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The Reaction of Malononitrile with Enamines of β-Ketocarbothionic Acid Anilides

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The reaction of β-morpholino-thiocinnamic acid anilides **1** with malononitrile yielded 2-arylimino-thiopyrans **3**, which in turn were converted under alkaline conditions into 6-thioxo-pyridines **5**. Their structures were elucidated on the basis of chemical properties and spectral data. The mechanism of the conversion **3** into **5** is discussed.

(Keywords: Thiopyrans; Thioxo-pyridines; Reactions with malonitrile)

Die Reaktion von Malononitril mit Enaminen von β-Ketocarbothionsäureaniliden

Die Reaktion von β-Morpholino-thiozimtsäureaniliden **1** mit Malononitril lieferte 2-Arylimino-thiopyrane **3**, die unter alkalischen Bedingungen zu 6-Thioxo-pyridinen **5** umgesetzt wurden. Die Struktur der dabei erhaltenen Verbindungen wurde mittels chemischer und spektroskopischer Eigenschaften zugeordnet. Der Mechanismus der Konversion von **3** zu **5** wird diskutiert.

Introduction

Enamines of β-ketoacid anilides have attracted considerable interest as useful intermediates in organic synthesis; they react with a wide range of compounds providing some heterocyclic systems of pharmacological activity.

Recently we have reported[1] that enamines of cyclic β-ketocarbothionic acid anilides reacted easily with malononitrile yielding *o*-aminonitriles, derivatives of cycloalkeno-thiopyrans and cycloalkeno-pyridines with excellent yield. This results prompted us to develop this method for synthesis of similar heterocyclic systems from easily available starting materials i. e. β-morpholino-thiocinnamic acid anilides (enamines **1a**–**1e**) and mononitrile.

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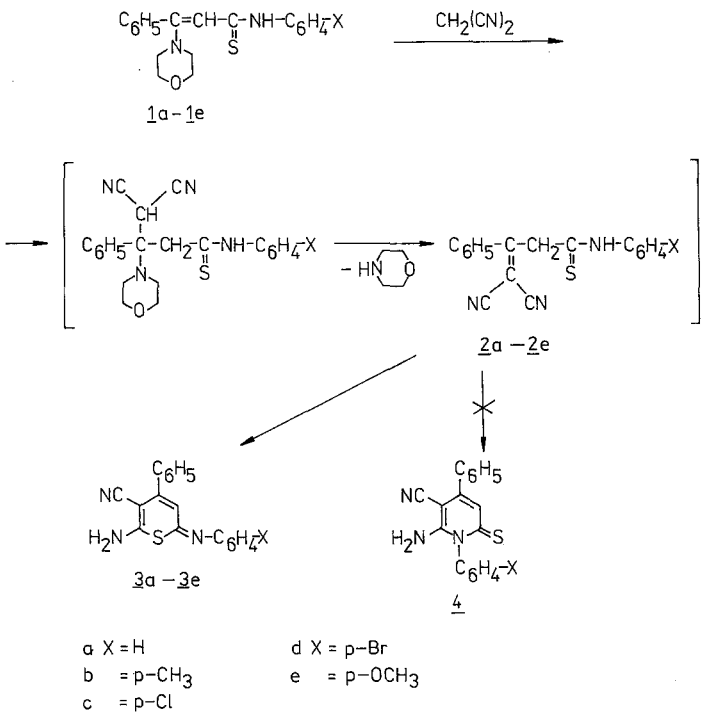
Results and Discussion

The reaction of enamines **1a–1e** with malononitrile in ethanolic or benzene solution proceed smoothly at reflux temperature affording products **3a–3e** in moderate yield. Taking into account our preliminary findings[1] we expect that this reaction may provide thiopyran **3** or pyridine **4** (Scheme 1). The structure elucidation of the obtained products **3a–3e** as thiopyran derivatives was based on analytical data as well as spectral studies.

