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An unexpected synthesis of 3,5-diaryl-1,2,4-thiadiazoles from thiobenzamides and methyl bromocyanoacetate

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ABSTRACT

Aryl thioamides undergo very rapid condensation in the presence of methyl bromocyanoacetate to provide quantitative yields of 3,5-diaryl-1,2,4-thiadiazoles with an easy work-up and a high degree of product purity. The method can be scaled up with no loss in efficiency.

Introduction

A number of methyl 2-aryl-4-methylthiazole-5-carboxylates **3** and their derivatives were previously prepared by the condensation of methyl α-chloroacetoacetate (**1**) with thiobenzamides **2** (Scheme 1).[1] In order to further study the potential of the arylthiazole class of compounds as antiviral agents, the preparation of methyl 4-amino-2-(4-chlorophenyl)thiazole-5-carboxylate (**6**) was attempted (Scheme 2).

Compound **6** was originally intended to be obtained by the condensation of methyl bromocyanoacetate (**4**) with thiobenzamide **2a** (Scheme 2). Compound **4**, prepared by bromination of the commercially available methyl cyanoacetate with *N*-bromosuccinimide (NBS), was allowed to react with thiobenzamide **2a**, but instead of the expected 4-amino-2-arylthiazole **6**, the diarylthiadiazole **5a** formed instantaneously and was isolated simply by filtration in a near quantitative yield. A mechanism for the expected conversion of **2a** and **4** into **6** is outlined in Scheme 3. The structure of **5a** was confirmed by the spectral data (see Supplementary data). To the best of our knowledge, this reaction has never been reported before. However, bromocyanoacetate **4**, together with other α-halocarbonyl compounds, has been reported as a mild oxidizing agent in the conversion of thiols into disufides.[2]

The goal of the present study was to determine the scope of the reaction of aryl thioamides **2** with methyl bromocyanoacetate (**4**) to determine if it could constitute a general method for the synthesis of 3,5-diaryl-1,2,4-thiadiazoles.

Results and discussion

First, to determine the solvent effects on the yield of compound **5a**, methyl bromocyanoacetate (**4**) was allowed to react with the thiobenzamide **2a** using different solvents (methanol, ethanol, dioxane, and dichloromethane). Thiadiazole **5a** was obtained without any significant differences in the reaction time or yield. Methanol was generally used as the solvent throughout this work as mentioned in the Supplementary data.

Next, a variety of commercially available aryl thioamides **2** were allowed to react with methyl bromocyanoacetate (**4**) at room temperature (Scheme 4). Among the 1,2,4-thiadiazoles reported in the chemical literature, the *ortho*-substituted derivatives have been more difficult to prepare and there are fewer examples of them.[3] Therefore, in this study more attention was given to the synthesis of products containing substituents in the ortho positions of the phenyl rings and six *ortho* substituted derivatives **5c**, **5d**, **5h**, **5i**, **5j** and **5k** were prepared. The reaction of *ortho*-substituted thiobenzamides **2c**, **2h**, **2i**, **2j**, and **2k** proceeded in quantitative yields; however, the *o*-trifluoromethyl derivative **5d** was obtained in a low yield (10%). Most of the other *meta*, *para*, and disubstituted thiobenzamide derivatives afforded the corresponding 1,2,4-thiadiazoles in essentially quantitative isolated yields of pure products regardless of differences in the electronic and steric

