary – Mixtures of acetaldehyde and active methylene reagent reacted with cyanothioacetamide to yield thiopyran **4** and pyridine thione **10**. The pyridine thiones **10** readily reacted with a wide variety of reagents to give novel heterocyclic systems.

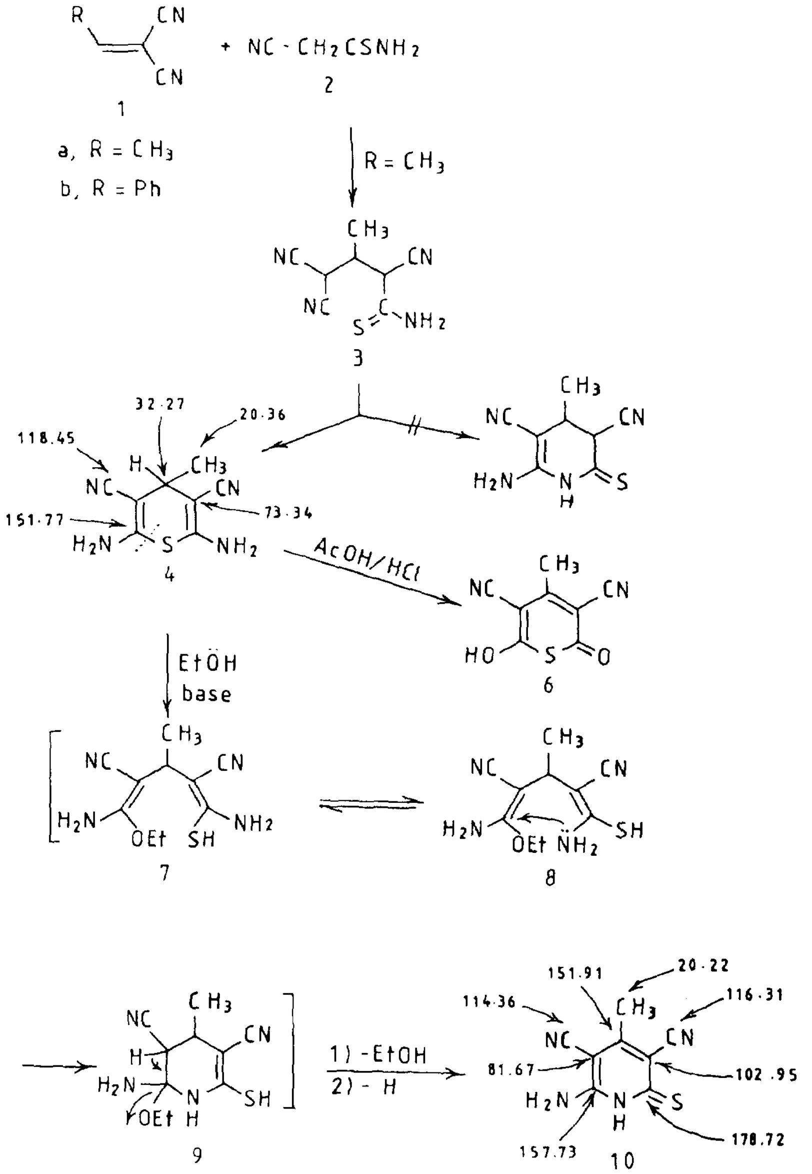
thiopyran / isoquinoline / enehydrazine / cinnoline

Alkylazinylcarbonitriles are important building blocks in synthetic heterocyclic chemistry and their utility for the preparation of condensed azines has been reported recently [1]. Following previous work in our laboratories we have reported several new syntheses of this class of heterocyclic synthons [2-4]. In a continuation of our research in this area, we report here results that enabled us to develop several new efficient syntheses for differently substituted pyridinyl carbonitriles and methylpyridazinyl carbonitriles.

