Reactions with Cyclic Amidines II. The Behaviour of Cyclic Amidines Toward Ethoxycarbonyl and Aroyl Isothiocyanates

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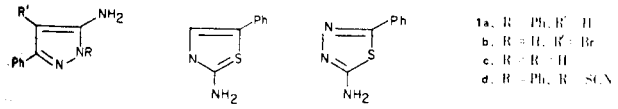
Received May 15, 1978

The behaviour of the aminopyrazole derivatives **1a-c**, 2-amino-4-phenylthiazole (**2**) and 2-amino-5-phenyl-1,3,4-thiadiazole (**3**) toward the action of ethoxycarbonyl and benzoyl isothiocyanate is reported. The data clearly demonstrates the dependence of the nature of the products obtained from the reaction of isothiocyanates with cyclic amidines on the nature of the substituents on the heterocyclic ring.

J. Heterocyclic Chem., 16, 61 (1979).

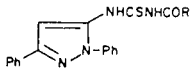
Alkoxycarbonyl, acyl and aroyl isothiocyanates have recently found extensive utility in heterocyclic synthesis (1-8). This utility is due to their high reactivity and because reactions at the unsaturated bonds in these reagents, either by 1,3-dipolarcycloaddition or by a Michael type additon followed by cyclisation through the alkoxycarbonyl, acyl or aroyl moieties, provides the double bond requisites to a heteroaromatic system. As a part of our program dealing with the utility of cyclic amidines as precursors for the synthesis of fused heterocyclic compounds (9-12), we have previously reported the behaviour of some 5-aminopyrazoles (7,9) and aminoisoxazoles (10) toward the action of isothiocyanates. In the present paper we report the behaviour of the amino azole derivatives **1a,b**, **2** and **3** toward the action of ethoxycarbonyl and benzoyl isothiocyanates. The results clearly indicate that the course of reaction of the above mentioned reagents with amino azoles depends both upon the substituents on the heterocyclic ring and the nature of the latter ring.



1 2 3

It has been found that 5-amino-1,3-diphenylpyrazole (**1a**) reacts with ethoxycarbonyl and benzoyl isothiocyanates to yield the corresponding pyrazol-5-ylthiourea derivatives **4a,b**. That the addition of isothiocyanates has involved the amino nitrogen and not the pyrazole C-4 position was inferred from the presence of the pyrazole CH in the ^{1}H-nmr of the reaction products. This is in contrast to the reported reaction of 5-amino-3-phenylpyrazole (**1c**) with benzoyl isothiocyanate to yield products resulting from electrophilic attack of the reagent at the C-4 position on the pyrazole ring (9).

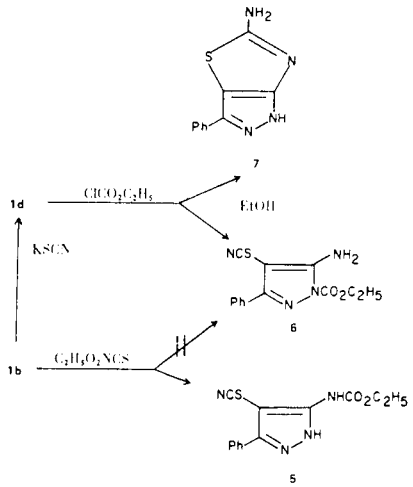
5-Amino-4-bromopyrazole (**1b**) reacted with ethoxycarbonyl isothiocyanate to yield a product in which the analytical data indicated a molecular formula of $C_{13}H_{12}N_4O_2S$. Although no molecular ion was revealed for this compound in the mass spectrometer, molecular



