# The Reaction of Isothiocyanates with 2-Cyanoethanoic Acid Hydrazide. A Novel Synthesis of 1,3,4-Thiadiazoles



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Benzoyl and ethoxycarbonyl isothiocyanates reacted with 2-cyanoethanoic acid hydrazide **2** to afford 1-cyanoacetyl-4-substituted thiosemicarbazide (**5a,b**). Compound **5a** afforded the pyrazolo[1,5-*a*]-*s*-triazine derivative **6** on treatment with 5% potassium hydroxide, and cyclised to 2-benzoylamino-5-cyanomethyl-1,3,4-thiadiazole (**8**) when boiled under reflux in glacial acetic acid. Compound **8** condensed with aromatic aldehydes to yield the corresponding arylidene derivatives **9a-c**. It undergoes coupling with aromatic diazonium salts to afford the hydrazones **11a-c**. Similarly, it coupled with diazotised aminopyrazole to afford the cyclic product **12**.

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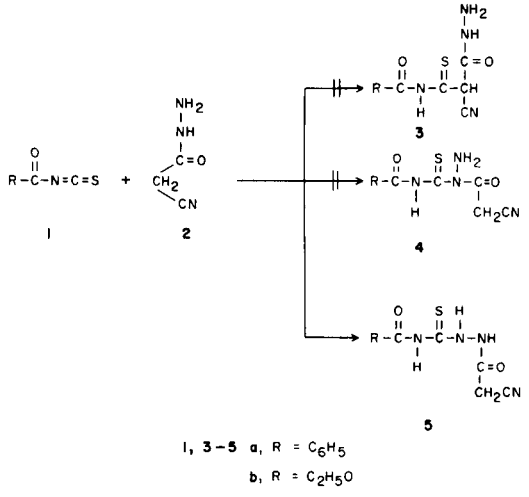
Aroyl and acyl isothiocyanates **1a,b** are versatile reagents and their chemistry has received considerable recent interest [1-4]. These reagents can react with a variety of polyfunctional molecules either *via* addition followed by cyclization or *via* cycloaddition to yield a variety of heterocyclic derivatives. In previous work we have described the utility of **1a,b** for the synthesis of a variety of fused azoles [5]. In continuation of this work we report here the reaction of 2-cyanoethanoic acid hydrazide **2** with **1a,b** and utility of the resulting reaction products for the synthesis of several new, otherwise difficult accessible, azoles and fused azoles. Thus, it has been found that **1a,b** react with **2** to yield 1:1 adducts. Three theoretically possible structures were considered (*cf.* structures **3-5**). Structure **3** was readily excluded based on $^1$H nmr spectra of the products which revealed a signal for $CH_2$ protons at 4 ppm. $^1$H nmr could be also utilized to exclude structure **4** as it revealed the absence of signal for $NH_2$ protons. Structure **5** was thus established for the reaction products.

