Nitriles in Heterocyclic Synthesis: Novel Synthesis of Pyrido-[2,1-b]benzothiazoles and 1,3-Benzothiazole Derivatives

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Novel synthesis of pyrido[2,1-b]benzothiazoles, pyridine, pyran, thiopyran, pyridazine and coumarin derivatives utilising benzothiazol-2-ylacetonitrile, as starting component are reported.

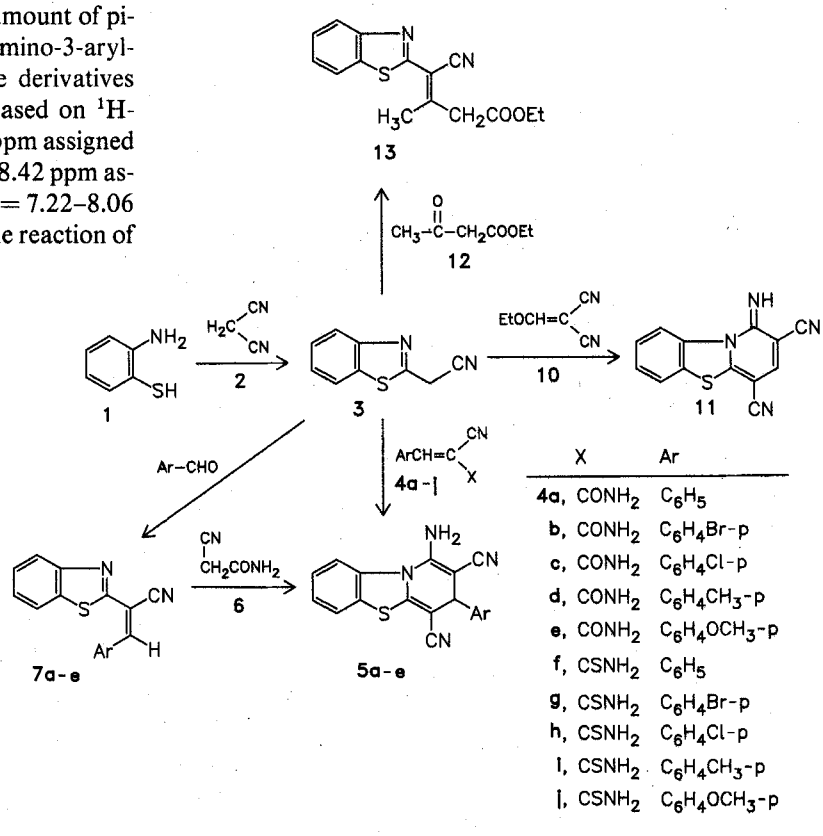
Aktivierte Nitrile in der Heterocyclen-Synthese: Neue Synthese von Pyrido[2,1-b]-benzothiazolen und 1,3-Benzothiazol-Derivaten

Verschiedene neue Pyrido[2,1-b]benzothiazoles, Pyridin-, Pyran-, Thiopyran-, Pyridazin- und Cumarin-Derivate wurden ausgehend von Benzothiazol-2-ylacetonitril synthetisiert.

The utilities of cyano compounds in organic synthesis are now receiving considerable interest[1]. In the last few years we were involved in a program aiming to develop synthetic approaches for polyfunctionally substituted heterocycles utilising readily obtainable nitriles as starting materials[2], we have previously reported several new approaches for the synthesis of condensed heterocycles utilizing azol-2-ylacetonitrile-[3] and benzimidazol-2-ylacetonitrile-[4] derivatives as starting materials.

In conjunction of this work we report here a novel synthesis of pyrido[2,1-b]benzothiazoles, pyridine, pyran, thiopyran, pyridazine and coumarin derivatives utilizing benzothiazol-2-ylacetonitrile **(3)** as starting material. **3** is prepared by the reaction of 2-mercaptoaniline **(1)** and malononitrile **(2)**. **3** reacted with **4a–j** in ethanol with a catalytic amount of piperidine in a 1:1 molar ratio to give the 1-amino-3-aryl-3H-pyrido[2,1-b]benzothiazol-2,4-dicarbonitrile derivatives **5a–e**. The structure **5a** could be established based on ^{1}H-NMR data which revealed a singlet at $\delta = 4.77$ ppm assigned to the pyridine H-3 proton, a broad band at $\delta = 8.42$ ppm assignable to the amino group and a multiplet at $\delta = 7.22$–8.06 ppm (4 aromatic H). The formation of **5** from the reaction of **3** and **4a–e** or **4f–j** is assumed to proceed via *Michael* type addition of the methylene function in **3** to the activated double bond to yield acyclic *Michael* adducts which then lose H_2O or H_2S, respectively, and cyclize into the final isolable thermodynamically stable compounds **5a–e**. This is similar to the behaviour of azol-2-ylacetonitriles[5].