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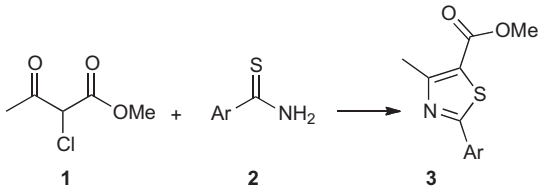
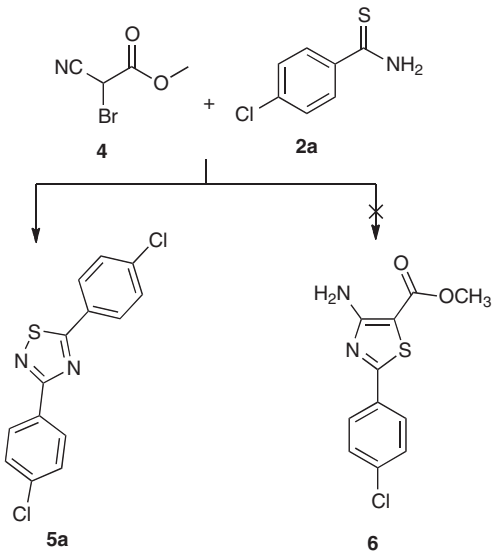
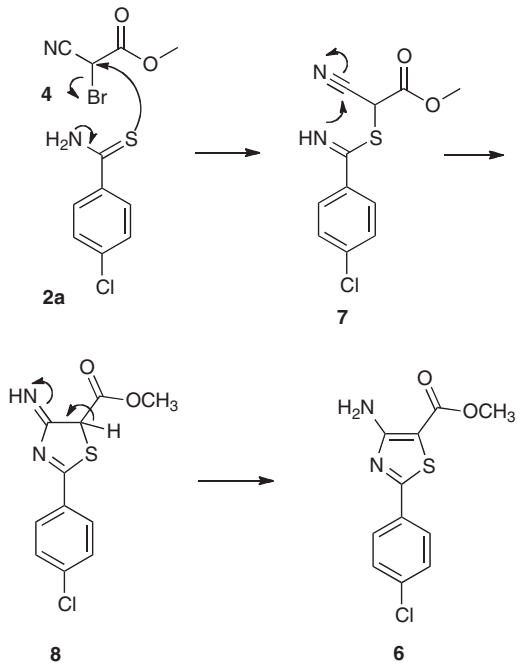


Scheme 1. Preparation of thiazoles.

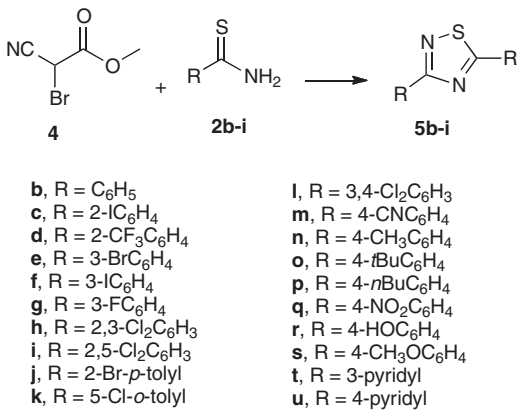


Scheme 2. Condensation of thiobenzamide **2a** with methyl bromocyanoacetate.



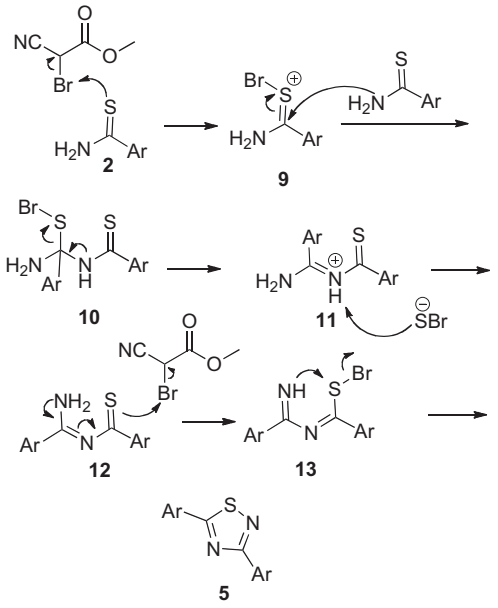
Scheme 3. Mechanism for expected formation of **6**.

properties of the substituent(s). The 3- and 4-pyridyl derivatives **5t** and **5u** were obtained in moderate yields (65–69%). However, the corresponding 2-pyridyl derivative could not be obtained in any yield and the starting materials decomposed under the reaction conditions. The condensation reaction to produce 3,



b, R = C_6H_5
c, R = 2-IC_6H_4
d, R = 2-$CF_3C_6H_4$
e, R = 3-BrC_6H_4
f, R = 3-IC_6H_4
g, R = 3-FC_6H_4
h, R = 2,3-$Cl_2C_6H_3$
i, R = 2,5-$Cl_2C_6H_3$
j, R = 2-Br-*p*-tolyl
k, R = 5-Cl-*o*-tolyl
l, R = 3,4-$Cl_2C_6H_3$
m, R = 4-CNC_6H_4
n, R = 4-$CH_3C_6H_4$
o, R = 4-*t*BuC_6H_4
p, R = 4-*n*BuC_6H_4
q, R = 4-$NO_2C_6H_4$
r, R = 4-HOC_6H_4
s, R = 4-$CH_3OC_6H_4$
t, R = 3-pyridyl
u, R = 4-pyridyl

Scheme 4. Condensation of aryl thioamides with methyl bromocyanoacetate.



Scheme 5. Mechanism for formation of **5**.