Chart I



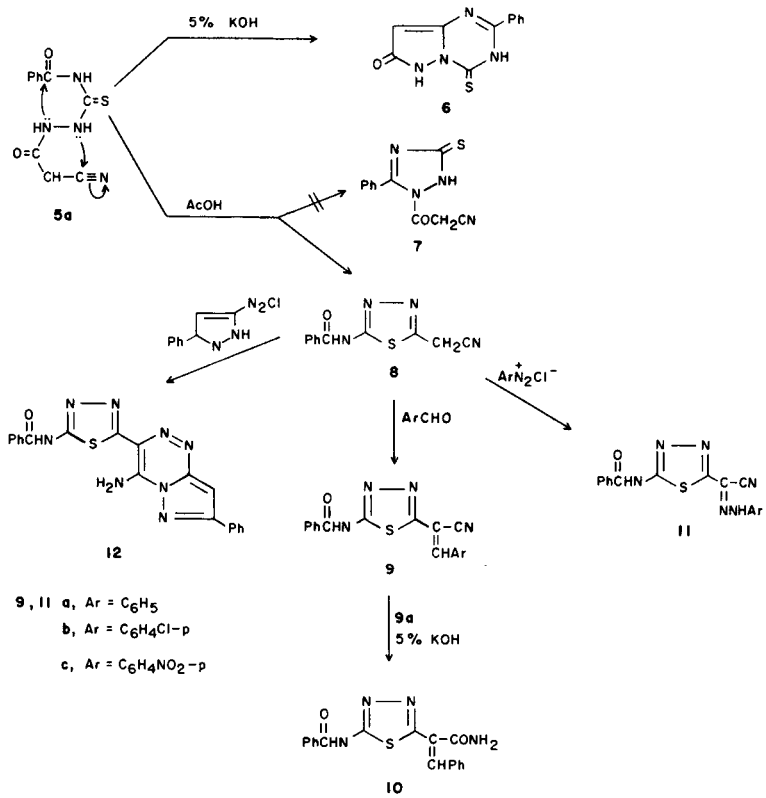

Treatment of compound **5a** with aqueous 5% potassium hydroxide or ethanolic sodium ethoxide has resulted in the formation of the pyrazolo[1,5-*a*]-*s*-triazine derivative **6**. The structure of compound **6** was inferred from correct elemental analysis, ir and $^1$H nmr spectral data. The ir spectrum showed the absence of CN absorption, and indicated the presence of carbonyl stretching and dimeric OH group. The $^1$H nmr spectrum of **6**, in addition to the multiplet at $\delta$ 7.5 ppm due to the aromatic protons, exhibited a singlet at $\delta$ 6.2 ppm for one proton attributable for the pyrazole C(4)-H and two broad signals for two protons at $\delta$ 11.9 and 12.4 ppm exchangeable with deuterium oxide due to NH protons.

Compound (**5a**) cyclized readily on boiling in acetic acid to yield a product of molecular formula $C_{11}H_8N_4OS$. Two theoretically possible structures were considered (*cf.* structures **7** and **8**). The thiadiazole structure (**8**) was considered most likely based on the stability of the reaction product toward mild acid or basic treatment. *N*-acylazoles are known to undergo ready deacylation when treated under similar conditions [6]. Moreover, hydrolysis of the reaction product with acetic acid/hydrochloric acid or 5% sodium hydroxide afforded benzoic acid as the sole isolable product. 1,2,4-Triazolethiones are reported to be stable under similar or even more drastic conditions [7]. Further evidence for the structure could also be inferred from $^1$H nmr data of the product. Thus, the methylene group signal appeared at $\delta$ 4.35 ppm typical for methylene group resonance of similar systems and is completely different than that observed for similar systems and lower for that anticipated for cyanoacetamides [9].

Attempts to effect cyclization of **5b** into either a pyrazolopyrimidine or thiadiazole derivative under a variety of conditions were unsuccessful. The molecule decomposed under all the applied cyclization conditions.

Similar to the behaviour of its recently reported thiazole analogues [8], compound **8** condensed with aromatic alde-

Chart 2




hydes to yield the corresponding arylidene derivatives **9a-c** in approximately quantitative yields. Hydrolysis of the benzylidene derivative **9a** with 5% sodium hydroxide has resulted in the formation of 2-amino-1,3,4-thiadiazole derivative **10**.

The coupling reaction of aromatic and heteroaromatic diazonium salts with compound **8** was studied. Thus, it has been found that aromatic diazonium salts coupled with compound **8** to afford the corresponding hydrazones **11a-c**. On the other hand compound **8** coupled with diazotised aminopyrazole to afford directly cyclic product **12**.

## EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded (potassium bromide) on a Pye Unicam SP-110 spectrophotometer. The $^1$H nmr spectra were obtained on a Varian EM-390 spectrometer at 90 MHz with DMSO-$d_6$ as solvent and TMS as internal reference. Analytical data were obtained from the Analytical Data Unit at Cairo University.

1-Cyanoacetyl-4-substituted Thiosemicarbazide (**5a,b**).

General Procedure.

A suspension of **2** (100 mmoles) in acetone (50 ml) was treated with the isothiocyanate solution (prepared from 120 mmoles of ammonium thiocyanate and the equivalent amount of either benzoyl chloride or ethyl chloroformate as has been previously described [5]. The reaction mixture was refluxed for 3 hours and then evaporated under reduced pressure. The remaining product was triturated with water, collected by filtration and crystallised from the appropriate solvent (Table 1).

