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Synthesis of 3-Bromo-4-phenylisothiazole-5-carboxylic Acid and 3-Bromoisothiazole-5-carboxylic Acid

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Abstract: Reactions of 3-bromo-4-phenylisothiazole-5-carboxamide and 3-bromoisothiazole-5-carboxamide with $NaNO_2$ (4 equiv.), in TFA, at *ca.* 0 °C gave the carboxylic acid products in 99% and 95% yields, respectively. The two compounds were fully characterized.

Keywords: heterocycle; isothiazole; carboxylic acid

1. Introduction

Isothiazoles are useful compounds owing to their wide biological activity, industrial applications, and their use as synthetic intermediates [1,2]. An example of a biologically useful isothiazole is the antibacterial drug sulfasomizole, while other isothiazoles have been studied as anticancer agents [3], or showed acaricidal, insecticidal, and fungicidal activity [4,5]. Carboxylic acid substituted isothiazoles in particular have shown useful biological activity, such as the anti-HIV activity of 3-benzyloxyisothiazole-4/5-carboxylic acids **1** and **2** [6], hypolipidemic activity of phenoxy derivative **3** [7], and anti-inflammatory activity of carboxamide **4** [8] (Figure 1).

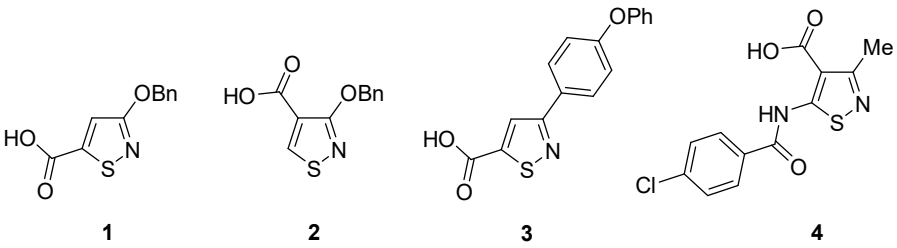

Figure 1. Biologically active isothiazole carboxylates.

Our interest in isothiazoles focuses on their formation from 1,2,3-dithiazole precursors **5** by treatment with gaseous HCl or HBr [9] (Scheme 1). We later investigated the CH arylation of both the 5 [10] and the 4 [11] positions to obtain arylisothiazole products. Since both of these investigations involved mainly cyano-substituted isothiazoles, we looked at the possibility of functional group modifications by performing their hydration reaction in the presence of conc. H_2SO_4. Carboxamide products **9** and **10** were isolated in high yields [11] (Scheme 1).

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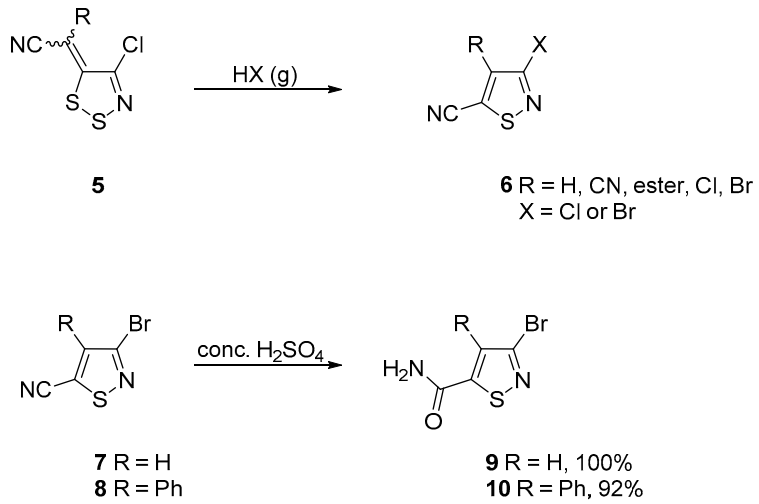
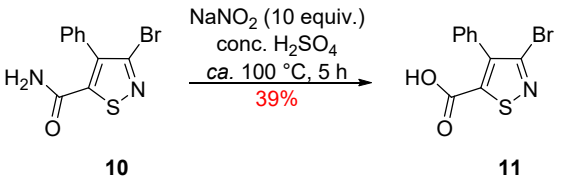


Scheme 1. Route to isothiazole-5-carbonitriles **6** from dithiazoles **5** and synthesis of isothiazole-5-carboxamides **9** and **10**.

As a continuation of the study on functional group modifications of these isothiazoles, we investigated the transformations of the carboxamide group to carboxylic acids. Similar transformations on isothiazole scaffolds were previously investigated by our team [12].

2. Results and Discussion

We started our investigation from 4-phenylisothiazole **10** by applying conditions used in the literature for a similar scaffold [12]. The reaction of 3-bromo-4-phenylisothiazole-5-carboxamide **10** with $NaNO_2$ (10 equiv.), in conc. H_2SO_4, at *ca*. 100 °C led to a complete consumption of the starting isothiazole and isolation of the desired compound **11** in 39% yield (Scheme 2), while no other products were observed by TLC.

