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# Heterocyclic Synthesis with Nitriles: Synthesis of Some New Thiocyanato-Substituted Heterocycles from Alkylidene Malononitrile

Fathy M. Abdelrazek*

*Chemistry Department, Faculty of Science, Cairo University, Giza, A. R. Egypt*

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## ABSTRACT

*α-(Thiocyanatomethyl)benzylidenemalononitrile undergoes bromination with N-bromo succinimide to afford α-(bromothiocyanatomethyl)benzylidenemalononitrile. This bromo derivative undergoes reactions with sodium hydrogen sulfide, thioglycollic acid, hydroxylamine hydrochloride, phenylhydrazine, and hydrazine hydrate to afford thiophene, 4H-thiopyran, 4H-oxazine, pyridazine, and bis(thiazol-2-ylidene)azine derivatives, respectively. Mechanistic explanations as well as structure elucidations are discussed.*

In continuation of a program aiming to develop new simple methods for the synthesis of functionally substituted heterocycles with anticipated biological activity that can be used as biodegradable agrochemicals, we have previously reported a novel thiophene synthesis from α-cyano-β-thiocyanatomethylcinnamonitrile (**1**) [1,2]. As the thiophene thiocyanate **3a** was needed, we tried unsuccessfully to obtain it from **1** and elemental sulfur via the Gewald synthesis [3,4]. Therefore, we thought that bromination of **1** and then subsequent reaction of the bromo derivative with sodium hydrogen sulfide might fulfill this objective.

Thus, compound **1** was smoothly brominated by N-bromosuccinimide (NBS) in dimethylformamide (DMF) at room temperature to afford the bromo derivative **2** in 72% yield. The IR spectrum of 2 showed absorption bands at $\nu$ 2200, 2180, and 2165 $cm^{-1}$ corresponding to CN and SCN groups, respectively. The $^1H$ NMR spectrum of this bromo derivative revealed an aromatic multiplet (5H) at $\delta$ 7.4–7.6 and two singlets centered at ~$\delta$ 7.85 and integrated for (1H). The low field shift of this last proton suggests that it is attached to an $sp^2$ carbon, and the appearance of two singlets for this proton may be attributed to the presence of two geometrical isomers. These data can only be interpreted in terms of the tautomeric form **2b**. It can be assumed that the bromination took place on the methylene group of **1** to afford **2a**, which is interchangeable to **2b** via the ion pair **2c**. In support of this assumption is the fact that both of the geometrical isomers of **2b** are present in solution, which strongly suggests the presence of the ionic form **2c**. Furthermore, all nucleophilic substitution products of **2** show that the attack is on the carbon atom bearing the SCN group, which agrees with an $SN_1$ mechanism involving **2c**. The direction of attack is controlled by steric factors. Mass spectral measurements and analytical data are in complete agreement with structure **2** (Tables 1 and 2, Scheme 1).

Compound **2** reacts with sodium hydrogen sulfide in refluxing ethanol to afford a dark green solid product. The IR spectrum of this product revealed the presence of a cyano absorption band at $\nu$ 2208 $cm^{-1}$ and the absence of the SCN band. Elemental analysis of this product showed the disappearance of the bromine atom and showed that it is in good

Dedicated to Prof. Shigeru Oae on the occasion of his seventy-fifth birthday.

*To whom correspondence should be addressed.



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**TABLE 1** Physical and Analytical Data of the New Compounds