4a, R = OC_2H_5
b, R = Ph

weight determination by classical methods were consistent with the suggested molecular formula. The ir spectrum of the product revealed absorptions for NH, CO and SCN groups. The ^{1}H-nmr of this product showed signals for ethyl ester, phenyl and two NH protons. Based on these data, structure **5** or isomeric **6** seemed possible for this product. Structure **5** was considered most likely since the reaction product proved stable under the conditions reported to effect decomposition of N-1 acylpyrazoles (13) or upon treatment with reagents that readily affected cyclisation of 5-amino-4-thiocyanate-3-phenylpyrazole (**1d**) (see latter). Attempted synthesis of **5** *via* the action of ethyl chloroformate on **1d**, prepared by the action of potassium thiocyanate on **1b**, were unsuccessful. Under a variety of conditions, **1d** cyclised into the thiazolo[4,5-c]-pyrazole derivative **7** on attempted condensation with ethyl chloroformate or afforded the 5-amino-3-ethoxycarbonyl-3-phenyl-4-thiocyanatopyrazole (**6**). Compound **6** readily afforded **7** under a variety of reaction conditions aimed to effect its rearrangement into **5**.

Compound **1b** reacted with benzoyl isothiocyanate to



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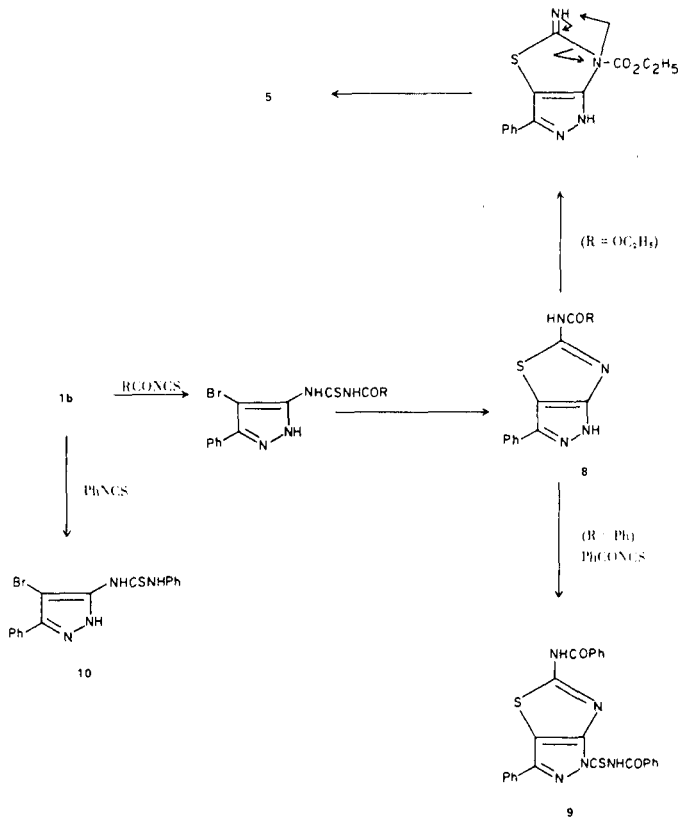
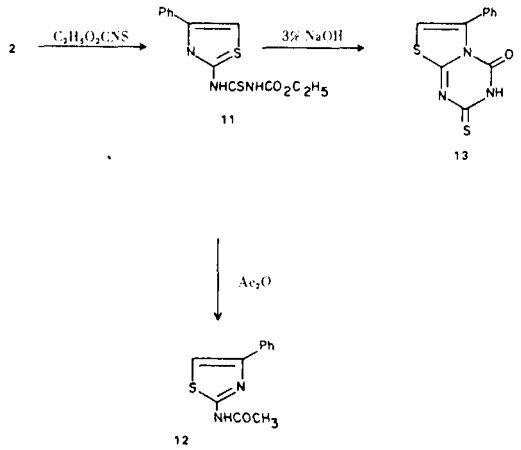
yield a mixture of the thiazolo[4,5-*c*]pyrazole **8** and the diadduct **9**. These were separated in 4 to 1 ratios. When an excess of benzoyl isothiocyanate was used, compounds **8** and **9** were formed in a 1:1 ratio. With a little excess of **1b**, compound **8** and unreacted **1b** were the only isolable products.

