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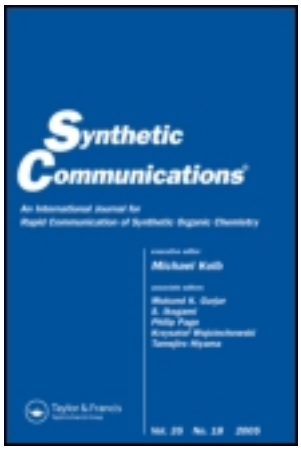

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Convenient One-Pot Synthesis of N,N′-bis(2-Mercaptophenyl)pyridine-2,6-dicarboxamide and N-2-Mercaptophenyl-2′-pyridinecarboxamide Without Protection of the Thiol Group(s)

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Convenient One-Pot Synthesis of *N*,*N*′-*bis*(2-Mercaptophenyl)pyridine-2,6-dicarboxamide and *N*-2-Mercaptophenyl-2′-pyridinecarboxamide Without Protection of the Thiol Group(s)

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ABSTRACT

A rapid and convenient procedure for the synthesis of *N*,*N*′-*bis*(2-mercaptophenyl)pyridine-2,6-dicarboxamide and *N*-2-mercaptophenyl-2′-pyridinecarboxamide from 2-aminothiophenol and the appropriate acid chloride is reported. The method is compatible only with aromatic acid chlorides containing a heteroatom. Aromatic acid chlorides with no heteroatom yield the corresponding 2-substituted benzothiazoles.

Key Words: Carboxamido nitrogen; Thiol; Benzothiazole.

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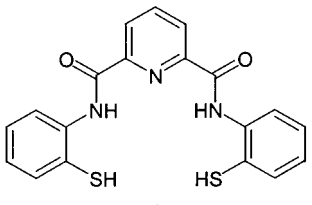
Heterocyclic molecules containing both nitrogen and sulfur atoms are of general interest in synthetic chemistry due to their presence in pharmacologically active compounds,[1] industrial polymers,[2] and enzyme active sites.[3] During the past several years, we and others have directed considerable effort toward the design and synthesis of *N*,*S*-ligands to model the metal-binding domain of the metalloenzyme nitrile hydratase (NHase).[4] NHase is involved in the assimilation of organic nitriles by various microorganisms and catalyzes the hydrolysis of a variety of nitriles into the corresponding amides. The enzyme contains either a low-spin Fe(III) or Co(III) center at its active site which is coordinated to two deprotonated carboxamido nitrogens from the protein backbone and three cysteine sulfur centers. Two of the three cysteine sulfurs are modified to a sulfenic and a sulfinic acid group. This unprecedented coordination sphere around the metal center is thought to play a crucial role in the catalytic activity of the NHases and is of prime interest in our laboratory.

Syntheses of *N*,*S*-ligands required in our modeling work often face difficulties due to the reactivity of the thiol group. In the conventional syntheses of amides from carboxylic acids (or derivatives thereof) and primary or secondary amines, the thiol group must be protected in order to prevent side reactions that interfere with the formation of the amide bond. To date, various techniques including the use of benzyl or triphenylmethyl (trityl) protecting groups and formation of disulfide have been employed.[5] Despite their wide use and success, such protection/deprotection steps do suffer from some drawbacks namely, an increase in the number of steps needed in the total synthesis, decrease in overall yield, and the need for using harsh conditions to remove the protecting groups. In order to generate a faster and milder route to compounds with carboxamide and thiol groups, we report herein an efficient one-pot synthesis of such compounds that does not require S-protecting group(s).

As part of our work in the area of modeling NHases, we have recently reported the synthesis of a *N*,*S*-ligand *N*,*N*′-*bis*(2-mercaptophenyl)pyridine-2,6-dicarboxamide ($PyPSH_4$, **1**).[4a] The reported synthesis of this ligand involves the following steps.



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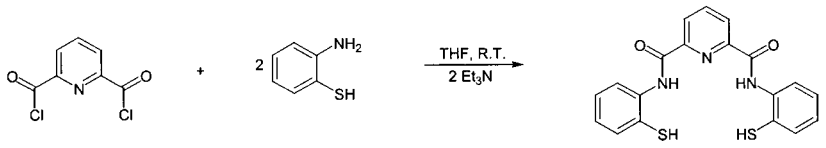
2-Aminothiophenol is first protected with triphenylmethanol in TFA. The S-protected 2-aminothiophenol is then mixed with 2,6-pyridinedicarbonyl dichloride in $CHCl_3$ and Et_3N to yield the S-protected amide compound. Finally, the *S*-trityl groups are cleaved in neat TFA with Et_3SiH to yield $PyPSH_4$ (**1**). Although these reactions are clean and finally afford **1** in high yield, the use of TFA and the amount of time needed to acquire reasonable amounts of **1** prompted us to look for an alternative synthetic route. In the present work, we have synthesized **1** under mild conditions in a one-pot reaction. The reaction involves mixing 2-aminothiophenol and 2,6-pyridinedicarbonyl dichloride in THF at room temperature followed by addition of Et_3N (Sch. 1).