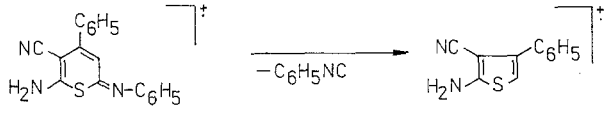
Scheme 1



Both IR and ^{1}H-NMR spectra did not allow unambigously to establish the structure of compounds **3**, because the isomeric pyridine derivatives **4** may have similar spectral features. Final structural assignment for **3a–3e** as thiopyran derivatives was based upon the detailed analysis of their mass spectra, which exhibited the characteristic fragmentation patterns[2–4]. The MS spectra of **3a–3e** revealed peaks of

high intensity (15-30%) in the molecular ions region. The main fragmentation pathway of molecular ions was connected with ejection of appropriate arylisocyanide (X-C_6H_4NC) and gave the ion (M-XC_6H_4NC)$^+$ which appeared as the base peak at m/z 200. For all compounds in question the abundance of the (M-XC_6H_4NC)$^+$ ion was equal 100%. The composition $C_{11}H_8N_2S$ of the ion m/z 200 suggests that the sulphur atom in **3** is a part of a heterocyclic ring, thus allowing to propose the structure of 2-arylimino-4-phenyl-5-cyano-6-amino-2H-thiopyran. The main fragmentation pathway of **3** is given in Scheme 2.

Scheme 2



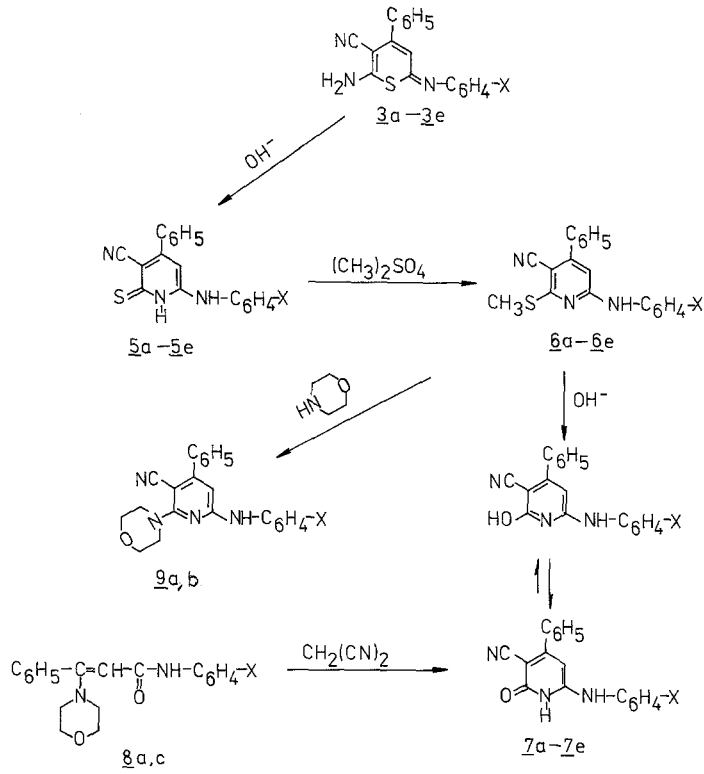
3a M$^+$, m/z 303/15,9%/ m/z 200/100%/

The reaction of enamines **1a**–**1e** with malononitrile may be assumed to proceed as shown in Scheme **1** via a *Michael* addition —elimination mechanism[5]. The resulting condensation products **2a**–**2e** underwent *in situ* cyclisation by nucleophilic attack of the sulphur atom on the cyano group to give thiopyrans **3a**–**3e**.

Thiopyrans **3a**–**3e** were stable under acidic conditions. In alkaline solution they underwent isomerisation to pyridine derivatives **5a**–**5e**. The course of this process was different from that reported earlier[1,6]. The isomerisation of **3** in alkaline solution can lead to either one of two products **4** or **5** or both (Scheme 3). When **3a** was refluxed in alkaline solution only one product was isolated, which was shown to have the structure **5a** on the basis of the following evidence.

To our knowledge compound **4a** was synthesised by *Gewald* et al.[7] in the reaction of α-methylbenzylidenomalononitrile with phenylisothiocyanate. The compound **4a**—synthesised according to *Gewald*'s procedure—was found to be different from **5a**, although its analytical data and molecular weight determined by MS spectrometry were consistent with these for **5a**. The IR spectra of both compounds were in general different particularly in the region of the stretching vibrations of the NH group[7]. The MS spectrum of **5a** exhibited a molecular ion as the base peak at m/z 303. Fragmentation of **5a** began with the loss of CS and $C_6H_5^+$ yielding fragmentary ions at m/z 259 (13.8%) and 226 (13.6%). The main fragmentation pathway of the molecular ion of **4a** m/z 303 (100%) was connected with the ejection of $C_6H_5^+$ m/z 77 (43.2%) and phenylisothiocyanate C_6H_5NCS m/z 135 (7.3%).