The formation of **5** or **8** and **9** from the reaction of **1b** with ethoxycarbonyl or with benzoyl isothiocyanates might be assumed to proceed *via* an intermediate thiourea derivative, which then readily cyclises into the thiazolo-[2,3-*c*]pyrazoles **8a,b**. Compound **8a** rearranges then

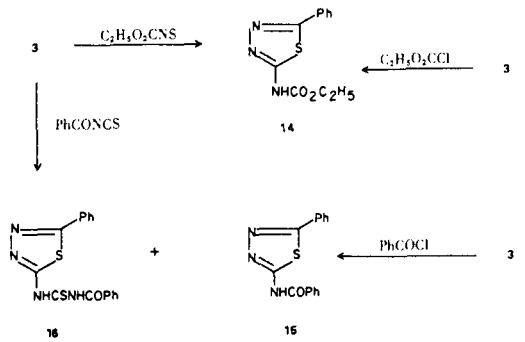


into the final isolable product **5** under the reaction conditions. On the other hand, **8b** does not rearrange under the same conditions and could be isolated as such or form the diadduct **9** with an excess of the reagent. Although attempts to isolate intermedaite thiourea derivatives in the above reactions were unsuccessful, the isolation of the thiourea derivative **10** from the reaction of phenyl isothiocyanate and **1b** may point to the intermediacy of thiourea derivatives in these reactions. However, it seems that a mechanistic study for these conversions is necessary to establish a rigid conclusion in this respect.

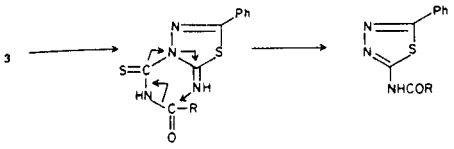
2-Amino-4-phenylthiazole (**2**) reacted with ethoxycarbonyl isothiocyanate to yield the thiazolylthiourea derivative **12**. The structure of **11** was inferred from its ^{1}H-nmr and its chemical behaviour. Thus, whereas *N*-thiocarbamoylazoles has been reported to decompose readily on treatment with acid or with methanolic sodium methoxide (11), compound **12** was recovered almost unaffected on treatment with both reagents. Attempted cyclisation of **11** by the action of acetic anhydride has resulted in its decomposition. 2-Acetamido-4-phenylthiazole (**13**) was the only isolable reaction product. The decomposition of **11** into **12** is similar to the previously reported decomposition of azolyl thioureas into the corresponding acylamino derivatives by the action of acetic anhydride (6). Compound **11** could be successfully cyclised into the thiazolo[2,3-*d*]-*s*-triazine derivative by the action of ethanolic sodium hydroxide solution.



The reaction of 2-amino-1,3,4-thiadiazoles with ethoxycarbonyl isothiocyanates is straight forward and affords the expected thiourea derivatives (13). We have found, however, that 2-amino-5-phenyl-1,3,4-thiadiazole (**3**) reacts with ethoxycarbonyl isothiocyanate to yield the ethoxycarbonylamino derivative **14** as the only isolable product (80% yield). Compound **3** also reacted with benzoyl isothiocyanate to yield the expected thiourea derivative **15** as a minor product. The major reaction product was found to be the benzoylamino derivative **16**. The structure of **15** and **16** was confirmed *via* synthesis from **3** and ethyl chloroformate or with benzoyl chloride respectively. Although the mechanism of this reaction is still uncertain and several logical routes leading to the formation of **14** and **15** cannot, based on the available data, be overlooked, it seems to us most likely that **14**



and **16** are formed *via* rearrangement of the initially formed 1-thiocarbamoylated adduct as illustrated in the equation below.



The formation of acyl derivatives on reaction of strongly basic acyclic amidines with ethoxycarbonyl isothiocyanate has been previously reported (14).