3 was easily condensed with aromatic aldehydes to give **7** in high yields. Treatment of **7** with cyanoacetamide **(6)** in ethanol yields **5**. The reaction of **7** with cyanothioacetamide **(8)** afforded the thiopyran derivatives **9a–d**. The ^{1}H-NMR-spectrum of compound **9a** revealed, in addition to a signal at $\delta = 4.9$ assigned for the thiopyran H-4, a multiplet at $\delta = 7.22$–8.46 ppm assigned for aromatic protons and amino groups.



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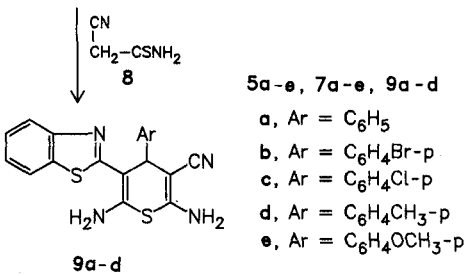
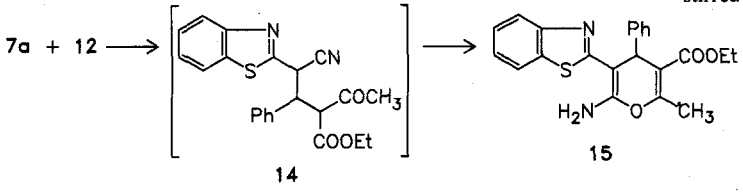




Experimental Part

Melting points are uncorrected. – IR spectra (KBr): Pye Unicam Sp-1000 or Shimadzu IR 200. – ^{1}H-NMR: Varian EM-390-90 MHz in DMSO using TMS as internal standard, chemical shifts as δ (ppm). Analytical data: Analytical data unit at Cairo University.

1,3-Benzothiazol-2-ylacetonitrile **(3)**

A solution of 2-aminobenzenethiol **(1)** (0.01 mole) in acetic acid (6 ml) was stirred with ethanol (10 ml) and malononitrile **(2)** (0.01 mole) at room temp. and allowed to stand overnight. The resulting yellow solid product was collected by filtration and crystallised from methanol; 85 %; m. p. 102–103 °C. – IR: 2220 (CN). – ^{1}H-NMR: 4.77 (s, 2H, CH_2), 6.82–7.66 (m, 2H, aromatic); 7.7–8.2 (m, 2H, aromatic). – $C_9H_6N_2S$ (174.1); $M^{+\cdot}$ = 174. – Calc. C 62.1 H 3.47 N 16.1 Found C 62.2 H 3.5 N 16.1.

2-(1,3-Benzthiazol)-2-ylcinnamonitriles **(7a–e)**

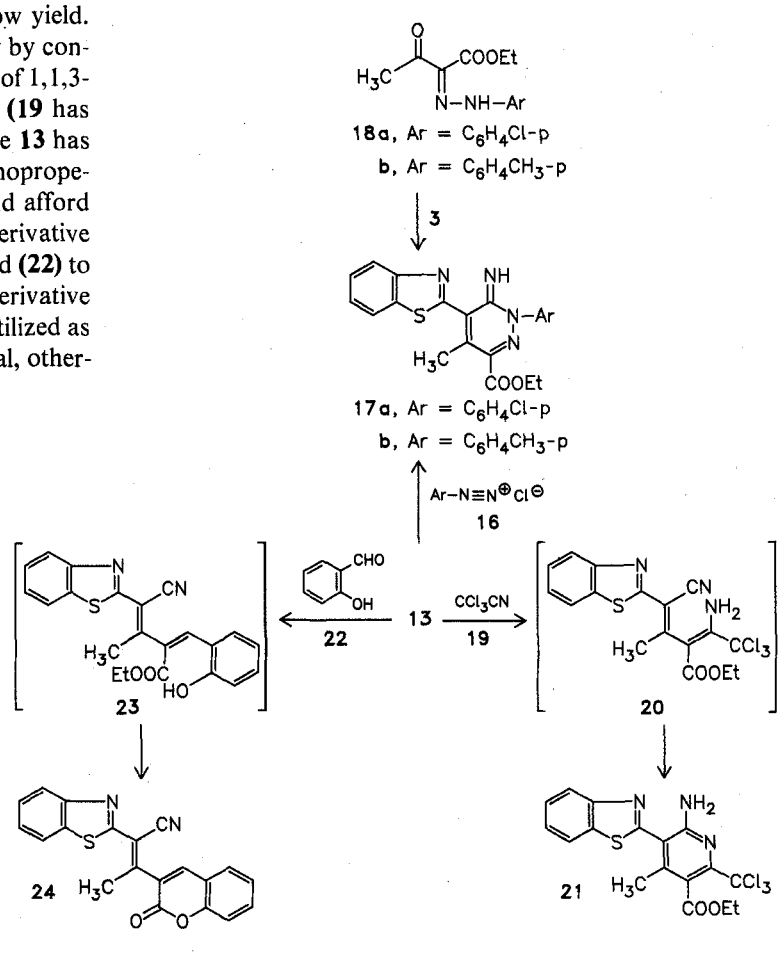
General procedure:

A mixture of **3** (0.01 mole), the aromatic aldehyde (0.01 mole) and 1 ml of triethylamine was dissolved in ethanol (30 ml) and stirred at room temp. for 1 h. The resulting solid product was filtered off and crystallised from the proper solvent.

Compound **7a** reacted with ethyl acetoacetate **(12)** to yield 1:1 adduct. ^{1}H-NMR- and IR-spectra establish structure **15** for this product. Thus, it revealed in addition to the ethyl ester protons and methyl protons (s at δ = 2.08) the pyran 4-H proton at δ = 4.1 ppm, amino protons at δ = 7.32 ppm and aromatic protons at δ = 6.66–7.22 ppm. **15** is assumed to be formed through the intermediate *Michael* adduct **14.**

Compound **3** reacted with ethoxymethylenemalononitrile **(10)** to give 1-imino-1H-pyrido[2,1-b]benzothiazol-2,3-dicarbonitrile **11.**

Compound **13** was prepared by condensation of equimolecular amounts of **3** with ethyl acetoacetate. **13** was coupled with aryldiazonium chloride **(16)** in ethanolic sodium acetate to yield the pyridazine-6-imine derivative **17a** in low yield. Thus, compounds **17** were synthesised alternatively by condensation of arylhydrazones **18** with **3.** The reaction of 1,1,3-tricyano-2-aminopropene with trichloroacetonitrile **(19** has recently been reported to afford pyrimidines[6]. Since **13** has functional moieties similar to those present in tricyanopropenes it was thought that their reaction with **19** would afford pyridines. In **13** reacts with **19** to yield the pyridine derivative **21** via **20.** Compound **13** reacted with salicylaldehyd **(22)** to yield **23** which cyclized into the isolable coumarine derivative **24.** These results indicate that compound **3** can be utilized as an excellent starting material for synthesis of several, otherwise difficult accessible, heterocyclic derivatives.



2-(1,3-Benzothiazol)-2-ylcinnamonitrile **(7a)**

Yellow crystals from ethanol; 98 %; m. p. 128 °C. – $M^{+\cdot}$ = 262. – $C_{16}H_{10}N_2S$ (262) Calc. C 73.3 H 3.8 N 10.7 Found C 73.0 H 3.5 N 10.3.

2-(1,3-Benzothiazol)-2-yl-4-bromocinnamonitrile) **(7b)**

Yellow crystals from ethanol, 95 %; m. p. 140–142 °C. – $C_{16}H_9BrN_2S$ (341.2) Calc. C 56.3 H 2.65 N 8.2 Found C 56.5 H 2.45 N 8.1.

2-(1,3-Benzothiazol)-2-yl-4-chlorocinnamonitrile **(7c)**

Yellow crystals from ethanol; 93 %; m. p. 150 °C. – $C_{16}H_9ClN_2S$ (296.5) Calc. C 64.8 H 3.0 N 9.4 Found C 64.5 H 3.4 N 9.0.

2-(1,3-Benzothiazol)-2-yl-4-methylcinnamonitrile **(7d)**

Yellow crystals from ethanol; 92 %; m. p. 147 °C. – $M^{+\cdot}$ = 276. – $C_{17}H_{12}N_2S$ (276) Calc. C 73.9 H 4.3 N 10.1 Found C 73.6 H 4.2 N 9.8.