| Compound | Mp (°C) Solvent | Yield (%) | Mol Formula Mol Wt | m/e | Calcd Found C | H | Anal. % N |
|---|---|---|---|---|---|---|---|
| **2** | 135–137 | 72 | $C_{12}H_6N_3SBr$ | | 47.37 | 1.99 | 13.81 |
| | EtOH | | 304.27 | 303,305 | 47.6 | 2.1 | 13.7 |
| **3b** | 210 | 65 | $C_{11}H_8N_2S_2$ | | 56.87 | 3.47 | 12.06 |
| | EtOH | | 232.33 | 232 | 56.5 | 3.6 | 12.1 |
| **5** | 198 | 73 | $C_{14}H_9N_3O_2S_2$ | | 53.32 | 2.88 | 13.32 |
| | EtOH | | 315.38 | — | 53.3 | 3.1 | 13.5 |
| **7** | 165–166 | 67 | $C_{12}H_8N_4OS$ | | 56.24 | 3.15 | 21.86 |
| | EtOH | | 256.29 | 256 | 56.1 | 3.4 | 21.9 |
| **9** | 235–236 | 78 | $C_{18}H_{13}N_5S$ | | 65.24 | 3.95 | 21.13 |
| | EtOH/DMF | | 331.40 | — | 65.3 | 4.1 | 21.2 |
| **12** | 287–289 | 73 | $C_{18}H_{18}N_8S_2$ | | 52.66 | 4.42 | 27.30 |
| | EtOH/DMF | | 410.53 | 205,410 | 52.8 | 4.2 | 27.4 |

**TABLE 2** IR and $^1$H NMR Data of the New Compounds

| Compound | IR $cm^{-1}$ (Selected Bands) | $^1$H NMR δ (DMSO-$d_6$) |
|---|---|---|
| **2** | 2200, 2180, 2165 | 7.4–7.6 (m, 5H); 7.84 and 7.87 (2 s, 1H) |
| **3b** | 3445, 2208 | 7.3–7.8 (m, 7H); 8.8 (s, 1H) |
| **5** | 3430–3250 ($NH_2$), 2205 (CN), 2175 (SCN), 1680 (CO) | 7.2–7.8 (m, 6H, aromatic H, and $C_4$–H); 8.6 (s, 2H, $NH_2$), 11.42 (s, 1H, COOH) |
| **7** | 3440–3230 ($NH_2$), 2230 (CN), 2190 (SCN) | 7.3–8.1 (m, 6H, aromatic H, and $C_4$–H); 8.9 (s, 2H, $NH_2$) |
| **9** | 3440–3260 ($NH_2$), 2220 (CN), 2185 (SCN) | 7.3–8.15 (m, 11H, aromatic H, and $C_4$–H); 8.78 (s, 2H, $NH_2$) |
| **12** | 3450–3230 ($NH_2$ and NH) | 5.5–6.2 (br s, 6H, NH, and $NH_2$); 7.4 and 8.0 (m, 10H, aromatic H); 7.75 (s, 2H, thiazole $C_5$–H) |