The data gathered from the present work when combined with the results of our previously published results clearly indicate that caution must be used in proposing structures by analogy to other reactions. The data also emphasise the importance of structural modifications on the reactivity of cyclic amidines and suggests that charge separate resonance forms for cyclic amidines plays a substantial role in determining C *vs.* ring N and *vs.* exocyclic amino group reactivities.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded (potassium bromide) on a Perkin-Elmer model 337 spectrophotometer. ^{1}H-nmr spectra were obtained with a Varian A-60 spectrophotometer using TMS as internal standard and chemical shifts are expressed as δ ppm.

1-Substituted-3-(1,3-diphenylpyrazol-5-yl)thiourea (**4a.b**).

Compound **1a** was treated with an equimolecular amount of either ethoxycarbonyl isothiocyanate or benzoyl isothiocyanate in acetone solution using the experimental procedure previously described for the reaction of **1c** with benzoyl isothiocyanate (6). The reaction products were crystallized from ethanol.

Compound **4a** formed pale yellow crystals, m.p. 154°, yield 85%; ir: 1735 cm^{-1} (ester CO), 3000-3080 and 3200 (NH); ^{1}H-nmr: 1.21 (t, 3H, CH_3), 4.13 (q, 2H, CH_2), 7.13 (s, 1H, pyrazole C-4 proton), 7.36-8.03 (m, 10H, 2 C_6H_5) and 11.50 (d, 2H, lost after deuterium oxide exchange, NH).

Anal. Calcd. for $C_{19}H_{18}N_4O_2S$: C, 62.2; H, 4.9; N, 15.3; S, 8.7. Found: C, 62.2; H, 5.3; N, 15.1; S, 8.7.

Compound **4b** formed pale yellow crystals, m.p. 160°, yield 30%; ir: 1615 cm^{-1} (C=N) and 1690 (benzoyl CO).

Anal. Calcd. for $C_{23}H_{18}N_4OS$: C, 69.33; H, 4.5; N, 14.0; S, 8.0. Found: C, 69.77; H, 4.3; N, 14.0; S, 7.8.

5-Ethoxycarbonylamino-4-thiocyanato-3-phenylpyrazole (**5**).

A suspension of **1b** (0.1 mole) in acetone (50 ml.) was treated with ethoxycarbonyl isothiocyanate solution (prepared from 0.12 mole of ammonium thiocyanate and an equivalent amount of ethyl chloroformate as has been previously described (9). The reaction mixture was refluxed for fifteen minutes and then evaporated *in vacuo*. The remaining product was triturated with water, collected by filtration and crystallised from ethanol.

Compound **5** formed colourless crystals, m.p. 162°, yield 80%, ir: 1730 cm^{-1} (ester CO) and 3300-3500 (NH bands); ^{1}H-nmr: 1.41 (t, 3H, CH_3), 4.5 (q, 2H, CH_2), 7.56-8.08 (m, 7H, integrated for 5 protons after deuterium oxide exchange, aromatic and NH protons).

Anal. Calcd. for $C_{13}H_{12}N_4O_2S$: C, 51.1; H, 4.2; N, 19.4; S, 11.1. Found: C, 53.8; H, 4.0; N, 19.1; S, 11.2.

5-Amino-4-thiocyanato-3-phenylpyrazole (**1d**).

A solution of **1b** (0.1 mole) in acetone (100 ml.) was treated with potassium thiocyanate (0.1 mole). The mixture was refluxed for three hours, left to cool and then poured onto water. The product, so formed, was collected by filtration and crystallised from ethanol.

Compound **1d** formed yellow crystals, m.p. 120°, yield 88%; ir: 1620 cm^{-1} (δ CH_2), 2180 (SCN) and a broad band at 3050-3350 (NH vibrations).

Anal. Calcd. for $C_{10}H_8N_4S$: C, 55.5; H, 3.7; N, 25.9; S, 14.8. Found: C, 55.4; H, 4.0; N, 26.0; S, 15.0.

5-Amino-1-ethoxycarbonyl-4-thiocyanatopyrazole (**6**).

A suspension of **1d** (0.1 mole) in acetone (100 ml.) and potassium carbonate (5.0 g.) was treated with ethyl chloroformate (0.1 mole). The reaction mixture was refluxed for two hours, then evaporated *in vacuo*. The remaining product was triturated with water and the resulting solid was collected by filtration, dried and crystallised from acetone.