2-(1,3-Benzothiazol)-2-yl-4-methoxycinnamonitrile **(7e)**

Yellow crystals from ethanol; 90 %; m. p. 143 °C. – $M^{+\cdot}$ = 292. – $C_{17}H_{12}N_2OS$ (292) Calc. C 69.9 H 4.1 N 9.6 Found C 69.6 H 3.8 N 9.4.

1-Amino-3-aryl-3H-pyrido[2,1-b]benzothiazol-2,4-dicarbonitriles **(5a–e)**

General Procedure:

Method a: **3** (0.01 mole) and **4a–j** (0.01 mole) were dissolved in ethanol (30 ml). Few drops of piperidine were added. The mixture was left at room temp. for 2 h. The precipitated solid was filtered off and crystallised from the proper solvent.

Method b: To a suspension of **7a–e** (0.01 mole) in ethanol (30 ml) and cyanothioacetamide **(8)** (0.01 mole) a few drops of piperidine were added. The reaction mixture was refluxed for 6 h, then cooled and the resulting solid product was collected by filteration and crystallised from the proper solvent.

Method c: To a suspension of **7a–e** (0.01 mole) in ethanol (30 ml) and cyanoacetamide **(6)** (0.01 mole) a few drops of piperidine were added. The reaction mixture was refluxed for 6 h, then cooled and the resulting solid product was collected by filteration and crystallised from the proper solvent.

1-Amino-3-phenyl-3H-pyrido[2,1-b]benzothiazol-2,4-dicarbonitrile **(5a)**

Pale yellow crystals from benzene/pet. ether 40–60 °C; 66 %; m. p. 222 °C. – IR: 3500 (NH_2), 2200 (CN). – ^{1}H-NMR: 4.77 (s, 1H, pyridine H-3), 7.22–7.88 (m, 9H, aromatic), 8.42 (s, 2H, NH_2). – $C_{19}H_{12}N_4S$ (328.4) Calc. C 69.5 H 3.68 N 17.1 Found C 69.1 H 3.60 N 17.2.

1-Amino-3-(4-bromophenyl)-3H-pyrido[2,1-b]benzothiazol-2,4-dicarbonitrile **(5b)**

Yellow crystals from benzene/pet. ether 40–60; 50 %; m. p. 242 °C. – IR: 3420 (NH_2), 2180 (CN), 1640 (NH_2). – ^{1}H-NMR: 4.82 (s, 1H, pyridine H-3), 7.2–8.2 (m, 8H, aromatic) 8.43 (d, 2H, NH_2). – $C_{19}H_{11}BrN_4S$ (407.3) Calc. C 56.0 H 2.72 N 13.8 Found C 56.5 H 3.2 N 13.5.

1-Amino-3-(4-chlorophenyl)-3H-pyrido[2,1-b]benzothiazol-2,4-dicarbonitrile **(5c)**

Yellow crystals from benzene/pet. ether 40–60 °C; 54 %; m. p. 236 °C. – IR: 3400 (NH_2), 2200 (CN). – $C_{19}H_{11}ClN_4S$ (362.8). Calc. C 62.9 H 3.05 N 15.4 Found C 63.4 H 3.49 N 15.4.

1-Amino-3-(4-methylphenyl)-3H-pyrido[2,1-b]benzothiazol-2,4-dicarbonitrile **(5d)**

Yellow crystals from ethanol; 65 %; m. p. 149 °C. – IR: 3400 (NH_2), 2210 (CN). – ^{1}H-NMR: 2.2 (s, 3H, CH_3), 6.25 (s, 1H, pyridine H-3), 7.18–8.15 (m, 10 H, aromatic protons and NH_2). – $C_{20}H_{14}N_4S$ (342.4). Calc. C 70.2 H 4.12 N 16.4 Found C 70.6 H 4.1 N 16.5.

1-Amino-3-(4-methoxyphenyl)-3H-pyrido[2,1-b]benzothiazol-2,4-dicarbonitrile **(5e)**

Pale yellow crystals from ethanol; 55 %; m. p. 206 °C. – IR: 3400 (NH_2), 2210 (CN). – $C_{20}H_{14}N_4OS$ (358.4) Calc. C 67.0 H 3.94 N 15.6 Found C 67.1 H 3.82 N 15.7.

2,6-Diamino-4-aryl-4H-thiopyrano-2-benzothiazol-3-carbonitriles **(9b–e)**

General Procedure:

To a solution of **7b–d** (0.01 mole) in ethanol (30 ml) cyanothioacetamide (0.01 mole) and a few drops of piperidine were added. The mixture was refluxed for 6 h. The solvent was evaporated *in vacuo* and the resulting solid was collected by filtration and crystallised from the proper solvent.

