One-Pot Multicomponent Domino Synthesis of 4-Aminothiazole-2(3H)-thiones

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Abstract A new multicomponent domino reaction has been developed for the synthesis of 4-aminothiazole-2(3H)-thiones. Carbon disulfide was successfully used in the preparation of 4-aminothiazole-2(3H)-thione derivatives through reaction with primary amines and 2-bromo-2-arylacetonitriles in the presence of sodium carbonate and a catalytic amount of sodium iodide.

Key words amines, catalysis, heterocycles, multicomponent reactions, domino reactions, cyclizations

Multicomponent reactions and domino reactions are among the most effective and straightforward methods for the diversity-oriented synthesis of heterocycles.^{1–8} The use of multicomponent domino reactions is effective in reducing amounts of chemical waste produced, with shorter reaction times, higher overall yields, and clean syntheses compared with multistep syntheses.

Thiazole-2(3H)-thione and its derivatives are important building blocks in various pharmaceutical and biologically active compounds.⁹ Several synthetic methodologies are available for the synthesis of the thiazole-2(3H)-thione skeleton.¹⁰ One general method for preparing thiazole-2(3H)-thiones involves the reaction of chloroacetaldehyde,¹¹ chloroacetone,¹² or phenacyl bromide¹² with ammonium dithiocarbamate. The reaction of *cis*- or *trans*-2,3-dialkylaziridines with carbon disulfide has also been successfully used to synthesize thiazole-2(3H)-thiones.¹³ Thiazole-2(3H)-thiones have also been prepared by the reaction triethylammonium salts of dithiocarbamates with 2-(4-nitrophenyl)oxirane followed by dehydrogenation of the thiazolidine ring.¹⁴ However, all these methods suffer from drawbacks such as extended reaction times, low yields, the use of toxic solvents or reagents, requirements for excess reagents or catalysts, difficult workup proce-

dures, or harsh reaction conditions. We therefore wished to develop a convenient, one-pot, practical method for the preparation of fully substituted 4-aminothiazole-2(3H)-thiones.

As part of our ongoing studies on the construction of sulfur-containing heterocycles,^{15–17} we report a novel one-pot, three-component, domino synthesis of 4-aminothiazole-2(3H)-thiones by the reaction of carbon disulfide with a primary aliphatic amine and an aryl(bromo)acetonitrile in the presence of sodium carbonate and a catalytic amount of sodium iodide in ethanol (Scheme 1).

Scheme 1

At the outset of our studies, we chose benzylamine (**1a**) as a substrate, and we treated it with bromo(phenyl)acetonitrile (**2a**) and carbon disulfide in the presence of sodium carbonate and a catalytic amount of sodium iodide in ethanol. As shown in Table 1, sodium iodide has a vital role in the reaction, and only a very small yield of product **3a** (10%) was obtained in its absence (Table 1, entry 1). The yield increased dramatically when a catalytic amount of sodium iodide was added to the mixture (entries 2 and 3). However, the yield fell on increasing the temperature to 50 or 70 °C (entries 6 and 7, Table 1), possibly due to unwanted side reactions. Finally, we optimized various reaction parameters such as the amount of catalyst, the type of solvent, and the temperature, and we found that 0.5 equivalents of sodium iodide at 25 °C in ethanol gave the desired product **3a** in excellent yield (94%; entry 3).

Table 1 Screening of Reaction Conditions in the Synthesis of 4-Amino-3-benzyl-5-phenyl-1,3-thiazole-2(3H)-thione (**3a**)^a

Entry	NaI (equiv)	Solvent	Temp (°C)	Yield ^b (%)
1	–	EtOH	r.t.	10
2	0.25	EtOH	r.t.	85
3	0.5	EtOH	r.t.	94
4	1.0	EtOH	r.t.	93
5	0.5	MeCN	r.t.	47
6	1.0	EtOH	50	75
7	1.0	EtOH	70	62

^a Reaction conditions: **1a** (1.0 mmol), **2a** (1 mmol), CS₂ (1.2 mmol), Na₂CO₃ (1.2 mmol), NaI, solvent (5 mL).
^b Isolated yield.

Next, we examine the scope of our method for a range of primary amines and bromo(phenyl)acetonitriles, and the results are summarized in Table 2.

Table 2 Synthesis of Various 4-Aminothiazole-2(3H)-thiones^a

Entry	R ¹	R ²	Product	Yield ^b (%)
1	Bn	Ph	3a	94
2	CH ₂ -4-MeC ₆ H ₄	Ph	3b	90
3	CH ₂ -3,4-(MeO) ₂ C ₆ H ₃	Ph	3c	84
4	Bn	4-ClC ₆ H ₄	3d	79
5	CH ₂ -4-MeC ₆ H ₄	4-ClC ₆ H ₄	3e	85
6	CH ₂ -3,4-(MeO) ₂ C ₆ H ₃	4-ClC ₆ H ₄	3f	81
7	CH ₂ -2-ClC ₆ H ₄	Ph	3g	78
8	CH ₂ -2-ClC ₆ H ₄	4-ClC ₆ H ₄	3h	88
9	CH ₂ -2,4-Cl ₂ C ₆ H ₃	Ph	3i	87
10	CH ₂ -2,4-Cl ₂ C ₆ H ₃	4-ClC ₆ H ₄	3j	76
11	CH ₂ -4-FC ₆ H ₄	Ph	3k	72
12	CH ₂ -4-FC ₆ H ₄	4-ClC ₆ H ₄	3l	70
13	<i>t</i> -Bu	Ph	3m	69
14	<i>t</i> -Bu	4-ClC ₆ H ₄	3n	73

^a Reaction conditions: R²CH(Br)CN (1 mmol), R¹NH₂ (1 mmol), CS₂ (1.2 mmol), Na₂CO₃ (1.2 mmol), NaI (0.5 mmol), EtOH, r.t.
^b Isolated yield.

A plausible mechanism for the reaction is shown in Scheme 2. Dithiocarbamate **5** formed by the initial reaction of amine **1a** with carbon disulfide, activated by sodium carbonate, undergoes nucleophilic attack on iodo(phenyl)acetonitrile (**4**), formed by displacement of bromine from nitrile **2a** by iodine. Subsequent cyclization of intermediate **6** and tautomerism affords product **3a**.

Scheme 2

In summary, we have developed a novel and efficient three-component protocol for the synthesis of 4-aminothiazole-2(3H)-thiones. Significant advantages of this method include the use of simple and readily available precursors, easy workup, and very short reaction times.

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- (18) **4-Aminothiazole-2(3H)-thiones 3a–n; General Procedure**
Na₂CO₃ (1.2 mmol, 128 mg) and NaI (0.5 mmol, 75 mg) were added to a mixture of the appropriate aryl(bromo)acetonitrile (1 mmol), primary amine (1 mmol), and CS₂ (1.2 mmol, 73 μ L) in EtOH (5 mL), and the mixture was stirred at r.t. for 10 min while the progress of the reaction was monitored by TLC (hexane–EtOAc, 5:1). When the reaction was complete, the mixture was filtered and concentrated in vacuo to give a crude product that was purified by recrystallization from a suitable solvent to afford the pure product as a yellow solid.