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# Reactions of selected 3-bromoisothiazole-5-carbonitriles with the secondary dialkylamines pyrrolidine and morpholine

Andreas S. Kalogirou, Panayiotis A. Koutentis *

*Department of Chemistry, University of Cyprus, P.O. Box 20537, 1678 Nicosia, Cyprus*

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Dedicated to the memory of Professor Sandy McKillop who sadly passed away on 20th Aug. 2013

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ABSTRACT

Readily available 3-bromoisothiazole-5-carbonitriles bearing various C-4 substituents [H, $CO_2R$ C≡N and halogen (Cl or Br)], react with either pyrrolidine or morpholine to give, in most cases, the 3-amino-substituted derivatives in high yields. The reaction of 3-bromoisothiazole-4,5-dicarbonitrile, however, varied with the nucleophilicity of the dialkylamine: pyrrolidine led to cleavage of the isothiazole ring to give 2-[di(pyrrolidin-1-yl)methylene]malononitrile while morpholine led to the expected 3-(morpholin-4-yl)isothiazole-4,5-dicarbonitrile. By comparison, 3-chloroisothiazole-4,5-dicarbonitrile reacted with pyrrolidine to give surprisingly, 3-chloro-5-(pyrrolidin-1-yl)isothiazole-4-carbonitrile as the major product, while with morpholine the major product was the expected 3-(morpholin-4-yl)isothiazole-4,5-dicarbonitrile. The mechanisms of the transformations are discussed, together with rationalization for the formation of side products. Furthermore, the hydrolytic decarboxylation of methyl and ethyl esters of 3-dialkylaminoisothiazoles using both conventional heating and microwave irradiation is reported.



## 1. Introduction

Isothiazoles (1,2-thiazoles) are isomers of the more commonly known thiazoles and their synthesis, chemistry, and applications have been extensively reviewed.[1] Unlike thiazoles, which are prevalent in nature, there are only a few isothiazole-containing natural products; e.g., the phytotoxins brassilexin[2] and sinalexin,[3] the prostaglandin release inhibitor pronqodine A,[4] and the cytotoxin aulosirazole.[5] Nevertheless, many isothiazoles exhibit useful biological properties that find uses in either medicinal (e.g., anticancer,[6] cathepsin C inhibitors,[7] antirhinoviral and enteroviral activity,[8] and mitostatic behavior[9]) or agrochemical (e.g., as insecticides, fungicides, and acaricides)[10] sciences. Other isothiazoles have industrial applications, e.g., as corrosion inhibitors,[11] dyes,[12] and wood preservatives.[13] Important commercial isothiazoles include the antibacterial drug Sulfasomizole,[14] the artificial sweetener Saccharin,[15] the novel fungicide Isotianil (Stout®),[10c] and methylchloroisothiazolone (MCIT) a major component of the Kathon preservatives with antibacterial and antifungal effects (Fig. 1). The antipsychotic pharmaceutical drugs ziprasidone[16] and perospirone[17] also contain a benzoisothiazole moiety. Isothiazoles are also useful synthetic intermediates (e.g., Woodward's synthesis of colchicine).[18]

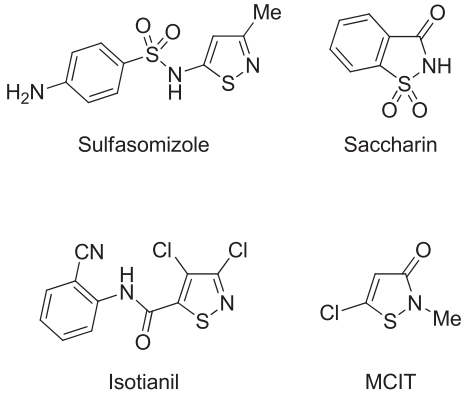


**Fig. 1.** Selected important commercial isothiazoles.

A group of important isothiazole scaffolds are haloisothiazole-carbonitriles.[19] In particular, 3,5-dichloroisothiazole-5-carbonitrile (**1**),[19d] is a versatile scaffold for a wide range of (het)aryl substituted derivatives[19f,g,20] and its derivatives have applications

* Corresponding author. E-mail address: koutenti@ucy.ac.cy (P.A. Koutentis).