5-diaryl-1,2,4-thiadiazoles did not work when 2,6-disubstituted thiobenzamides were used. To date, there are no efficient methods reported for the synthesis of 3,5-bis(2,6-dichlorophenyl)-1,2,4-thiadiazole, although it has been obtained as a by-product from the reaction of thioamides with nitrous acid.[4] Moreover, oxidation of 2,6-dichlorothiobenzamide was reported to yield the corresponding isothiocyanate.[5] We are unaware of any efficient methods reported for the preparation of 3,5-di(2-pyridyl)-1,2,4-thiadiazole or any 3,5-[(2,6-disubstituted)aryl]-1,2,4-thiadiazole, including the presently reported method. Thioacetamide was tried as an example of an aliphatic thioamide and it was unsuccessful.

To investigate the applicability of this method for large-scale synthesis, four grams of thiobenzamides **2a** and **2g** was allowed to react with a slight excess (1.3 equiv) of methyl bromocyanoacetate (**4**). The reaction mixtures were stirred vigorously for 2–3 min to ensure the consumption of all of the starting materials, and the corresponding thiadiazoles **5a** and **5g** were isolated in a high degree of purity in 95% and 97% yields, respectively.

Several literature precedents suggest a mechanism for the condensation of two molecules of the aryl thioamides **2** to form 3,5-diaryl-1,2,4-thiodiazoles **5** in the presence of **4** (Scheme 5). The question of S–Br versus S–C bond formation resulting from

the reaction of thiols with α-bromo esters has been studied before, with S–Br bond formation being documented in cases in which the anion is more highly resonance stabilized (e.g., diethyl bromomalonate).[2] This suggests the initial bromination of the sulfur of the thioamide with methyl bromocyanoacetate to form the intermediate **9**. Treatment of thioamides with alkylating agents that form stable carbocations was reported to afford the more thermodynamically stable *N*-alkylated product instead of the less stable *S*-analogue.[6] Therefore, the formation of intermediate **10** from the stable carbocation **9** is suggested. Elimination of HSBr will afford aminoarylmethylenethioamide **12**. Oxidation of the sulfur of thioamides is reported to facilitate N–S bond formation,[7] which, in this case, could be achieved by a second bromocyanoacetate molecule. Therefore, S-bromination of **12** followed by tautomerization and elimination of HBr would provide diarylthiadiazole **5**. The reaction stoichiometry supports this mechanism. When thiobenzamide **2a** was allowed to react with 0.5 M equiv of **4**, the thiadiazole product **5a** was obtained in about 50% yield and approximately 50% of the thiobenzamide starting material was left unchanged in the reaction mixture as estimated by the NMR. Using of 1.2 equiv of **4** results in complete conversion of the thiobenzamides **2** to the final products.

The reported methods for the preparation of 3,5-diaryl-1,2,4-thiadiazoles from the corresponding thioamides include using different oxidants such as hypervalent iodine,[3] dimethyl sulfoxide (DMSO)/2-chloro-1,3-dimethylimidazolinium chloride (DMC),[8] DMSO/haloiminium salt,[9] DMSO/HCl,[7] methanesulfonic acid derivative with benzenetellurinic acid,[10] and telluroxide or selenoxide.[11] Other more complicated methods are also reported: from the corresponding oxathiazolone,[12] benzenecarboximidamide and diethyl azodicarboxylate,[13] or from 1,2,4-oxathiazoles and Lewis acid.[14] The thermal cycloreversion of 6*H*-1,3,5-oxathiazine *S*-oxides followed by ring closure of the resulting intermediates is also reported to yield 1,2,4-thiadiazoles.[15] More recently, Khosropour and Noei described the preparation of 1,2,4-thiadiazoles using 2,4,6-trichloro-1,3,5-triazine, DMSO and polyethylene glycol 400.[16] Many of the reported methods that provide high yields (>80%) require specific alkaline or acidic reagents that might be incompatible with some sensitive groups, tedious work up and longer reaction times than the presently reported method, or cannot be applied for larger-scale reactions.

Conclusion

In conclusion, a new and an efficient method for the synthesis of the 3,5-diaryl-1,2,4-thiadiazole system was investigated using methyl bromocyanoacetate (**4**), which can be prepared easily in one step. This method was found to be applicable with sensitive groups such as the hydroxyl group, ortho derivatives, and on gram-scale reactions with easy work-up, high yield, very short reaction times, and a very high degree of product purity. These features compare favorably with many of the other methods of 3,5-diaryl-1,2,4-thiadiazoles synthesis.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.068.

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