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**Short Report**

# A One-Pot Domino Synthesis of 5-(Trifluoromethyl)-2-thiazolamine

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5-(Trifluoromethyl)-2-thiazolamine is a key intermediate for manufacturing numerous pharmaceuticals and chemicals. Here, a low-cost, one-pot multicomponent domino synthetic route has been reported for the synthesis of 5-(trifluoromethyl)-2-thiazolamine, which was successfully prepared from 3-bromo-1,1,1-trifluoro-2-propanone, phosphorus pentasulfide and cyanamide in the presence of sodium carbonate with the yield of 56%.

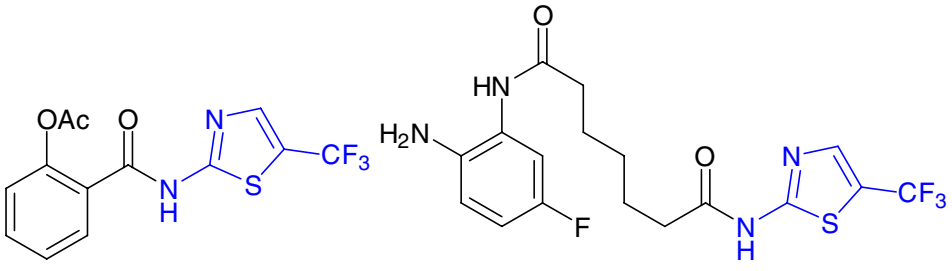
**Keywords:** 5-(trifluoromethyl)-2-thiazolamine, one-pot, domino synthesis, nitrogen heterocycle

## Introduction

In the field of medicinal chemistry, 2-aminothiazole plays an important role in drug design, and the incorporation of trifluoromethyl into 2-aminothiazole often enhances potent drugs' bioavailability, reduces toxicity or improves affinity for the target receptor.[1-4] In general, fluoroalkyl-substituted 2-aminothiazoles are regarded as privileged structure motifs in medicinal chemistry due to its presence in antimicrobial or antiviral agents, anticancer agents, etc. (Figure 1).[5-8]

5-(Trifluoromethyl)-2-thiazolamine is an important building block in various pharmaceutical and biologically-active compounds.[9] Several synthetic methodologies are available for the synthesis of the 5-(trifluoromethyl)-2-thiazolamine. In general, fluoroalkyl-substituted 2-aminothiazoles are synthesized through condensation of thiourea with fluoroalkyl-substituted synthons[10-12] or copper-mediated nucleophilic polyfluoroalkylation of halogen-substituted 2-amino-thiazoles.[13,14] However, all of these methods suffer from drawbacks such as tedious procedures, low yields, requirements for excess reagents or catalysts and difficult workup procedures. 5-(Trifluoromethyl)-2-thiazolamine has also been prepared by the reaction of 2-aminothiazoles with $CF_3I$ (or $CF_3Br$), but this is expensive and requires harsh conditions: (*i*) low temperature (−78 °C), (*ii*) a large amount of solvent and (*iii*) special apparatus.[15-17]

In our previous unpublished work,, we attempted to prepare 5-(difluoromethyl)-2-thiazolamine via reaction of 2-thiazolamine with $CHF_2Cl$, which led to *N*-alkylated product quantitatively. The *N*-alkylated product could also be obtained even using 2-thiazolamine amino-protected with acetyl or Boc. So we did not adopt the reaction between 2-aminothiazoles and $CF_3I$ to prepare 5-(trifluoromethyl)-2-thiazolamine.




anti-HCV agent anticancer agent

**Figure 1.** Examples of drug candidates with 5-(trifluoromethyl)-2-thiazolamine moiety.

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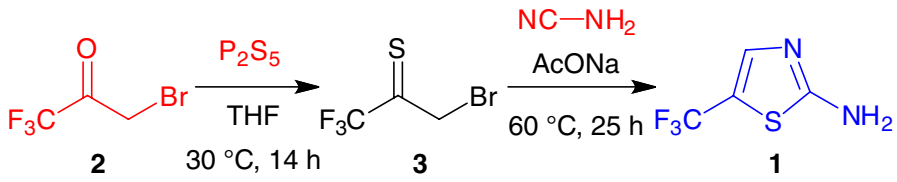



**Scheme 1.** The synthesis of 5-(trifluoromethyl)-2-thiazolamine.

Herein we report a new method for the synthesis of 5-(trifluoromethyl)-2-thiazolamine (**1**) from 3-bromo-1,1,1-trifluoro-2-propanone (**2**) in one-pot procedure. Commercially available **2** reacted with phosphorus pentasulfide to yield the key intermediate 3-bromo-1,1,1-trifluoropropane-2-thione (**3**). Then cyanamide was added and the cyclization reaction furnished **1** on a multi-gram scale with acceptable yield (Scheme 1).