The use of non-protected aminothiols for amide bond formation with retention of the thiol group is not a new concept. The synthesis of high molecular weight protein molecules through native chemical ligation developed by Kent and coworkers utilizes similar chemistry.[6] Here, two peptide fragments are joined together by reaction of the unprotected N-terminal cysteine end of one fragment with the thioether end of the other fragment resulting in a thioether linked intermediate. Rapid intramolecular rearrangement finally results in the formation of an amide bond and a cysteine thiol group. We propose a similar mechanism for the formation of our ligand **1**. The initial nucleophilic attack on the carbonyl carbon by sulfur generates a thioether intermediate with protonated amine group. Addition of Et_3N produces the free amine. Nucleophilic attack by the amine on the carbonyl carbon (intramolecular *S,N*-acyl rearrangement) finally results in formation of **1** with carboxamide and thiol groups (Sch. 2). The reaction is notably clean and **1** is the only product isolated in 91% yield.

To explore the generality of this synthetic method, several other acid chlorides were used including 2-pyridinecarbonyl chloride, isophthaloyl dichloride, and benzoyl chloride (Sch. 3). Reaction of 2-aminothiophenol with 2-pyridinecarbonyl chloride under the conditions described above afforded the corresponding amide-thiol compound *N*-2-mercaptophenyl-2′-pyridinecarboxamide ($PyPepSH_2$, **2**). Interestingly, the remaining two acid chlorides produced the 2-arylbenzothiazole species **3** and **4** (Sch. 3).



Scheme 1.

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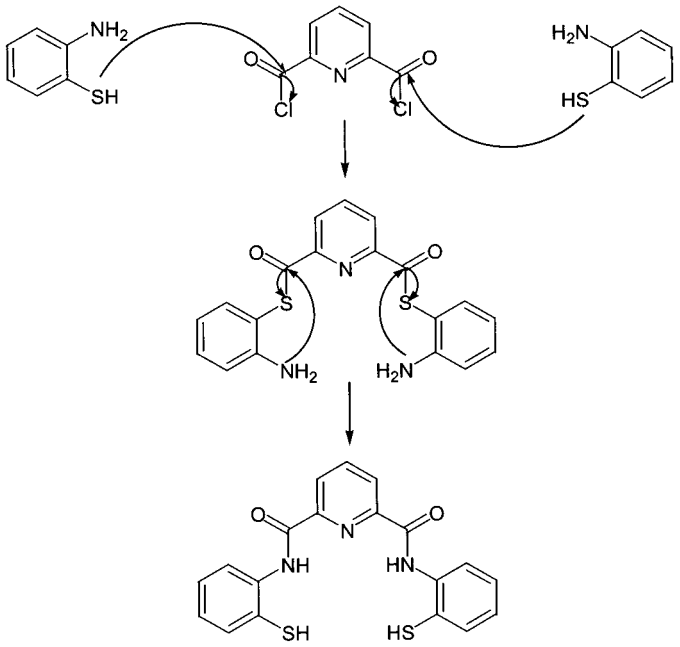
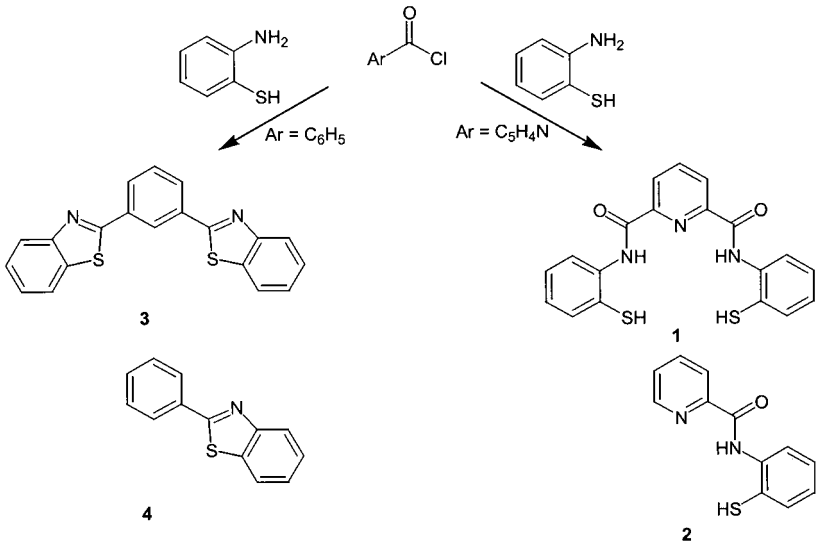


Scheme 2.



Scheme 3.