Compound **6** formed colourless crystals, m.p. 120°, yield 45%; ir: 1630 cm^{-1} (NH_2), 2160 (SCN) and 3200-3300 (NH bands).

Anal. Calcd. for $C_{13}H_{12}N_4O_2S$: C, 51.1; H, 4.2; N, 19.4; S, 11.1. Found: C, 53.9; H, 4.4; N, 19.6; S, 11.1.

2-Amino-6-phenylthiazolo[4,5-*c*]pyrazole (**7**).

A solution of **1d** (2.0 g.) in ethanol (100 ml., 95%) was refluxed for four hours, then evaporated *in vacuo*. The remaining solid produced was triturated with water, collected by filtration and crystallised from ethanol.

Compound **6** formed yellow crystals, m.p. 177°, yield 88%; ir: 1620 cm^{-1} (o-NH_2) and a broad band at 3050-3350 (NH vibrations).

Anal. Calcd. for $C_{10}H_8N_4S$: C, 55.5; H, 3.7; N, 25.9; S, 14.8. Found: C, 55.4; H, 4.0; N, 26.0; S, 15.0.

Reaction of **1b** with Benzoyl Isothiocyanate.

A solution of **1b** (0.1 mole) in acetone (150 ml.) was treated with a solution of benzoyl isothiocyanate (prepared from 0.15 mole of ammonium thiocyanate and 0.17 mole of benzoyl chloride as has been previously described). The reaction mixture was refluxed for three hours and then filtered while hot. The collected product was washed several times with cold water and crystallised from ethanol to yield compound **9** as colourless crystals, m.p. 275°, yield 15%.

Anal. Calcd. for $C_{25}H_{17}N_5O_2S_2$: C, 62.1; H, 3.5; N, 14.4; S, 13.25. Found: C, 62.0; H, 3.6; N, 14.7; S, 13.0.

Evaporation of the filtrate afforded a pale yellow solid which was purified by crystallisation from ethanol to yield compound **8** (R = Ph) as yellow crystals, m.p. 230°, yield 55%.

Anal. Calcd. for $C_{17}H_{12}N_4OS$: C, 63.7; H, 3.7; N, 17.4; S, 10.0. Found: C, 63.5; H, 4.0; N, 17.3; S, 10.0.

N-(4-Bromo-3-phenylpyrazol-5-yl)-*N'*-phenylthiourea (**10**).

A mixture of **1b** (2.0 g.) and phenyl isothiocyanate (2.0 ml.) was heated on a boiling water bath for one hour. The reaction product was then treated with ethanol and the solid product, so formed, was collected by filtration and crystallised from ethanol.

Compound **10** formed pale yellow crystals, m.p. 170°, yield 60%.

Anal. Calcd. for $C_{16}H_{13}BrN_4S$: C, 51.4; H, 3.4; N, 14.8; S, 8.5; Br, 21.4. Found: C, 51.2; H, 3.4; N, 15.0; S, 8.5; Br, 21.2.

N-Ethoxycarbonyl-*N'*-(4-phenylthiazol-2-yl)thiourea (**11**).

Compound **2** was treated with ethoxycarbonyl isothiocyanate using the experimental conditions utilised for the reaction of **1** with the same reagent. The formed **11** was purified by crystallisation from ethanol. Compound **11** formed yellow crystals, m.p. 205°, yield 75%; ^{1}H-nmr: 1.31 (t, 3H, CH_3), 4.43 (q, 2H, CH_2), 7.4-8.5 (m, 6H, phenyl and thiazole ring protons), 11.93 (1H, deuterium oxide exchangeable, NH) and 13.16 (br, 1H, deuterium oxide exchangeable, NH).

Anal. Calcd. for $C_{13}H_{13}N_3O_2S_2$: C, 50.8; H, 4.2; N, 13.6; S, 21.0. Found: C, 50.7; H, 4.3; N, 13.4; S, 20.9.