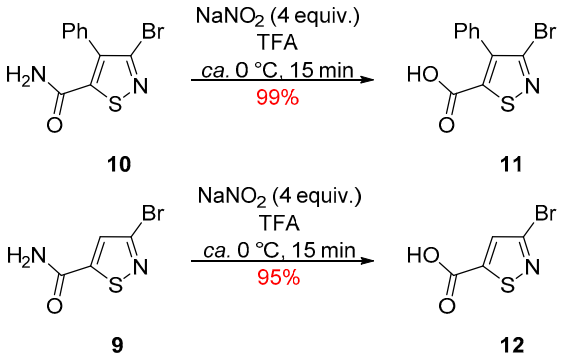


Scheme 2. Synthesis of 3-bromo-4-phenylisothiazole-5-carboxylic acid (**11**).

Product **11** was isolated as colorless needles, mp 180–182 °C (from PhH). UV-vis spectroscopy in dichloromethane supported an intact isothiazole ring (λ_{max} 298 nm, log ε 3.89). Mass spectrometry revealed a molecular ion (M^+-H) peak of *m*/*z* 282 (87%) along with a M^+-H^++2 isotope peak at 284 (100%) that supported the presence of one bromine, while FTIR spectroscopy showed the presence of a broad carboxylic acid ν(O-H) stretch at 2926 cm^{-1} along with a strong ν(C=O) stretch at 1736 cm^{-1} compared to the 1672 cm^{-1} frequency of the amide carbonyl in the starting material **10** [11]. ^{13}C NMR spectroscopy showed the presence of three aromatic CH resonances and five quaternary carbon resonances, with a downfield shift in the resonance of the carbonyl carbon from 160.7 ppm in the starting amide to 163.1 ppm for the carboxylic acid (see Supplementary materials for NMR spectra). Moreover, a correct elemental analysis (CHN) was obtained for the molecular formula $C_{10}H_6BrNO_2S$.

In an attempt to improve the yield of carboxylic acid **11**, we investigated a milder set of conditions that avoided the use of conc. H_2SO_4 as the solvent and required fewer equivalents of $NaNO_2$ and a lower temperature [13]. The reaction of 4-phenylisothiazole **10** with $NaNO_2$ (4 equiv.), in TFA, at *ca*. 0 °C led to a fast consumption of the starting isothiazole and isolation of the desired compound **11** in an excellent 99% yield (Scheme 3).

The same reaction conditions were also applied to the reaction of 3-bromoisothiazole-5-carboxamide (**9**), which gave the desired carboxylic acid **12** in an excellent 95% yield (Scheme 3). Compound **12** has a PubChem number and is commercially available but no synthesis or data are reported on it.



Scheme 3. Synthesis of 3-bromo-4-phenylisothiazole-5-carboxylic acid (**11**) and 3-bromoisothiazole-5-carboxylic acid (**12**).

Product **12** was isolated as colorless plates, mp 139–141 °C (from *c*-hexane). UV-vis spectroscopy in dichloromethane supported an intact isothiazole ring (λ_{max} 284 nm, log ε 3.37). Mass spectrometry revealed a molecular ion (MH^+) peak of *m/z* 208 (97%) along with a MH^++2 isotope peak at 210 (100%) that supported the presence of one bromine, while IR spectroscopy showed the presence of a broad carboxylic acid ν(O-H) stretch at 2874–2515 cm^{-1} along with strong ν(C=O) stretches at 1719 cm^{-1} compared to the 1674 cm^{-1} frequency of the amide carbonyl in the starting material **9** [11]. ^{13}C NMR spectroscopy showed the presence of one CH resonance and three quaternary carbon resonances (see Supplementary materials for NMR spectra), while a correct elemental analysis (CHN) was obtained for the molecular formula $C_4H_2BrNO_2S$.

Both isothiazole products **11** and **12** are multifunctional and potentially useful scaffolds for the synthesis of isothiazole derivatives.

3. Materials and Methods

The reaction mixture was monitored by TLC using commercial glass-backed thin layer chromatography (TLC) plates (Merck Kieselgel 60 F_{254}). The plates were observed under a UV light at 254 and 365 nm. The melting point was determined using a PolyTherm-A, Wagner & Munz, Kofler—Hotstage Microscope apparatus (Wagner & Munz, Munich, Germany). The solvent used for recrystallization is indicated after the melting point. The UV-vis spectrum was obtained using a PerkinElmer Lambda-25 UV-vis spectrophotometer (PerkinElmer, Waltham, MA, USA) and inflections are identified by the abbreviation "inf". The IR spectrum was recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer (Shimadzu, Kyoto, Japan) with a Pike Miracle Ge ATR accessory (Pike Miracle, Madison, WI, USA) and strong, medium and weak peaks are represented by s, m and w, respectively. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 machine [at 500 and 125 MHz, respectively, (Bruker, Billerica, MA, USA)]. Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. Attached proton test (APT) NMR studies were used for the assignment of the ^{13}C peaks as CH_3, CH_2, CH and Cq (quaternary). MALDI-TOF mass spectra were recorded on a Bruker Autoflex III Smartbeam instrument. 3-Bromoisothiazole-5-carboxamide (**9**) and 3-bromo-4-phenylisothiazole-5-carboxamide (**10**) were prepared according to the literature procedure [11].