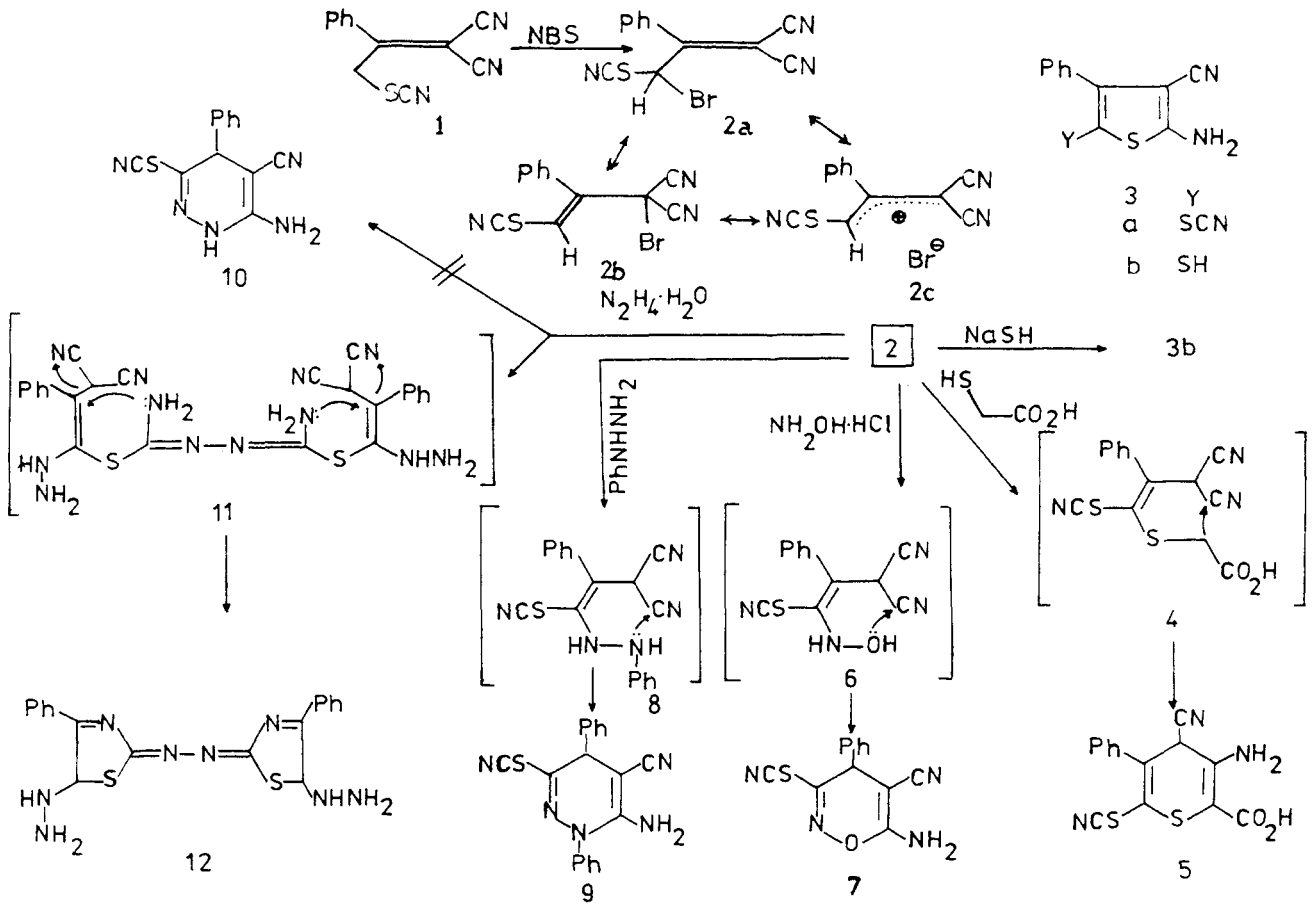
agreement with structure **3b**. It is assumed that the bromine atom in compound **2** is substituted by SH, which brings about cyclization by adding to one of the CN groups, the SCN group being hydrolyzed to SH under these basic conditions to afford the thiophene derivative **3b**. Mass spectral measurements and the $^1$H NMR spectrum are consistent with structure **3b** (Tables 1 and 2). The hydrolysis of SCN to SH under basic conditions has also been reported [5].

The synthetic potentialities of compound **2** have been explored for other syntheses. Thus, it reacts with thioglycollic acid in the presence of sodium acetate to afford a dark-colored product. The thiopyran structure **5** was suggested for this product on the basis of analytical and spectral data (Tables 1 and 2). Compound **5** is assumed to be formed via the acyclic intermediate **4**.

Compound **2** reacts with hydroxylamine hydrochloride and with phenylhydrazine to afford solid products for which structures **7** and **9**, respectively, were assigned (Scheme 1) on the basis of analytical and spectral data. The formation of **7** and **9** is assumed to proceed via the acyclic intermediates **6** and **8**, respectively [7].

Compound **2** reacts also with hydrazine hydrate in refluxing ethanol to afford a solid crystalline product of mp 287°C. Structure **10** was expected for this product based on analogy with the products of hydroxylamine and phenylhydrazine reactions and with the literature [7]. However, the IR spectrum of this product did not reveal any cyano or thiocyanato absorption bands. Elemental analysis showed the presence of sulfur and led to an empirical formula of $C_9H_9N_4S$. The $^1$H NMR spectrum of this product revealed three signals: a broad singlet (3H) at δ 5.5–6.2, a two multiplet signal integrated for (5H) centered at δ 7.4 and 8.0, and a singlet (1H) at δ 7.75. On shaking the compound with $D_2O$, the broad signal at δ 5.5–6.2 vanished. Based on the foregoing data, structure **12** was assigned for this product.