One of the most frequently utilized syntheses of pyridinyl carbonitriles involves addition of active methylene nitriles to arylidenemalononitrile (**1b**; R = Ar) [1-5]. We investigated the possible utility of (**1a**; R = CH_3) for the synthesis of target methylpyridinyl carbonitriles. As **1** (R = CH_3) is difficult to isolate in a pure form, we used a mixture of acetaldehyde and malononitrile, which on treatment with a base generates **1** (R = CH_3). We found that a mixture of acetaldehyde, malononitrile and cyanothioacetamide **2** reacts in ethanolic piperidine at room temperature to yield a product of molecular formula $C_8H_8N_4S$ (192 M^+). This formula is consistent with the acyclic structure **3**, thiopyran **4** or pyridinethione **5**. The thiopyran structure **4** could be readily established based on the ^{13}C NMR spectrum, which showed only five carbon signals. If the product had been **3** or **5**, seven signals for magnetically different carbons would have been observed. ^1H NMR spectra also supported the proposed structure since they revealed a doublet for methyl group at $\delta = 1.18$ ppm and a multiplet at $\delta = 3.07$ ppm of thiopyran H-4 as well as a four proton D_2O exchangeable signal at $\delta = 6.75$ for NH_2 protons. Compound **4** is assumed to be formed *via* the intermediacy of the acyclic Michael adduct **3**.

It has been recently reported by Geies *et al* [6] that pyridinethione **10** is the sole product of the reactions of cyanothioacetamide, aldehydes and active methylene reagents, and that formation of this product results from addition of cyanothioacetamide to its ylidene and subsequent cyclization [6]. The formation of **10**, upon the attempted addition of diethyl malonate or 3-methylpyrazolone to ylidenecyanothioacetamide, led the authors to conclude that our previously reported [7-13] preparation of pyridinethiones by reacting malononitrile or ethyl cyanoacetate with ylidenecyanothioacetamide was incorrect, and further, that active methylenes did not in fact add to ylidenecyanothioacetamide. Although this conclusion seems highly improbable in the light of repeated successful additions of active methylenes to ylidenecyanothioacetamide [7-9] and the addition of cyanothioacetamide to α,β-unsaturated ketones [10, 11], it seems important to check our previous results. We can now confirm that thiopyrans **4** are the only products of the reaction of malononitrile with ylidenecyanothioacetamide at room temperature. They are formed very readily upon adding a base to the reaction mixture without H_2S elimination. The same thiopyrans are also produced by adding cyanothioacetamide to ylidenemalononitrile [7-8]. No H_2S elimination was observed in these reactions. Other active methylene compounds, like acetylacetone [12], ethyl acetoacetate [1], cyclic ketones [1] and 5,5-dimethylcyclohexane-1,3-dione [13] all afford the previously reported products. Only when the active methylene moiety in the reagent is highly unreactive is **10** formed [6]. Furthermore, thiopyrane **4** was hydrolyzed in acetic acid in the presence of hydrochloric acid to give thiopyranone **6**. The structure of thiopyranone **6** could be readily established on the basis of its spectral data (for further details see *Experimental section*).

Compound **4** was readily converted to the pyridinethione **10** by refluxing in ethanolic piperidine solution. It is assumed that the thiopyran ring in **4** is opened in

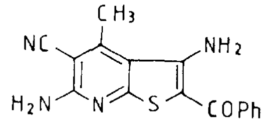


Scheme 1

hot basic media to yield intermediates **7** and **8** which cyclize to **9** *via* nucleophilic addition to the unsaturated vinyl ether linkage. Compound **9** undergoes aromatization and autooxidation under the reaction conditions to yield **10**. Compound **10** could be also directly formed on refluxing a solution of acetaldehyde, malononitrile and **2** in ethanolic piperidine (scheme 1). The pyridinethione **10** could be converted into the thieno[2,3-*b*]pyridine **11** on treatment with phenacyl bromide **12** in refluxing pyridine solution. On refluxing benzylidenemalononitrile **1b** compound **10** for extended periods, a product of condensation *via* hydrogen cyanide elimination was formed. This product can be formulated as **13** or its isomer **14**. Structure **13** was established on the basis of the fact that the product of reaction of phenacyl bromide with this compound showed a CH_2 signal in the ^1H NMR at $\delta = 5.1$ ppm, which is typical for the expected acyclic structure **15**. If the reaction product was **14**, we would expect formation of **16** which does not have any CH_2 signal. Trials to prepare **16** from reaction of **11** with **1b** under a variety of conditions failed.