2,6-Diamino-4-(4-bromophenyl)-4H-thiopyrano-2-benzothiazol-3-carbonitrile **(9b)**

Pale yellow crystals from benzene/pet. ether 40–60; 18 %; m. p. 222 °C. – IR: 3400 (NH_2), 2200 (CN). – ^{1}H-NMR: 4.82 (s, 1H, thiopyran H-4), 7.2–8.1 (m, 12H, 2 C_6H_4 and 2 NH_2). – $C_{19}H_{13}BrN_4S_2$ (441.4) Calc. C 57.7 H 2.96 N 12.7 Found C 57.6 H 3.30 N 12.3.

2,6-Diamino-4-(4-chlorophenyl)-4H-thiopyrano-2-benzothiazol-3-carbonitrile **(9c)**

Pale yellow crystals from ethanol; 25 %; m. p. 207 °C decompn. – IR: 3400 (NH_2), 2200 (CN). – $C_{19}H_{13}ClN_4S_2$ (396.9) Calc. C 57.5 H 3.30 N 14.1 Found C 57.5 H 3.50 N 14.3.

2,6-Diamino-4-(4-methylphenyl)-4H-thiopyrano-2-benzothiazol-3-carbonitrile **(9d)**

Yellow crystals from ethanol; 32 %; m. p. 260 °C. – IR 3350 (NH_2), 2200 (CN). – $C_{20}H_{16}N_4S_2$ (376.5). – Calc. C 63.8 H 4.28 N 14.9 Found C 64.0 H 4.30 N 14.8.

2,6-Diamino-4-(4-methoxyphenyl)-4-H-thiopyrano-2-benzothiazol-3-carbonitrile **(9e)**

Yellow crystals from ethanol; 26 %; m. p. 243 °C decompn. – IR: 3350 (NH_2), 2200 (CN). – $C_{20}H_{16}N_4S_2O$ (392.5) Calc. C 61.2 H 4.11 N 14.3 Found C 61.5 H 3.88 N 14.4.

1-Imino-1H-pyrido[2,1-b]-[1,3]benzothiazol-2,4-dicarbonitrile **(11)**

A suspension of **3** (0.01 mole) in ethanol (30 ml), ethoxymethylenemalononitrile **(1c)** (0.01 mole) and two drops of piperidine was refluxed for 6 h, and then left to cool at room temp. The crystals separated on cooling were filtered off and crystallised from ethanol; 65 %. m. p. 234–235 °C. – IR: 3380; 3300 (NH), 2220 (CN). – ^{1}H-NMR: 2.6 (s, br, 1H, NH), 7.23–7.85 (m, 2H, aromatic), 8.02–9.66 (m, 3H, aromatic protons and pyridine-3H). – $M^{+\cdot}$ – 250. – $C_{13}H_6N_4S$ (250) Calc. C 62.4 H 2.4 N 22.4 Found C 62.0 H 2.8 N 21.9.

Ethyl 3-(1,3-Benzothiazol-2-yl)-3-cyano-2-methyl-buten(3)oate **(13)**

A mixture of equimolecular amounts of **3** and ethyl acetoacetate **(12)** (0.01 mole) in dry benzene (50 ml) containing ammonium acetate (2 g) under a condenser fitted with a water separator was refluxed for 12 h. The solvent was evaporated under reduced pressure. The oily residue was extracted several times with petroleum ether 60–80 °C. The extract was concentrated to produce a solid product crystallised from petroleum ether b. p. 60.80 °C; 60 %; m. p. 97–98 °C. – IR: 2250 (CN), 1730 (CO). – ^{1}H-NMR: 1.22 (t, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.9–4.2 (m, 4H, $2CH_2$),

7.22–8.0 (m, 4H, aromatic). $C_{15}H_{14}N_2O_2S$ (286.3). Calc. C 62.9 H 4.93 N 9.8 Found C 63.0 H 4.6 N 9.6.

Ethyl 2-amino-4-phenyl-6-methyl-4H-pyrano-3-(2-benzothiazolyl)-5-carboxylate **(15)**

A mixture of **7a** (0.01 mole), ethyl acetoacetate (0.01 mole) and a few drops of piperidine in ethanol (30 ml) was refluxed for 5 h. The solution was concentrated, the formed solid was collected by filtration and crystallised from ethanol; 65 %; m. p. 163 °C. – IR: 3350 (NH_2), 1700 (CO). – ^{1}H-NMR: 1.18 (t, 3H, CH_3), 2.08 (s, 3H, CH_3), 3.9 (q, 2H, CH_2), 4.35 (2, 1H, pyran H-4), 6.86–7.42 (m, 9H, aromatic), 7.88 (s, br, 2H, NH_2). – $C_{22}H_{20}N_2O_3S$ (392.5) Calc. C 67.3 H 5.14 N 7.1 Found C 67.3 H 5.50 N 7.1.