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Reaction of acyl chlorides (and other derivatives) with 2-aminothiophenol is known to afford substituted 2-arylbenzothiazoles and the reaction has been used widely to synthesize benzothiazoles with pharmacological activities.[7] Our results now show that compounds with carboxamide and thiol groups (like **1** and **2**) are readily formed when acid chlorides contain a pyridine ring adjacent to the carbonyl carbon(s). We propose that the electron donating pyridine ring prevents the formation of the carbinolamine intermediate normally formed when carbonyl derivatives react with amines, which then undergoes dehydration to form the C=N bond in the thiazole ring. With 2-pyridinecarbonyl chloride and 2,6-pyridinedicarbonyl dichloride, the mechanism is the one noted in peptide ligation reactions developed by Kent and coworkers and hence compounds like **1** and **2** are formed instead of benzothiazoles.

In summary, a synthetic procedure has been reported for compounds with both carboxamide and thiol groups (like **1** and **2**). The reaction is clean, fast, and occurs under mild conditions without the need for any S-protecting group.

EXPERIMENTAL

All reactions were carried out under an N_2 atmosphere. THF was distilled from Na in the presence of sodium benzophenone ketyl. THF was degassed by the freeze-thaw technique. 2-pyridinecarbonyl chloride was synthesized by following a published procedure.[4b] 2-Aminothiophenol, 2,6-pyridinedicarbonyl dichloride, isophthaloyl dichloride, and benzoyl chloride were purchased from Aldrich and used without further purification. Both ^{1}H and ^{13}C NMR spectra were recorded on a Varian 500 MHz Unity Plus instrument. Infrared spectra were obtained with a Perkin-Elmer 1600 FTIR spectrophotometer.

General Procedure

To a solution of the aromatic acid chloride (2.6 mmol) in dry/degassed THF (25 mL) was added dropwise 2-aminothiophenol (2.6 mmol for mono-acid chlorides, 5.2 mmol for diacid chlorides) at room temperature. The mixture was allowed to stir at room temperature for 1 h, after which Et_3N (2.6 mmol for mono-acid chlorides, 5.2 mmol for diacid chlorides) was added. Following stirring for 24 h at room

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temperature, the reaction mixture was filtered to remove the insoluble triethylamine hydrochloride salt and the filtrate was evaporated in vacuo. The isolated oil was dissolved in $CHCl_3$/TFA (25 mL, 24/1) and washed with 10% aqueous $NaHCO_3$ (25 mL), then saturated aqueous NaCl (25 mL). The $CHCl_3$ layer was dried ($MgSO_4$), filtered, and the filtrate was evaporated to dryness. The residual oil (except **1** was a solid) was triturated with Et_2O (2×5 mL) to yield the solid compound.

***N,N′-bis*(2-mercaptophenyl)pyridine-2,6-dicarboxamide (1):** White solid (903 mg, 91%), IR (KBr, cm^{-1}): 3300 (N-H), 2525 (S-H), 1684 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm from TMS): 10.49 (s, 2H, amide NH, D_2O exchangeable), 8.53 (d, 2H, ArH), 8.36 (d, 2H, ArH), 8.19 (t, 1H, ArH), 7.56 (d, 2H, ArH), 7.36 (t, 2H, ArH), 7.12 (t, 2H, ArH), 3.39 (s, 2H, SH, D_2O exchangeable). All spectral data were identical to those reported.[4a]

***N*-2-Mercaptophenyl-2′-pyridinecarboxamide (2):** Light yellow solid (401 mg, 67%), IR (KBr, cm^{-1}): 3285 (N-H), 2511 (S-H), 1688 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm from TMS): 10.80 (s, 1H, amide NH, D_2O exchangeable), 8.68 (d, 1H, ArH), 8.52 (d, 1H, ArH), 8.29 (d, 1H, ArH), 7.91 (t, 1H, ArH), 7.52 (m, 2H, ArH), 7.36 (t, 1H, ArH), 7.06 (t, 1H, ArH), 3.28 (s, 1H, SH, D_2O exchangeable). All spectral data were identical to those reported.[4b]

Meta-*bis*(2-benzothiazolyl)benzene (3): Off-white solid (681 mg, 76%), m.p. 170–172°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm from TMS): 8.81 (s, 1H, ArH), 8.24 (d, 2H, ArH), 8.14 (d, 2H, ArH), 7.95 (d, 2H, ArH), 7.64 (t, 1H, ArH), 7.54 (t, 2H, ArH), 7.42 (t, 2H, ArH); ^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm from TMS): 167.1 (CN), 154.1 (ArC), 135.3 (ArC), 134.6 (ArC), 131.1 (ArC), 129.9 (ArC), 127.6 (ArC), 126.7 (ArC), 125.6 (ArC), 123.5 (ArC), 121.8 (ArC). IR (KBr, cm^{-1}): 1510, 1314, 960, 751, 719. Anal. calcd. for $C_{20}H_{12}N_2S_2$ (344.45): C, 69.74; H, 3.51; N, 8.13. Found: C, 69.23; H, 3.60; N, 8.19.

2-Phenylbenzothiazole (4): White solid, (450 mg, 82%), IR (KBr, cm^{-1}): 1477, 1308, 962, 759, 686. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm from TMS): 8.10 (m, 3H, ArH), 7.92 (d, 1H, ArH), 7.51 (m, 4H, ArH), 7.40 (t, 1H, ArH). All spectral data were identical to those reported.[8]

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