## Results and Discussion

Initially, the reaction between 3-bromo-1,1,1-trifluoro-2-propanone (1.0 equiv), different amounts of phosphorus pentasulfide, and then cyanamide (1.0 equiv), in the presence of AcONa (1.0 equiv), was used as a model reaction to optimize the thionation conditions. The thionation reaction was performed at 30 °C and the cyclization took place at 60 °C for 30 h, then product **1** was isolated by column chromatography on silica gel and its structure was confirmed by $^1$H nuclear magnetic resonance (NMR) and electrospray ionization mass spectrometry (ESI-MS). Results are summarized in Table 1.

As shown in Table 1, the amount of phosphorus pentasulfide had a significant influence on the yields of target compound, 0.6 equiv of phosphorus pentasulfide gave the highest yield up to 45% (entries 1-4). From 10 h or 18 h reaction, a small decrease in product yield occurred, which may be due to the incompletion of the reaction and the degradation of the product, respectively (entries 5-6). Encouraged by Scheeren's report[18] on the sulfurization of carbonyl groups in the presence of sodium hydrogen carbonate ($NaHCO_3$) as an activator, we tested this in several experiments, but the addition of sodium hydrogen carbonate (6 equiv) did not accelerate the transformation nor reduce the requirement of phosphorus pentasulfide (entries 7-9). We also investigated the influence of solvents (entries 10-14). Non-polar solvent (toluene or chloroform) provided poor yields of 5-(trifluoromethyl)-2-thiazolamine (**1**), and the reaction in dimethylformamide (DMF) did not present the formation of product probably due to the reaction between DMF and phosphorus pentasulfide. In tetrahydrofuran (THF), an acceptable yield was obtained (45%). These results proved that THF is a good solvent for the reaction.

With the optimized reaction conditions in hand for thionation reaction, cyclization conditions were optimized by using 1.0 equiv of cyanamide (Table 2). The reaction with increased amounts of NaOAc afforded higher yields, and in the absence of base, the reaction did not take place (entries 1-5). When the reaction temperature was changed to

**Table 1.** Optimization of the thionation conditions

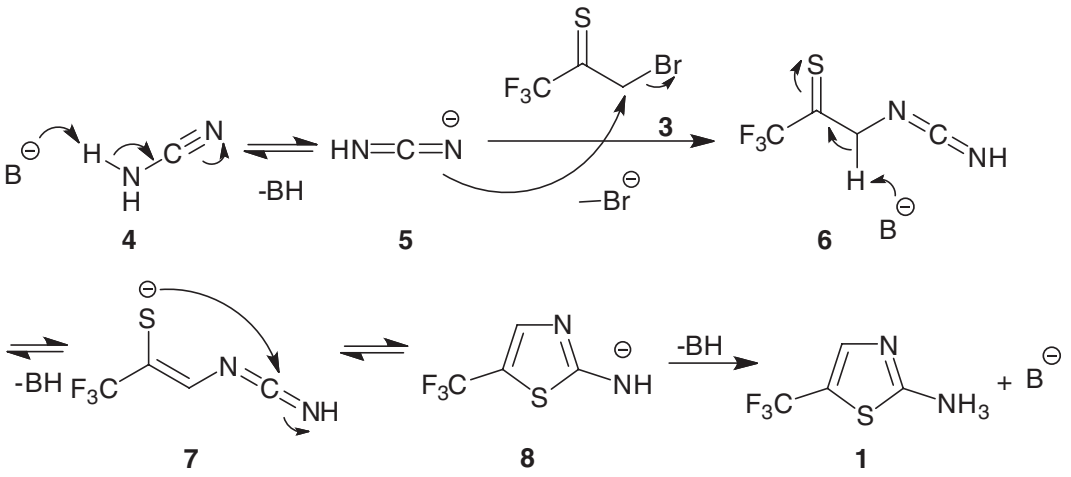
| entry | $P_2S_5$ / equiv | Additive | Solvent | Thionation time / h | Yield[a] / % |
|---|---|---|---|---|---|
| 1 | 1.5 | – | THF | 14 | 30 |
| 2 | 1.0 | – | THF | 14 | 39 |
| 3 | 0.6 | – | THF | 14 | 45 |
| 4 | 0.4 | – | THF | 14 | 37 |
| 5 | 0.6 | – | THF | 10 | 41 |
| 6 | 0.6 | – | THF | 18 | 43 |
| 7 | 0.6 | $NaHCO_3$ | THF | 14 | 44 |
| 8 | 0.4 | $NaHCO_3$ | THF | 14 | 38 |
| 9 | 0.6 | $NaHCO_3$ | THF | 10 | 42 |
| 10 | 0.6 | – | DMF | 14 | – |
| 11 | 0.6 | – | $CH_3CN$ | 14 | 36 |
| 12 | 0.6 | – | MTBE | 14 | 31 |
| 13 | 0.6 | – | toluene | 14 | 4 |
| 14 | 0.6 | – | $CHCl_3$ | 14 | 5 |