Formation of Ethyl 5-(Benzothiazolyl-2-)-6-imino-4-methyl-1-phenyl-pyridazine-3-carboxylates **17**

General procedure:

Method A: A solution of aryldiazonium chloride [prepared from (0.01 mole) of aromatic amine and the appropriate quantity of hydrochloric acid and sodium nitrite] (0.01 mole) was added portionwise to a solution of **13** (0.01 mole) in ethanol DMF mixture containing sodium acetate (3 g) while stirring at 0 °C. The reaction mixture was left at room temp. for 1 h, then poured into water. The formed solid was filtered off and crystallised from the proper solvent.

Method B: To a suspension of **18a, b** (0.01 mole) in ethanol (30 ml) and **3** (0.01 mole), a few drops of piperidine were added. The reaction mixture was refluxed for 3 h, then cooled, filtered off and crystallised.

17a: yellow powder from ethanol-water; 47 %, m. p. 150 °C. – IR: 1720 (CO). – $C_{21}H_{17}ClN_4O_2S$ (424.9) Calc. C 59.4 H 4.03 N 13.2 Found C 59.1 H 4.12 N 13.4.

17b: green crystals from ethanol-water mixture, 55 %, m. p. 220 °C. – $C_{22}H_{20}N_4O_2S$ (404.5). Calc. C 65.3 H 4.98 N 13.9 Found C 65.3 H 4.60 N 13.6.

Formation of Ethyl 6-Amino-5-(benzothiazolyl-2-)-4-methyl-2-trichloromethylpyridine-3-carboxylate **(21)**

To a solution of **13** (0.01 mole) in ethanol (30 ml), trichloroacetonitrile (0.01 mole) and two drops of piperidine were added. The mixture was refluxed for 6 h. The resulting yellow solid was collected by filtration and crystallised from ethanol-DMF mixture; 55 %, m. p. > 300 °C IR: 3420 (NH_2), 1710 (CO). – ^{1}H-NMR: 1.12 (t, 3H, CH_3), 2.22 (s, 3H, CH_3), 4.02 (q, 2H, CH_3), 7.02–9.08 (m, 6H, aromatic protons and NH_2). $C_{17}H_{14}N_3O_2Cl_3S$ (430.736) Calc. C 47.4 H 3.27 N 9.76 Found C 47.6 H 3.00 N 10.0.

Formation of 2-(Benzo[b]pyran-2-on-3-yl)-3-benzothiazol-2-yl)-3-cyanopropen(2) **(24)**

To a solution of **13** (0.01 mole) in ethanol (30 ml), salicylaldehyde (0.01 mole) and two drops of piperidine were added. The mixture was refluxed for 5 h and the resulting solid was collected by filtration and crystallised from DMF; 60 %; m. p. > 300 °C. – IR: 2210 (CN), 1740 (CO). – ^{1}H-NMR: 2.18 (s, 3H, CH_3), 5.88 (s, 1H, pyran-H), 7.48–8.99 (m, 8H, aromatic). – $C_{20}H_{12}N_2O_2S$ (344) Calc. C 69.8 H 3.5 N 8.1 Found C 69.6 H 3.5 N 7.8.

References

1 G. E. H. Elgemeie, H. A. Elfahham, S. Elgamal, and M. H. Elnagdi, Heterocycles *23*, 1999 (1985).
2 G. E. H. Elgemeie, B. Y. Riad, G. A. Nawwar, and S. Elgamal, Arch. Pharm. (Weinheim) *320*, 223 (1987).
3 G. E. H. Elgemeie, H. A. Elfahham, S. M. Hassan, and M. H. Elnagdi, Z. Naturforsch. *38b*, 781 (1983).
4 M. A. Hammad, G. A. Nawwar, G. E. H. Elgemeie, and M. H. Elnagdi, Heterocycles, *23*, 2177 (1985).
5 S. Kambe, K. Saito, A. Sakurai, and H. Midorikawa, Synthesis, 531 (1981).
6 K. Gewald, U. Hain, and M. Gruner, Chem. Ber. *118*, 2198 (1985).

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