*3.1. 3-Bromo-4-phenylisothiazole-5-carboxylic Acid (***11***)*

To a stirred suspension of 3-bromo-4-phenylisothiazole-5-carboxamide (**10**) (56.6 mg, 0.20 mmol) in TFA (0.5 mL) cooled to *ca*. 0 °C was added $NaNO_2$ (55.2 mg, 0.80 mmol) and the reaction mixture was stirred at this temperature until the consumption of the starting material (TLC, 15 min). The mixture was then poured onto water (5 mL) and extracted with *t*-BuOMe (3 × 10 mL), dried over Na_2SO_4 and evaporated to give the *title compound* **11** (56.2 mg, 99%) as colorless needles, mp 180–182 °C (from PhH); R_f 0.24 (*t*-BuOMe); (found: C, 42.21; H, 2.08; N, 4.93. $C_{10}H_6BrNO_2S$ requires C, 42.27; H, 2.13; N, 4.93%); λ_{max}(DCM)/nm 298 (log ε 3.89); v_{max}/cm^{-1} 2926 br (CO_2H), 1736 s (C=O), 1530 w, 1485 w, 1443 w, 1393 m, 1348 w, 1329 w, 1213 s, 1179 m, 1153 m, 1088 w, 1074 w, 1034 w, 920 m, 887 w, 853 m, 799 m, 750 m; δ_H (500 MHz; $CDCl_3$) 8.81 (1H, br s, CO_2H), 7.49–7.43 (3H, m, Ar C*H*), 7.37–7.32 (2H, m, Ar C*H*); δ_C(125 MHz; $CDCl_3$) 163.1 (*C*q), 151.2 (*C*q), 143.3 (*C*q), 141.4 (*C*q), 131.0 (*C*q), 129.8 (*C*H), 129.2 (*C*H), 128.2 (*C*H); *m/z* (MALDI-TOF) 284 (^{81}Br-M^+–H, 100%), 282 (^{79}Br-M^+–H, 87), 271 (89), 264 (10).

*3.2. 3-Bromoisothiazole-5-carboxylic Acid (***12***)*

To a stirred suspension of 3-bromoisothiazole-5-carboxamide (**9**) (41.4 mg, 0.20 mmol), in TFA, (0.5 mL) cooled to *ca*. 0 °C was added $NaNO_2$ (55.2 mg, 0.80 mmol) and the reaction mixture was stirred at this temperature until the consumption of the starting material (TLC, 15 min). The mixture was then poured onto water (5 mL) and extracted with *t*-BuOMe (3 × 10 mL), dried over Na_2SO_4 and evaporated to give the *title compound* **12** (39.6 mg, 95%) as colorless plates, mp 139–141 °C (from *c*-hexane); R_f 0.20 (*t*-BuOMe); (found: C, 22.75; H, 0.96; N, 7.08. $C_4H_2BrNO_2S$ requires C, 23.09; H, 0.97; N, 6.73%); λ_{max}(DCM)/nm 284 (log ε 3.37); v_{max}/cm^{-1} 3094 w (aryl C-H), 2874 w, 2754 w, 2706 w, 2567 w and 2515 w (CO_2H), 1719s (C=O), 1653 w, 1558 w, 1512 m, 1420 w, 1364 m, 1315 s, 1260 m, 1240 m, 1215 s, 1140 m, 1067 w, 893 s, 878 m, 820 m, 752 s; δ_H (500 MHz; $CDCl_3$+DMSO-d_6) 7.52 (1H, s, Ar C*H*), 6.65 (1H, br. s, CO_2H); δ_C (125 MHz; $CDCl_3$+DMSO-d_6) 160.3 (*C*q), 160.1 (*C*q), 137.0 (*C*q), 129.5 (*C*H); *m/z* (MALDI-TOF) 210 (^{81}Br-M^++H, 100%), 208 (^{79}Br-M^++H, 97).

Supplementary Materials: The following supporting information can be downloaded at: mol file, ^{1}H and ^{13}C NMR and IR spectra.

Author Contributions: A.S.K. and P.A.K. conceived the experiments; A.S.K. designed the experiments; A.S.K. wrote the paper; A.S.K. and P.A.K. edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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