Compound **12** is assumed to be formed via the substitution of Br by -$NHNH_2$ and the addition of hydrazine to two SCN groups of two molecules of **2** to afford the acyclic intermediate **11**, which then undergoes cyclization via loss of two molecules of



**SCHEME 1**

malononitrile. Similar behavior of phenacyl thiocyanate toward hydrazine and the elimination of malononitrile has been reported recently by us [8].

## *EXPERIMENTAL*

All melting points are uncorrected. IR spectra were recorded as KBr pellets on a Perkin-Elmer 580 spectrophotometer. $^1$H NMR spectra were recorded on a Varian Gemini 200 (200 MHz) spectrometer in DMSO-$d_6$ using TMS as an internal reference. Mass spectra were taken on a GCMS-QP 1000 EX, Schimadzu (Japan) with ionization potential 70 eV. Elemental analyses were carried out in the microanalytical center at Cairo University.

### *Bromination of* **1**: *Preparation of the Bromo Derivative* **2**

To a solution of 2.25 g (0.01 mole) of **1** in 25 mL of dry DMF was added 1.78 g (0.01 mole) of NBS. The reaction mixture was stirred for 4 hours at room temperature and then left overnight. The mixture was then poured on ice-cold water and acidified with a few drops of HCl whereupon a solid precipitate appeared, which was filtered off and recrystallized to afford 2.2 g of **2**.

### *2-Amino-4-phenyl-5-mercaptothiophene-3-carbonitrile* **3b**

To a solution of 3.04 (0.01 mole) of **2** in 25 mL of ethanol was added 0.56 g (0.01 mole) of sodium hydrogen sulfide and the reaction mixture was heated on a water bath for 1 hour. After cooling, the mixture was poured on ice-cold water and acidified with HCl till just neutral. The dark green precipitate that had formed was filtered off and recrystallized to afford 1.5 g of **3b**.

### *3-Amino-4-cyano-5-phenyl-6-thiocyanato-4H-thiopyran-2-carboxylic acid* **5**

To a mixture of 3.04 g (0.01 mole) of **2** and 0.92 g (0.01 mole) of thioglycollic acid in 30 mL of ethanol was added 1.64 g (0.02 mole) of sodium acetate, and the mixture was refluxed for 2 hours. After cooling, the mixture was poured on crushed ice and

neutralized with HCl. The dark-colored precipitate thus formed was filtered off and recrystallized to afford 2.3 g of **5**.

### *6-Amino-5-cyano-4-phenyl-3-thiocyanato-4H-1,2-oxazine* **7**

To a mixture of 3.04 g (0.01 mole) of **2** and 0.7 g (0.01 mole) of hydroxylamine hydrochloride in 30 mL of ethanol was added a solution of potassium carbonate (2.76 g; 0.02 mole in a minimum amount of water), and the reaction mixture was refluxed for 2 hours. The mixture was left to cool to room temperature, then poured on crushed ice and neutralized with HCl. The brown precipitate that appeared was filtered off and recrystallized from ethanol to give 1.7 g of **7**.

### *6-Amino-5-cyano-1,4-diphenyl-3-thiocyanato-1,4-dihydropyridazine* **9**

A mixture of 3.04 g (0.01 mole) of **2** and 1.08 g (0.01 mole) of phenylhydrazine in 30 mL of ethanol was refluxed for 2 hours, whereupon a solid precipitate appeared. The mixture was allowed to cool to room temperature and then was filtered, and the solid product obtained was recrystallized from DMF/EtOH (2:1) to give 2.6 g of **9**.

### *Bis[4-phenyl-5-hydrazino-$\Delta^{3,4}$-5H-thiazol-2-ylidene] azine* **12**

To a solution of 3.04 g (0.01 mole) of **2** in 25 mL of ethanol was added an excess of hydrazine hydrate (~2 mL), and the reaction mixture was refluxed for 2 hours, after which it was left overnight. The solid precipitate was filtered off and recrystallized from DMF/EtOH (2:1) to afford 1.5 g of **12**.

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