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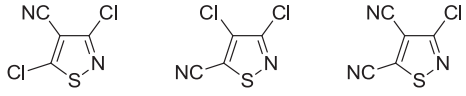
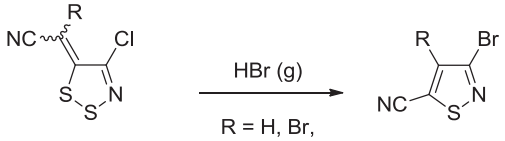
as fungicides,[10c] insecticides,[21] herbicides,[22] and cathepsin C inhibitors.[7] Moreover 3,4-dichloroisothiazole-5-carbonitrile (**2**),[19h] is a precursor to various isothiazole herbicides including the rice blast fungicide Isotianil,[10c] while 3-chloroisothiazole-4,5-dicarbonitrile (**3**)[19a] is also a precursor to various potent biocides.[23]



**1** **2** **3**

Several routes to isothiazolecarbonitriles have been reported.[19d,h,i,24] Recently, we described the efficient conversion of (4-chloro-5*H*-1,2,3-dithiazolylidene)acetonitriles **4** into 3-bromoisothiazole-5-carbonitriles **5** on treatment with gaseous HBr[19a,b,25] (Scheme 1).




**4** **5**

**Scheme 1.** Route to 3-bromoisothiazole-5-carbonitriles **5** via (dithiazolylidene)acetonitriles **4**.

Since we had a number of 3-bromoisothiazole-5-carbonitriles available, we compared their reactivity towards the cyclic secondary amines pyrrolidine and morpholine. The results of our study are described herein.

## 2. Results and discussion

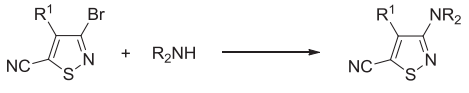
### 2.1. Reactions of isothiazoles with cyclic secondary amines

To the best of our knowledge, the only reported examples of nucleophilic aromatic substitution on 3-haloisothiazole-5-carbonitriles are the reactions of 3-chloro- or 3-bromoisothiazole-4,5-dicarbonitriles **3** and **5e** with morpholine to afford 3-(morpholin-4-yl)isothiazole-4,5-dicarbonitrile (**6i**).[19a,b] Having developed synthetic routes to the 3-bromoisothiazole-5-carbonitriles **5a**–**e**, we investigated their reactions with the cyclic secondary amine morpholine and the more nucleophilic pyrrolidine (Table 1).

The reactions of morpholine or pyrrolidine (2 and 8 equiv) with 4-unsubstituted 3-bromoisothiazole-5-carbonitrile (**5a**) gave complex reaction mixtures containing only traces of the expected 3-(morpholin-4-yl)- and 3-(pyrrolidin-1-yl)isothiazole-5-carbonitriles **6a** and **6b**, respectively, and some elemental sulfur (by TLC) that supported cleavage of the isothiazole ring. Worthy of note was that highly electrophilic isothiazoles bearing leaving groups at C-3 were known to suffer ring opening via nucleophilic attack at either C-5 or at S-1,[19f,26] however, in this case we were unable to isolate any carbon containing products originating from cleavage of the isothiazole. By comparison with the remaining isothiazoles, the 4-unsubstituted 3-bromoisothiazole-5-carbonitrile (**5a**) was the least reactive toward nucleophilic aromatic substitution.

3,4-Dibromoisothiazole-5-carbonitrile (**5b**) treated with either morpholine or pyrrolidine underwent regioselective nucleophilic substitution at C-3 to give the 3-(morpholin-4-yl)- and 3-(pyrrolidin-1-yl)-4-bromoisothiazole-5-carbonitriles **6c** and **6d** in yields as high as 70% (entry 5) and 55% (entry 7), respectively, depending on the equivalents of amine used. However, the reaction of the dibromoisothiazole **5b** with 2 equiv of morpholine at ca. 110 °C

**Table 1**
Reaction of 3-bromoisothiazole-5-carbonitriles **5a**–**e** with either morpholine or pyrrolidine in PhMe heated at reflux