Action of Aqueous Potassium Hydroxide on **5a** and **8**.

A solution of each of **5a** and **8** (10 mmoles) was treated with 5% potassium hydroxide (20 ml), then refluxed for 2 hours, left to cool, diluted with water and acidified with dilute hydrochloric acid. The solid product formed was collected by filtration and crystallised from the appropriate solvent (*cf.* Table 1).

Cyclization of Compound **5a** by Acetic Acid.

A solution of compound **5a** (1.0 g) in glacial acetic acid (30 ml) was refluxed for five hours, then evaporated *in vacuo*. The remaining product was triturated with ethanol and the resulting solid product was collected by filtration and crystallised from the appropriate solvent (*cf.* Tables 1 and 2).

Reaction of Compound **8** with Aromatic Aldehydes.

A solution of **8** (10 mmoles) in ethanol (30 ml) was treated with the equivalent quantity of the aromatic aldehyde (12 mmoles) and then with the catalytic amount of piperidine. The reaction mixture was refluxed for 3 hours and the the precipitated product was filtered off and crystallised from the appropriate solvent (Table 1).

Coupling of Aromatic Diazonium Salts with Compound **8**.

A solution of the appropriate aromatic diazonium salt (100 mmoles) was added gradually to a cold solution of compound **8** (100 mmoles) in

Table 1

| Compound | Solvent (Colour) | Mp (°C) | Yield (%) | Mol Formula (Mol Weight) | Analysis (%) Found/Required C | H | N | S |
|---|---|---|---|---|---|---|---|---|
| **5a** | AcOH | 198 | 95 | $C_{11}H_{10}N_4O_2S$ | 50.4 | 3.8 | 21.0 | 12.3 |
| | (Colourless) | | | (262.29) | 50.4 | 3.8 | 21.2 | 12.2 |
| **5b** | $H_2O$ | 161 | 86 | $C_7H_{10}N_4O_3S$ | 36.1 | 4.4 | 24.2 | 13.6 |
| | (Colourless) | | | (230.23) | 36.5 | 4.3 | 24.3 | 13.9 |
| **6** | DMF | 302 | 92 | $C_{11}H_8N_4OS$ | 54.2 | 3.4 | 22.7 | 12.8 |
| | (Colourless) | | | (244.27) | 54.1 | 3.3 | 22.9 | 13.1 |
| **8** | AcOH | 235 | 85 | $C_{11}H_8N_4OS$ | 53.9 | 3.4 | 22.6 | 12.7 |
| | (Pale Yellow) | | | (244.27) | 54.1 | 3.3 | 22.9 | 13.1 |
| **9a** | AcOH | 182 | 80 | $C_{18}H_{12}N_4OS$ | 64.9 | 3.5 | 16.6 | 9.4 |
| | (Yellow) | | | (332.28) | 65.1 | 3.6 | 16.8 | 9.6 |
| **9b** | AcOH | >290 | 76 | $C_{18}H_{11}ClN_4OS$ | 58.5 | 3.1 | 15.3 | 8.5 |
| | (Yellow) | | | (367.83) | 58.7 | 3.0 | 15.2 | 8.7 |
| **9c** | DMF | >300 | 82 | $C_{18}H_{11}N_5O_3S$ | 57.3 | 2.8 | 18.4 | 8.6 |
| | (Yellow) | | | (377.28) | 57.3 | 2.9 | 18.6 | 8.5 |
| **10** | EtOH | | 5 | $C_{11}H_{10}N_4OS$ | 53.4 | 3.9 | 22.8 | 12.9 |
| | (Yellow) | | | (246.28) | 53.6 | 4.1 | 22.7 | 13.0 |
| **11a** | AcOH | >280 | 73 | $C_{17}H_{12}N_6OS$ | 58.4 | 3.4 | 23.8 | 8.9 |
| | (Orange) | | | (348.38) | 58.6 | 3.5 | 24.1 | 9.2 |
| **11b** | EtOH | >280 | 78 | $C_{17}H_{11}ClN_6OS$ | 53.4 | 2.6 | 21.5 | 8.2 |
| | (Orange) | | | (383.83) | 53.2 | 2.8 | 21.9 | 8.4 |
| **11c** | AcOH | >280 | 82 | $C_{17}H_{11}N_7O_3S$ | 51.7 | 3.2 | 24.3 | 7.9 |
| | (Orange) | | | (394.48) | 51.7 | 3.1 | 24.4 | 8.1 |
| **12** | DMF | >300 | 65 | $C_{20}H_{14}N_8OS$ | 57.6 | 3.3 | 26.8 | 7.5 |
| | (Yellow) | | | (414.45) | 57.9 | 3.4 | 27.1 | 7.7 |