Similarly, the reaction of **10** with β-nitrostyrene **17** afforded the isoquinoline derivative **18**.

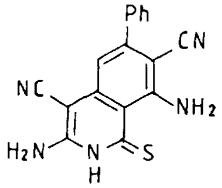
Attempts to prepare the pyridinethione **20** by direct reaction of a mixture of acetaldehyde, cyanothioacetamide and the β-functionalized enamines **21a,b** failed. Instead the aminopyridinethione **10** was obtained. In this reaction 3-aminocrotononitrile did not undergo an addition reaction and thus another molecule of cyanothioacetamide reacted to afford **10**, which of course could also be formed from acetaldehyde and **2**. Although β-enaminonitriles have been extensively employed in organic synthesis [14], there are few reports on the use of these versatile reagents for constructing pyri-



11

$PhCOCH_2Br$

12



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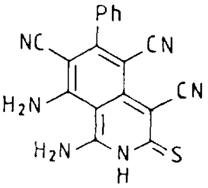

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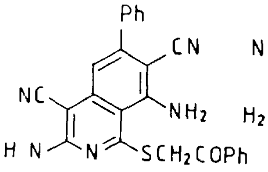

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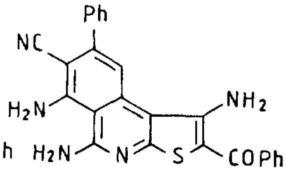

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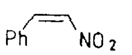

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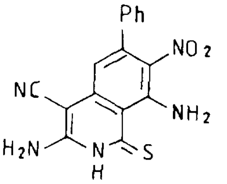

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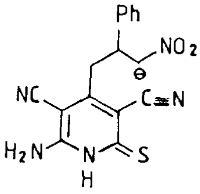

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dazines. Reaction of β-functionalized enamines **21a,b** with cyanoacetic hydrazide gives pyridazines *via* an unexpected cyclization. Thus, condensing **21a,b** with cyanoacetic hydrazide **22** gave the enehydrazine **23a,b**, which upon melting in presence of air cyclized into **25a,b**. We believe that **23a,b** are first oxidized into the eneazo derivatives **24a,b** which then cyclize readily into pyridazine derivatives **25a,b**. To our knowledge, this is the first reported formation of pyridazines by means of fusion of enehydrazine compounds. The methyl group in **25a** showed high reactivity with benzylidenemalononitrile **1b**. Thus, the cinnoline **26** could be prepared by reacting **25a** with **1b**.

Experimental section

All melting points are uncorrected. Analytical data were obtained from the Microanalytical Data Unit at Cairo University. The IR spectra were obtained on a Pye-Unicam Sp-1000 spectrophotometer. NMR spectra were measured in DMSO on a Varian EM-360-60 MHz, using TMS as an internal standard; chemical shifts are expressed as δ ppm. Mass spectra were recorded on a Varian MAT 311A spectrometer.

2,6-Diamino-4-methyl-4H-thiopyran-3,5-dicarbonitrile 4

To a solution of cyanothioacetamide (3 g, 0.03 mol) and malononitrile (2 g, 0.03 mol) in 15 mL absolute ethanol with one drop of piperidine, was added acetaldehyde (2 mL). The reaction mixture was warmed for 2 min. The solid product formed after cooling at room temperature was collected by filtration and washed 3 times with ethanol and crystallized from ethanol as white crystals, yield 4 g (50%), mp 200°C.

IR (KBr): ν = 3 380–3 240 cm^{-1} (NH_2), 2 221, 2 218 cm^{-1} (CN).

^{1}H NMR (DMSO) δ = 1.17 (d, 3H, CH_3); 3.04 (q, 1H, CH), 6.75 (s, 4H, $2NH_2$).

^{13}C NMR (see formula 2).

MS: m/z = 192 (M^+).

Anal calc for $C_8H_8N_4S$ (192.18): C, 50.0; H, 4.1; N, 29.1; S, 16.6. Found: C, 50.2; H, 4.0; N, 29.2; S, 16.7.