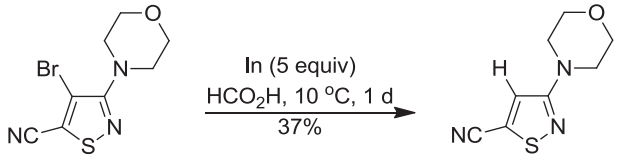
**5** **6**

| Entries | **5** ($R^1$) | $R_2NH$ (equiv) | Time (h) | Yields **6** (%) |
|---|---|---|---|---|
| 1 | **5a** (H) | Morpholine (2) | 48 | [a] |
| 2 | **5a** (H) | Morpholine (8) | 1 | **6a** (11) |
| 3 | **5a** (H) | Pyrrolidine (2) | 0.75 | **6b**[a] |
| 4 | **5b** (Br) | Morpholine (2) | 48 | [a] |
| 5 | **5b** (Br) | Morpholine (8) | 24 | **6c**(70) |
| 6 | **5b** (Br) | Morpholine (16) | 3 | **6c** (67) |
| 7 | **5b** (Br) | Pyrrolidine (2) | 2 | **6d** (55) |
| 8 | **5b** (Br) | Pyrrolidine (8) | 0.5 | **6d** (54) |
| 9 | **5c** ($CO_2Me$) | Morpholine (2) | 24 | **6e** (98) |
| 10 | **5c** ($CO_2Me$) | Morpholine (2) | 0.5[b] | **6e** (89) |
| 11 | **5c** ($CO_2Me$) | Morpholine (8) | 1 | **6e** (99) |
| 12 | **5c** ($CO_2Me$) | Pyrrolidine (2) | 0.17 | **6f** (86) |
| 13 | **5d** ($CO_2Et$) | Morpholine (2) | 14 | **6g** (99) |
| 14 | **5d** ($CO_2Et$) | Pyrrolidine (2) | 0.08 | **6h** (92) |
| 15 | **5e** (CN) | Morpholine (2) | 30 | **6i** (59) |
| 16 | **5e** (CN) | Morpholine (8) | 1.5 | **6i** (81) |
| 17 | **5e** (CN) | Pyrrolidine (2) | 1.5 | **6j** (11)[c] |

[a] Complicated mixture, trace of **6**.
[b] Microwave, 150 °C, 60 PSI, 250 W.
[c] Colorless product also observed (see Table 2).

failed to go to completion even after 2 days, while increasing the equivalents of morpholine to 8 and 16 led to significant reductions in reaction time (24 and 3 h, respectively) and gave the expected 4-bromo-3-(morpholin-4-yl)isothiazole-5-carbonitrile (**6c**) in 67–70% yields (entries 5 and 6). No trace of other products was seen in the reaction mixture, and attempts to reduce the reaction time by using microwave irradiation (150 °C, 60 PSI, 250 W) gave mainly degradation when either 2 or 8 equiv of amine were used.

The C-3 regioselectivity of the nucleophilic substitution reaction was confirmed by protodehalogenating 4-bromo-3-(morpholin-4-yl)isothiazole-5-carbonitrile (**6c**) using In powder (5 equiv) in $HCO_2H$ at ca. 10 °C[19f] to give 3-(morpholin-4-yl)isothiazole-5-carbonitrile (**6a**) in 37% yield (Scheme 2). Protodebromination using Zn powder (5 equiv) in $HCO_2H$ at ca. 10 °C[19f] for 1 day was too aggressive and gave lower yields (23%). Additional efforts to protodebrominate via a palladium catalyzed silane-mediated protodehalogenation using polymethylhydrosiloxane (5 equiv), $Pd(Ph_3P)_2Cl_2$ (5 mol %), and $Et_3N$ (2 equiv) in dioxane at ca. 100 °C,[27] or via hydrogenation with Pd/C (10 mol %) in EtOH at ca. 20 °C under 44 PSI of $H_2$(g) gave mainly recovered starting material, while an attempted lithium/halogen exchange with *n*-BuLi (−78 °C, THF) followed by quenching with MeOH led to degradation of the starting material.




**6c** **6a**

**Scheme 2.** Protodebromination of 4-bromoisothiazole **6c**.

During protodehalogenation with either In or Zn powder, the formation of hydrogen sulfide was detected (Dräger detector), which indicated reductive cleavage of the isothiazole ring and