Scheme 3

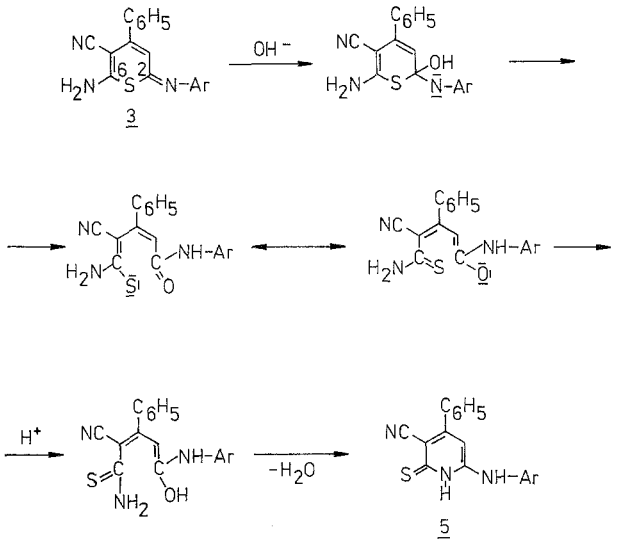


On the basis of literature reports[6] regarding the isomerisation of 2-arylimino-thiopyrans we suspected a conversion of **3** into **4**, hence the conversion of **3** into **5** was surprising. Nucleophilic attack of a hydroxide anion on the C-2 carbon atom involved an open-chain intermediate, which subsequently cyclized to **5**. The alternative isomerisation of **3** into **4** might proceed by a nucleophilic attack on the C-6 carbon atom. The exclusive formation of **5** suggests that the C-2 atom is the more prefered site for nucleophilic attack. The proposed mechanism of this conversion is outlined in Scheme 4.

In further experiments it was interesting to study the replacement of the sulphur atom by oxygen for compounds **5a–5e**. For this purpose we utilized the easy formation of S-alkyl derivatives by **5a–5e**. Compounds **5a–5e** reacted smoothly with dimethyl sulphate in boiling toluene yielding methylthiopyridines **6a–6e** with good yield. Crude solids of **6a–6e** reacted in turn with a concentrated solution of sodium

hydroxide to give **7a–7e**. The assigned structure was in two cases confirmed additionally by comparison with the samples independently prepared from β-morpholino-cinnamic acid anilides (**8a, 8c**) and malononitrile. S-Methyl derivatives **6a, 6b** underwent also nucleophilic substitution by *sec.* amines[8, 9] e.g. morpholine yielding **9a, 9b** with moderate yield. The raction sequence is ilustrated in Scheme 3.

Scheme 4



3 5

Experimental

Melting points are uncorrected. IR spectra were recorded on an UR-10 (Zeiss, Jena) spectrophotometer in Nujol mulls or in KBr disks. ^{1}H-NMR spectra were taken on a Jeol 100 spectrometer in deutero-chloroform and *DMSO* (*TMS* as internal standard). Mass spectra were taken on an LKB-9000 S spectrometer. Elemental analyses were performed in the Regional Laboratory of Physico-Chemical Analyses and Structural Studies in Kraków. The analytical data for C, H, N, S, for all compounds are in full agreement with the proposed sturctures.

Enamines **1a–1e** and **8a–8c** were prepared according to the method described in Ref.[10] and α-methylbenzylidenomalononitrile according to Ref.[11].

2-Arylimino-4-phenyl-5-cyano-2H-thiopyran (**3a–3e**)

General Procedure

A solution of malononitrile (0.02 mol) in ethanol or benzene (10 ml) was added to a solution of enamine **1** (0.02 mol) in ethanol (100 ml). The reaction mixture was boiled under reflux for 1 h. After cooling, the precipitated

crystalline yellow product was filtered off, washed with cold ethanol and crystallyzed from ethanol. Yellow prisms; average yield 37–70%. The compounds **3a, 3c, 3d** crystallized with one molecule of ethanol. For analyses the compounds were dried under reduced pressure at 80 °C.