Table 2

Selected IR and Complete $^1$H-NMR Data for the Compounds Listed in Table 1

| Compound | max $cm^{-1}$ | δ H |
|---|---|---|
| **5a** | 3300, 3200 and 3050 (NH), 2260 (unconjugated CN), and 1680-1660 (CO) | 3.9 (s, 2H, $CH_2$), 7.5-8.2 (m, 5H, Ph), 11.4 (br s, 1H, NH), 11.9 (s, 1H, NH), and 12.8 (br s, 1H, NH) |
| **5b** | 3300-3100 (NH), 2255 (unconjugated CN), 1700 (ester CO), and 1660 (amide CO) | 1.35 (t, 3H, $CH_3$), 3.8 (s, 2H, $CH_2$), 4.35 (q, 2H, $CH_2$), 8.2 (br s, 1H, NH), 9.2 (br s, 1H, NH), 11.5 (br s, 1H, NH) |
| **6** | 3250 and 3050 (NH), 2900-2600 (OH dimer), and 1625 (CO) | 7.55-8.35 (m, 5H, Ph), and 6.15 (s, 1H, pyrazole CH-3) |
| **8** | 3160 (NH), 2255 (unconjugated CN), and 1650 (amide CO) | 13.15 (br s, 1H, NH), 7.55-8.25 (m, 5H, Ph), and 4.6 (s, 2H, $CH_2$) |
| **9a** | 3180 (NH), 2230 (conjugated CN), and 1665 (amide CO) | 7.05 (br s, 1H, NH), 7.35-8.15 (m, 10H, 2 × Ph), and 8.2 (s, 1H, CH) |
| **9b** | 3150 (NH), 2225 (conjugated CN), and 1665 (amide CO) | Insoluble |
| **10** | 3480-3300, 3200, 3080 ($NH_2$) and 1670 (amide CO) | 9.3 (br s, 2H, $NH_2$), 7.2-8.25 (m, 11H, 2 × Ph and CH), 5.95 (br s, 1H, NH) |
| **11a** | 3225, 3150 (NH), 2205 (conjugated CN), and 1672 (amide CO) | 7.2 (br, 2H, 2NH), and 7.45-8.3 (m, 10H, 2 × Ph) |
| **11b** | 3450, 3200 (NH), 2210 (conjugated CN), and 1675 (amide CO) | Insoluble |
| **11c** | 3275-3100 (NH), 2210 (conjugated CN), and 1672 (amide CO) | Insoluble |
| **12** | 3500-3100 (NH and $NH_2$), 1675 (amide CO), and 1625 ($NH_2$) | 7.55-8.3 (m, 10H, 2 × Ph), 7.35 (s, 1H, pyrazole CH), and 7.2 (br, 1H, NH) |

ethanol (100 ml), and sodium acetate (13 g) with continuous stirring. The solid product formed, was collected by filtration, washed with water, dried, and crystallised from the appropriate solvent (*cf.* Table 1).

Coupling of Diazotised 5-Amino-3-phenylpyrazole with Compound **8**.

A solution of compound **8** (100 mmoles) in pyridine (50 ml) was treated with a solution of anhydrous sodium acetate (5 g) in 10 ml of water. To this solution was added a solution of 3-phenylpyrazole-5-diazonium chloride (100 mmoles prepared as previously described) [10] in water (50 ml). The reaction mixture was stirred at room temperature for 3 hours diluted with water, and the solid product so formed, was collected by filtration and crystallised from acetic acid.

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