6-Amino-4-methyl-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile 10

To a solution of cyanothioacetamide (3 g, 0.03 mol) and malononitrile (2 g, 0.03 mol) in 15 mL absolute ethanol with one drop of piperidine was added acetaldehyde (2 mL). The reaction mixture was heated under reflux for 30 min. A solid product formed during heating. It was collected by filtration and crystallized from dioxane, as yellow crystals, yield 3 g (45%), mp 280°C.

IR (KBr): ν = 3 420–3 200 cm^{-1} (NH_2), 2 221, 2 219 cm^{-1} (CN).

^{1}H NMR (DMSO) δ = 2.38 (s, 3H, CH_3); 7.83 (br, 2H, NH_2), 12.77 (br, 1H, NH).

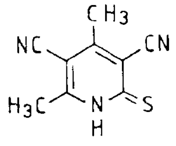
^{13}C NMR (see formula **10**).

MS: m/z = 190 (M^+).

Anal calc for $C_8H_6N_4S$ (190.18): C, 50.5; H, 3.1; N, 29.4; S, 16.8. Found: C, 50.4; H, 3.2; N, 29.3; S, 16.9.

6-Hydroxy-4-methyl-2-oxo-2H-thiopyran-3,5-dicarbonitrile 6

Compound **4** (1.9 g, 0.01 mol) was stirred with concentrated hydrochloric acid/acetic acid 3:1 mixture for 24 h. The solid



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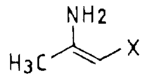

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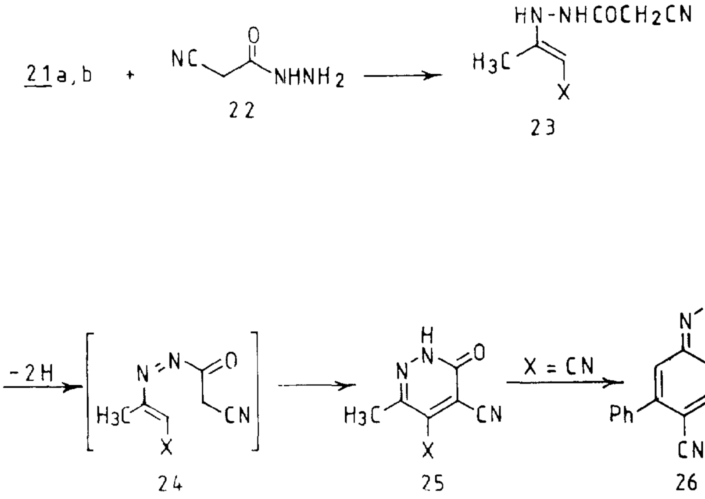
a, X = CN
b, X = CO_2Et



21,23-25 a, X = CN
b, X = CO_2Et

product was collected by filtration and crystallized from dioxane as yellow crystals, yield 0.8 g (50%), mp 280°C.

IR (KBr): ν = 3480, 3400 cm^{-1} (OH), 2221 cm^{-1} (CN), 1710 cm^{-1} (C=O).

^1H NMR (DMSO) δ = 2.29 (s, 3H, CH_3), 12.8 (br, 1H, OH).

^{13}C NMR δ = 20.20 (CH_3), 81.71 (C-5), 102.94 (C-3), 114.33 (CN), 116.28 (CN), 154.19 (C-4), 157.70 (C-6), 179.11 (C=O).

MS: $m/z = 192$ (M^+).

Anal calc for $C_8H_4N_2O_2S$ (192.16): C, 49.95; H, 2.08; N, 14.58; S, 16.66. Found: C, 49.8; H, 2.1; N, 14.3; S, 16.7.

2-Benzoyl-5,6-diaminothieno[2,4-b]pyridine-5-carbonitrile **11**

A mixture of compound **10** (1.9 g; 0.01 mol) and phenacyl bromide 12 (2 g, 0.01 mol) in 20 mL dioxane containing 2 g K_2CO_3 was refluxed for 2 h. The solid product formed on dilution and neutralization by HCl was collected by filtration and crystallized from dioxane as yellow crystals; yield 3 g (75%), mp 170°C.