3a: m. p. 156–158 °C; 67%; IR (Nujol): 3430, 3320, 3140 (NH_2), 2215 (CN), 1660 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$): 5.75 (m, 2H, NH_2), 6.32 (s, 1H, CH), 6.98–7.61 (m, 10H arom.); MS (m/z): 303 (15.9%), 200 (100%).

3b: m. p. 166–167 °C; 53%; IR (Nujol): 3370, 3280, 3180 (NH_2), 2210 (CN), 1625 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$): 2.85 (s, 3H, CH_3), 5.96 (m, 2H, NH_2), 6.36 (s, 1H, CH), 7.02–7.67 (m, 9H arom.); MS (m/z): 317 (22.4%), 200 (100%).

3c: m. p. 187–188 °C; 46%; IR (Nujol): 3450, 3320, 3110 (NH_2), 2205 (CN), 1650 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$): 5.92 (m, 2H, NH_2), 6.44 (s, 1H, CH), 6.92–7.61 (m, 9H arom.); MS (m/z): 337 (15.7%), 200 (100%).

3d: m. p. 198–201 °C; 70%; IR (Nujol): 3340, 3290, 3200 (NH_2), 2220 (CN), 1620 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$): 5.44 (m, 2H, NH_2), 6.40 (s, 1H, CH), 6.72–7.54 (m, 9H arom.); MS (m/z): 381 (19.4%), 383 (17.1%), 200 (100%).

3e: m. p. 153–156 °C; 37%; IR (Nujol): 3370, 3260, 3220 (NH_2), 2210 (CN), 1625 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$): 3.92 (s, 3H, CH_3), 5.82 (m, 2H, NH_2), 6.31 (s, 1H, CH), 7.02–7.56 (m, 9H arom.); MS (m/z): 333 (33.1%), 200 (100%).

2-Arylamino-4-phenyl-5-cyano-6-thioxo-1,6-dihydropyridine (**5a–5e**)

General Procedure

To a solution of thiopyran **3** (0.05 mol) in 50 ml of ethanol 2 ml of a 5% solution of NaOH was added. The reaction mixture was refluxed for 30 min. The deep yellow solution was poured into 100 ml of ice water and the aqueous suspension was neutralised with dilute hydrochloric acid. The precipitate was filtered off, washed with water and purified by recrystallization from ethanol. Average yield 77–87%.

5a: 324–326 °C; 87%; IR (Nujol): 3460, 3305, 3210 (NH), 2220 cm^{-1} (CN); ^{1}H-NMR (*DMSO*): 6.96 (s, 1H, CH), 7.16 (s, 1H, NH), 7.32 (s, 1H, NH), 7.44–7.68 (m, 10H arom.); MS (m/z): 303 (100%), 259 (13.8%, M^+-CS).

5b: m. p. 257–258 °C; 82%; IR (Nujol): 3460, 3390, 3300 (NH), 2205 cm^{-1} (CN); ^{1}H-NMR (*DMSO*): 2.95 (s, 3H, CH_3), 6.88 (s, 1H, CH), 7.44 (m, 2H, 2NH), 7.24–7.85 (m, 9H arom.); MS (m/z): 317 (100%), 273 (14.3%, M^+-CS).

5c: m. p. 267–268 °C; 77%; IR (Nujol): 3430, 3320, 3210 (NH), 2210 cm^{-1} (CN); ^{1}H-NMR (*DMSO*): 6.94 (s, 1H, CH), 7.61 (m, 2H, 2NH), 7.36–7.79 (m, 9H arom.); MS (m/z): 337 (100%), 293 (15.3%, M^+-CS).

5d: m. p. 287–288 °C; 83%; IR (Nujol): 3440, 3310, 3220 (NH), 2220 cm^{-1} (CN); ^{1}H-NMR (*DMSO*): 6.82 (s, 1H, CH), 7.32 (m, 2H, 2NH), 7.21–7.87 (m, 9H arom.); MS (m/z): 381 (100%), 383 (88%), 337 (17.4%, M^+-CS), 339 (11.7%, M^+-CS).

5e: m. p. 264–265 °C; 81%; IR (Nujol): 3430, 3310, 3190 (NH), 2200 cm^{-1} (CN); ^{1}H-NMR (*DMSO*): 3.92 (s, 3H, CH_3), 6.93 (s, 1H, CH), 7.21–7.32 (m, 2H, 2NH), 7.14–7.68 (m, 9H arom.); MS (m/z): 333 (100%), 289 (16.8%, M^+-CS).