[a]Isolated yield of 5-(trifluoromethyl)-2-thiazolamine.

**Table 2.** Optimization of the cyclization conditions

| entry | Base / equiv | Temperature / °C | Cyclization time / h | Yield[a] / % |
|---|---|---|---|---|
| 1 | AcONa(0.5) | 60 | 30 | 24 |
| 2 | AcONa(1.0) | 60 | 30 | 45 |
| 3 | AcONa(1.5) | 60 | 30 | 53 |
| 4 | AcONa(2.0) | 60 | 30 | 55 |
| 5 | – | 60 | 30 | – |
| 6 | AcONa(1.5) | 30 | 30 | 25 |
| 7 | AcONa(1.5) | 45 | 30 | 44 |
| 8 | AcONa(1.5) | 60 | 25 | 56 |
| 9 | AcONa(1.5) | 60 | 40 | 51 |
| 10 | *t*-BuOK(1.5) | 60 | 25 | 54 |
| 11 | *t*-BuOK(1.5) | 25 | 30 | 49 |
| 12 | *n*-BuLi(1.5) | -78 - 0 | 22 | 53 |

[a]Isolated yield of 5-(trifluoromethyl)-2-thiazolamine.



**Scheme 2.** The possible mechanism of cyclization reaction.

30 or 45 °C, the yields of product diminished to 25 and 44%, respectively (entries 6-7). Meanwhile, we investigated the influence of the reaction time: by shortening the time, a slight increase was obtained (entries 8-9). In addition, the results demonstrate that other bases such as *t*-BuOK and *n*-BuLi can afford similar yields (entries 3, 10-12). While considering the safety and simplicity of operation, sodium acetate and potassium *t*-butoxide are better choices for this reaction.

A plausible mechanism for cyclization reaction is shown in Scheme 2. Cyanamide **4** deprotonates into its anion **5** via hydrogen abstraction reaction by the base. Successively, a nucleophilic substitution reaction with **3** gives carbodiimide intermediate **6**, which becomes prone to attack due to keto-enol tautomerism forming tautomer **7** and the attack takes place on the carbon of the carbodiimide producing anion **8**. Finally, compound **8** abstracts a hydrogen from conjugate acid to furnish the desired compound 5-(trifluoromethyl)-2-thiazolamine (**1**) and regenerate the base.

## Conclusions

We have developed a novel, mild, efficient method for the preparation of 5-(trifluoromethyl)-2-thiazolamine. Significant advantages of this method include simple and readily available precursors, easy workup, and acceptable yield.

## Experimental

The NMR spectra were recorded on a Bruker Ascend 400 using trimethylsilyl (TMS) as an internal standard. The reactions were monitored by TLC (HG/T2354-92, GF254), and the products were purified by column chromatography on silica gel (200-300 mesh) made in Qingdao Puke Parting Materials Co., Ltd.

To a mixture of 3-bromo-1,1,1-trifluoro-2-propanone (20 g, 0.1 mol) in 100 mL dry THF was added phosphorus pentasulfide (13.4 g, 0.06 mol). Then the mixture was continually stirred at 30 °C for 14 h. Then $NH_2CN$ (6.3 g, 0.15 mol) and AcONa (12 g, 0.15 mol) were added, and the mixture was heated with stirring at 60 °C for 25 h. After completion of the reaction, the solid in the reaction mixture were filtered out and the filtrate was concentrated under vacuum, then the residue was dissolved in water, and extracted with dichloromethane. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the filtrate was evaporated to obtain crude product, which was purified by column chromatography on silica gel (petroleum ether:ethyl acetate 3:1 as the eluent) to afford a light yellow oil (9.5 g, 56% yield). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.97 (s, 1H, Ar-H), 5.41 (s, 2H, $NH_2$), ESI-MS *m/z* 169.1 $[M + H]^+$.

## Supplementary Information

Additional spectroscopic data are available free of charge at http://jbcs.sbq.org.br.

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