2-Acetamido-4-phenylthiazole (**12**).

A suspension of **11** (2.0 g.) in acetic anhydride (30 ml.) was refluxed for three hours. The solvent was then removed *in vacuo* and the resulting solid product was triturated with water and collected by filtration. The reaction product was identified (m.p. and mixed m.p.) as **12**.

3,4-Dihydro-5-oxo-8-phenyl-3-thioxothiazolo[2,3-*d*]-*s*-triazine (**13**).

A solution of **11** (2.0 g.) in aqueous sodium hydroxide (20 ml., 5%) was kept overnight at room temperature and then neutralised by concentrated hydrochloric acid. The solid product, so formed, was collected by filtration and crystallised from ethanol. Compound **13** formed colourless crystals, m.p. 205°, yield 58%.

Anal. Calcd. for $C_{11}H_7N_3OS_2$: C, 50.7; H, 2.7; N, 16.0; S, 24.4. Found: C, 50.7; H, 3.0; N, 16.0; S, 24.2.

2-Ethoxycarbonylamino-5-phenyl-1,3,4-thiadiazole (**14**).

To an ethoxycarbonyl isothiocyanate solution (prepared from 0.12 mole of ammonium thiocyanate and 0.1 mole of ethyl chloroformate in dry acetone) 0.1 mole of **3** was added. The reaction mixture was heated for ten hours and then allowed to cool. The solid product, obtained on cooling was collected by filtration and washed well with water to afford crude **14**. Evaporation of the filtrate afforded additional quantity of the same compound. Compound **14** formed colourless crystals from ethanol, m.p. 307°, yield 80%; ir: 1730 cm^{-1} (ester CO), 2900-3250 (chelated NH).

Anal. Calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.0; H, 4.4; N, 16.8; S, 12.8. Found: C, 52.5; H, 4.4; N, 17.2; S, 13.0

Reaction of 2-Amino-5-phenyl-1,3,4-thiadiazole (**3**) with Benzoyl Isothiocyanate.

To an acetone solution of benzoyl isothiocyanate (prepared from ammonium thiocyanate (0.1 mole) and the appropriate quantity of benzoyl chloride in 100 ml. of acetone as has been previously described), 0.1 mole of compound **3** was added. The reaction mixture was refluxed for 8 hours and then left to cool. The solid product, separated, was collected by filtration and washed well with water to yield 62% of **15**. Evaporation of the filtrate afforded a solid product which was also collected by trituration with water and crystallised from ethanol to afford 20% of compound **16**.

Compound **15** formed colourless crystals, m.p. 230°, yield 62%; ir: 1700 cm^{-1} (CO group).

Anal. Calcd. for $C_{15}H_{11}N_3OS$: C, 64.0; H, 3.9; N, 14.9; S, 11.4. Found: C, 64.2; H, 4.0; N, 14.7; S, 11.4.

Compound **16** formed pale yellow crystals, m.p. 227°, yield 20%.

Anal. Calcd. for $C_{16}H_{12}N_4OS_2$: C, 56.4; H, 3.5; N, 16.4; S, 18.8. Found: C, 56.2; H, 3.6; N, 16.7; S, 19.0.

Reaction of Compound **3** with Benzoyl Chloride and with Ethyl Chloroformate.

A solution of compound **3** (0.1 mole) in pyridine (100 ml.) was treated with an equimolecular amount of either ethyl chloroformate or benzoyl isothiocyanate. After refluxing the reaction mixture for 10 hours, the solvent was removed *in vacuo*. The remaining products were triturated with water, collected by filtration and crystallised from ethanol. The reaction products were identified as compounds **14** and **15**, respectively. Identification was carried out by m.p. and mixed m.p. determinations.

Acknowledgement.

The authors are deeply indebted to Prof. K. Undeheim and Dr. M. Gacek for discussions and for the Royal Norwegian Council for Scientific and Industrial Research for partial support of this work.

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