1-Aryl-2-thioxo-4-phenyl-5-cyano-6-amino-1,2-dihydropyridine (**4a–4e**)

4a was prepared according to the method described in Ref.[7]. Compounds **4a–4e** were unknown and were synthesized in the same manner from α-methylbenzylidenomalononitrile and the appropriate arylisothiocyanate in *DMF* solution in the presence of triethylamine. Average yield 38–63%. The crude solids boiled in ethanol gave satisfactory analytical values for N. Because

of poor solubility in organic solvents it was difficult to record their ^{1}H-NMR spectra.

4a: m.p. 220–223 °C; IR (KBr): 3060–3330 (NH_2), 2205 cm^{-1} (CN).
4b: m.p. 185–188 °C; IR (KBr): 3180–3460 (NH_2), 2195 cm^{-1} (CN).
4c: m.p. 217–218 °C; IR (KBr): 3200–3450 (NH_2), 2200 cm^{-1} (CN).
4d: m.p. 225–227 °C; IR (KBr): 3160–3370 (NH_2), 2195 cm^{-1} (CN).
4e: m.p. 196–198 °C; IR (KBr): 3220–3450 (NH_2), 2215 cm^{-1} (CN).

2-Arylamino-4-phenyl-5-cyano-6-methylthiopyridine (**6a–6e**)

A mixture of (1.5 g, 0.005 mol) of pyridine **5a**, dimethyl sulphate (1.3 g, 0.01 mol) and toluene (10 ml) was refluxed for 1 h. The precipitate was filtered off and washed with ligroin. The crude solid was suspended in 100 ml of water and neutralized with a dilute solution of NaOH. The precipitated deep yellow product was filtered off and crystallyzed from methanol. Yield 1,4 g (89%). Deep yellow prisms, m.p. 214–215 °C. IR (Nujol): 3290, 3280 (NH), 2200 cm^{-1} (CN).

An analogous procedure was applied for the preparation of **6b–6e**. The crude solids were used without purification for further reactions.

2-Arylamino-4-phenyl-5-cyano-6-oxo-1,6-dihydropyridine (**7a–7e**)

a) By Hydrolysis of Compounds **6a–6e**

To a solution of 0.0025 mol of **6** in 20 ml of ethanol 10 ml of a 25% solution of NaOH was added. The reaction mixture was refluxed for 2.5 h. The mixture was dissolved in 100 ml of water and neutralized with dilute HCl. The precipitate was filtered off and crystallyzed from ethanol. Average yield 40–59%.

IR spectral data and m.p.'s for **7a, 7b, 7e** were identical with these reported in Ref.[12].

7c: m.p. 305–306 °C, colourless needles from methanol; IR (Nujol): 1685 (CO), 2220 (CN), 3200, 3330, 3470 cm^{-1} (NH).

7d: m.p. 303–305 °C, colourless needles from ethanol; IR (Nujol): 1670 (CO), 2210 (CN), 3190, 3320, 3470 cm^{-1} (NH).

b) By Condensation of Enamines **8a** *or* **8c** *with Malononitrile*

A mixture of 3.3 g (0.01 mol) of enamine **8a**, 0.07 g malononitrile (0.01 mol) was refluxed in 50 ml of benzene for 1 h. The precipitate was filtered off and crystallyzed from ethanol. Colourless needles with m.p. 284–286 °C[12]; yield 96%.

An analogous procedure was applied for the synthesis of **7c**. Colourless needles, m.p. 305–306 °C; yield 97%.

The identity of samples obtained by method a and b was confirmed by m.p., mixed m.p., and comparison of IR spectra.

2-Arylamino-4-phenyl-5-cyano-6-(N-morpholino)-pyridine (**9a, 9b**)

To a solution of 1 g (0.003 mol) of **6a** in 10 ml of ethanol 5 g of morpholine was added. The reaction mixture was refluxed for 3 h. After cooling the mixture was poured into ice water and neutralized with dilute HCl. The semisolid product was filtered off and crystallyzed from ethanol. Pale yellow needless, m.p. 186–188 °C; yield 42%. IR (Nujol): 2200 (NC), 3350 cm^{-1} (NH).

An analogous procedure was applied for compound **9b**. Pale yellow prisms from ethanol, m.p. 241–243 °C; yield 36%. IR (Nujol): 2205 (CN), 3360 cm^{-1} (NH).

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