IR (KBr): ν = 3400-3330 cm^{-1} (NH_2), 2222 cm^{-1} (CN), 1690 cm^{-1} (C=O).

^1H NMR (DMSO) δ = 2.21 (s, 3H, CH_3), 3.85 (br, 4H, $2NH_2$), 7.12-7.51 (m, 5H, aromatic protons).

Anal calc for $C_{16}H_{12}N_4OS$ (308.26): C, 62.3; H, 3.8; N, 15.1; S, 10.3. Found: C, 62.2; H, 3.7; N, 15.7; S, 10.4.

3,8-Diamino-6-phenyl-1-thioxo-1,2-dihydroisoquinoline-4,7-dicarbonitrile **13**

To a solution of **10** (1.9 g, 0.01 mol) in 20 mL dioxane, was added benzylidene-malononitrile **1b** (1.5 g, 0.01 mol) with few drops of piperidine. The reaction mixture was refluxed for 5 h. The solid product formed on dilution was collected by filtration and crystallized from dioxane as brown crystals, yield 1.9 g (61%), mp > 280°C.

IR (KBr): ν = 3420-3300 cm^{-1} (NH_2), 2222 cm^{-1} (CN).

^1H NMR (DMSO) δ = 3.52 (br, NH_2), 7.0-7.71 (m, 5H, aromatic protons), 8.0 (s, 1H, aromatic protons), 8.82 (br, 1H, NH).

Anal calc for $C_{17}H_{11}N_5S$ (317.37): C, 64.3; H, 3.4; N, 22.0; S, 10.0. Found: C, 64.2; H, 3.4; N, 22.1; S, 9.9.

3,8-Diamino-1-phenacylthio-6-phenylisoquinoline-4,7-dicarbonitrile **15**

A mixture of compound **13** (3 g, 0.01 mol) and phenacyl bromide (2 g, 0.01 mol) in 20 mL dioxane containing 2 g K_2CO_3 was refluxed for 2 h. The solid product formed on addition of ethanol was collected by filtration and crystallized from dioxane/DMF (1:1) as brown crystals; yield 1 g (25%), mp > 280°C.

IR (KBr): ν = 3450-3300 cm^{-1} (NH_2), 2222-2218 cm^{-1} (CN), 1695 cm^{-1} (C=O).

^{1}H NMR $\delta = 3.61$ (br, 2NH$_2$), 5.1 (s, 2H, CH$_2$), 6.91–7.9 (m, 11H, aromatic protons).

Anal calc for $C_{25}H_{17}N_5OS$ (435.50): C, 68.93; H, 3.4; N, 16.0; S, 7.3. Found: C, 69.0; H, 3.8; N, 16.1; S, 7.3.

3,8-Diamino-7-nitro-6-phenyl-1-thioxo-1,2-dihydroisoquinoline-4-carbonitrile **18**

To a solution of **10** (1.9 g, 0.01 mol) in 20 mL dioxane, was added β-nitrostyrene **17** (1.4 g, 0.01 mol) with few drops of piperidine. The reaction mixture was refluxed for 3 h. The solid product that formed on addition of ethanol was collected by filtration and crystallized from dioxane as dark-brown crystals, yield 1 g (30%), mp > 280°C.

IR (KBr): $\nu = 3\,430$–$3\,350$ cm^{-1} (NH$_2$), 2 220 cm^{-1} (CN).

^{1}H NMR (insoluble compound).

MS: $m/z = 337$ (M$^+$).

Anal calc for $C_{16}H_{11}N_5O_2S$ (337.34): C, 56.97; H, 3.26; N, 20.77; S, 9.49. Found: C, 57.0; H, 3.2; N, 20.8; S, 9.4.

Condensation of **21a,b** *with cyanoacetic hydrazide (preparation of* **23***)*

A solution of **21** (0.01 mol) in acetic acid (10 mL) and cyanoacetic hydrazide (1 g, 0.01 mol) was stirred at room temperature for 4 h. The solid product that formed on dilution with water was collected by filtration and crystallized from ethanol to give **23**.

Compound **23a** (colorless crystals) yield 0.5 g (62%), mp 130°C.

IR (KBr): $\nu = 3\,400$, $3\,350$ cm^{-1} (NH), 2 220, 2 218 cm^{-1} (CN) and 1 690 cm^{-1} (CO).

^{1}H NMR (CDCl$_3$) $\delta = 2.0$ (s, 3H, CH$_3$), 3.72 (s, 2H, CH$_2$), 4.21 (s, 1H, CH), 8.92 (s, 1H, NH) and 10.23 (s, 1H, NH).

MS: $m/z = 164$ (M$^+$).

Anal calc for $C_7H_8N_4O$ (164.1): C, 41.21; H, 4.87; N, 34.14. Found: C, 51.2; H, 4.8; N, 34.2.

Compound **23b** (colorless crystals) yield 1.4 g (78.2%), mp 160°C.

IR (KBr): $\nu = 3\,350$ cm^{-1} (NH); 2 220 cm^{-1} (CN); 1 700–1 680 cm^{-1} (C=O).

^{1}H NMR $\delta = 1.2$ (t, 3H, CH$_3$); 2.1 (s, 3H, CH$_3$); 3.91 (s, 2H, CH$_2$); 4.21 (q, 2H, CH$_2$); 4.32 (s, 1H, CH); 9.8 (br, 2H, NH$_2$).

Anal calc for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.16; N, 19.90%. Found: C, 51,17; H, 6.15; N, 19.89.

3-Methyl-6-oxo-1,6-dihydropyridazine-4-carbonitrile derivatives **25a,b**. *General method*

Compound **23** (0.02 mol) was fused at 140°C in an oil bath for 5 min. The solid product obtained after fusion was crystallized from dioxane as pale yellow crystals.

3-Methyl-6-oxo-1,6-dihydropyridazine-4,5-dicarbonitrile **25a**

Yield 2.5 g (78%), mp 210°C.

IR (KBr): $\nu = 2\,221$–$2\,214$ cm^{-1} (CN), 1 690 cm^{-1} (C=O).

^{1}H NMR (CDCl$_3$) $\delta = 2.3$ (s, 3H, CH$_3$), 8.5 (s, 1H, NH).

MS: m/z: 160 (M$^+$).

Anal calc for $C_7H_4N_4O$ (160.1): C, 52.5; H, 2.5; N, 35.0. Found: C, 52.5; H, 2.6; N, 25.0.

Ethyl-5-cyano-3-methyl-6-oxo-1,2-dihydropyridazine-4-carboxylate **25b**

Yield (0.8 g, 35%) mp 240°C.

IR (KBr): $\nu = 3\,320$ cm^{-1} (NH); 2 218 cm^{-1} (CN); 1 700–1 680 cm^{-1} (C=O).

^{1}H NMR (DMSO) $\delta = 1.21$ (t, 3H, CH$_3$); 2.30 (s, 3H, CH$_2$); 4.27 (q, 2H, CH$_2$); 10.80 (br, 1H, NH).

Anal calc for $C_9H_9N_3O_3$ (207.21): C, 52.17; H, 4.34; N, 20.28. Found: C, 52.1; H, 4.3; N, 20.3.

5-Amino-3-oxo-7-phenyl-2,3-dihydrocinnoline-4,6-dicarbonitrile **26**

To a solution of **25a** (1,6 g, 0.01 mol) in 20 mL pyridine, **1b** (1.5, 0.01 mol) was added. The reaction mixture was heated under reflux for 4 h. The solid product that formed on dilution with water was collected by filtration and crystallized from dioxane as brown crystals, yield 1 g (35%), mp 275°C.

IR (KBr): $\nu = 3\,400$–$3\,200$ cm^{-1} (NH$_2$), 2 220–2 218 cm^{-1} (CN), 1 690 cm^{-1} (C=O).

^{1}H NMR (DMSO) $\delta = 3.5$ (br, NH$_2$), 6.81–7.26 (m, 6H, aromatic protons), 11.1 (s, 1H, NH).

MS: $m/z = 287$ (M$^+$).

Anal calc for $C_{16}H_9N_5O$ (287.26): C, 66.8; H, 3.1; N, 24.3. Found: C, 66.8; H, 3.0; N, 24.4.

Acknowledgments

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