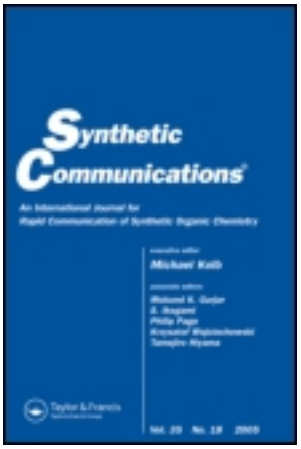

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Efficient Preparation of 5-Amino-4-cyano-N-(cyclopropylcarbamoyl)-3-aryl-2,3-dihydrothiophene-2-carboxamide Derivatives Without Using Any Other Catalysts

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EFFICIENT PREPARATION OF 5-AMINO-4-CYANO-N-(CYCLOPROPYLCARBAMOYL)-3-ARYL-2,3-DIHYDROTHIOPHENE-2-CARBOXAMIDE DERIVATIVES WITHOUT USING ANY OTHER CATALYSTS

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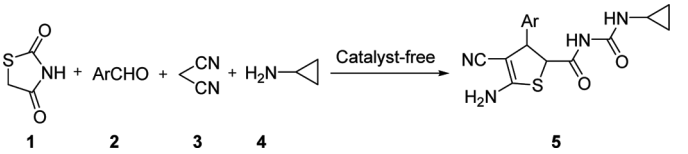
GRAPHICAL ABSTRACT



Abstract *An efficient synthesis of 5-amino-4-cyano-*N*-(cyclopropylcarbamoyl)-3-aryl-2,3-dihydrothiophene-2-carboxamide derivatives by the reaction of thiazolidine-2,4-dione, aromatic aldehydes, malononitrile, and cyclopropylamine has been reported. This reaction could be carried out smoothly without using any other catalysts in anhydrous ethanol. The advantages of this procure were good yields, short reaction time, and mild reaction conditions. Moreover, the purification process of products was very simple. The products could be gained only as the reactants were cooled under room temperature, and the precipitate could be brought out. These precipitate only need to filter out, without further purification.*

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Keywords Cyclopropylamine; 2,3-dihydrothiophene; multicomponent reactions; synthesis; thiazolidine-2,4-dione

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INTRODUCTION

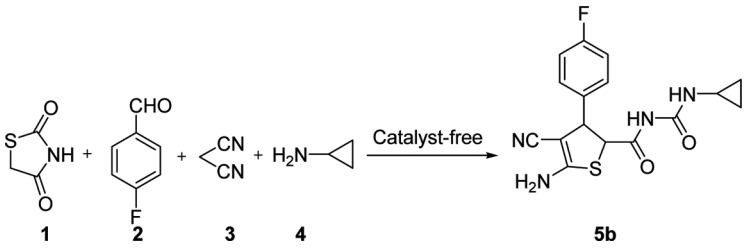
Multicomponent reactions (MCRs) have recently become one of the favored methods to prepare organic compounds.[1] Among many kinds of multicomponent reactions, four-component reactions are some of the most efficient and convenient methods to achieve many valuable organic molecules. For example, the Ugi reaction,[2] discovered more than 40 years ago, is without any doubt the most widely exploited, not only to prepare peptide-like molecules, but also to achieve many different types of other biologically active targets. At the present time, many four-component reactions[3] are used to obtain various compounds. In addition, MCRs are useful approaches for the construction of diverse chemical libraries of "drug-like" molecules[4] (i.e., heterocyclic scaffolds compounds), and this has also attracted much attention from chemists.

Thiophenes, which are used in medicinal chemistry and materials science, have grown enormously during the past several years.[5] For example, thiophene is the mother nucleus of several important pharmaceuticals such as reloxifen, duloxetine (Cymbalta), tiotropium (Spiriva), and Cosopt (dorzolamide). Importantly, the syntheses of the aforementioned drugs often use simple thiophenes as starting materials. The quest for these important molecules has been brought forth by modification of classical methods and, more importantly, novel synthesis by highly creative synthetic chemists. Similar attention has been drawn to the efficient synthesis of thiophene-containing organic materials because of the importance of atom economy and green chemistry. Recently, many novel thiophenes derivatives were synthesized by different methods.[6] Herein, we report preparation of some novel thiophene compounds by four-component reactions under catalyst-free conditions.

RESULTS AND DISCUSSION

Recently, some researchers have reported synthesizing thiophene derivatives by four-component reactions from thiazolidine-2,4-dione, aromatic aldehyde, malononitrile, and different organic amines.[7] However, in these reported methods, the reactions were carried out in CH_3CN, and the yields of products were very poor. Moreover, the catalyst Et_3N is required. Upon investigating, we found cyclopropylamine has not been used in similar syntheses. In our research, we want to find other useful methods to prepare new thiophene derivatives using cyclopropylamine as starting reagent.

At the beginning of our research, we wanted to find the best reaction conditions in which to carry out this synthesis. Thiazolidine-2,4-dione, 4-fluorobenzaldehyde, malononitrile, and cyclopropylamine were chosen as starting materials for the model reaction under different solvents, such as H_2O, CH_3CN, CH_3OH, EtOH, and tetrahydrofuran (THF), and in solvent-free condition, without using any other catalysts (Scheme 1). We found that in CH_3CN (used in literature) the reaction could be carried out, but the yield was very poor (only 25%). The reaction in water was such also (only 18%). The desired product did not form under solvent-free conditions, and only condensation products of 4-fluorobenzaldehyde and malononitrile could be gained. Then, other solvents, such as CH_3OH, anhydrous EtOH, and THF were chosen to try this model reaction. Eventually, we found the reactions could operate



Scheme 1. Synthesis of 3-(4-fluorophenyl)-2,3-dihydrothiophene-2-carboxamide.

very well under anhydrous EtOH conditions. We thought that ethanol was a good organic polar solvent, efficiently dissolving substances and reaction intermediates, and so was beneficial to the formation of the products. The results of model reaction are listed in Table 1.

To test the scope of the substrates under this optimizing condition, we used different aromatic aldehydes **2** with either electron-withdrawing groups or electron-donating groups to react with thiazolidine-2,4-dione **1**, malononitrile **3**, and cyclopropylamine **4**, and we found all the reactions could be carried out smoothly with good yields (Scheme 2). The results of reactions showed that the properties of substituted groups have no effect on these syntheses. Taking into account these results, we reasoned these conditions were the perfect conditions for this synthesis. In these reactions, cyclopropylamine behaves both as a base catalyst and the reagent, so it did not require any other catalysts. Furthermore, the purification of reactions was very simple. The products could be gained only as the reactants were cooled under room temperature, and then the precipitate could be brought out. These precipitates only need to be filtered out, without the need for further purification. The results of reaction are summarized in Table 2.

According to the obtained product, the possible mechanism could be explained by Scheme 3. First, **1** reacted with **2** or **2** reacted with **3** to give **6** and **7** respectively. Then, **6** reacted with **3** and **7** reacted with **1** to give the same intermediate **8**.

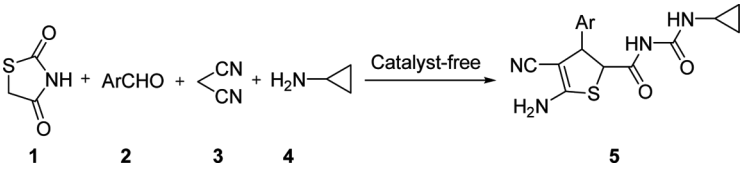
Table 1. Synthesis of **5b** using different reaction conditions

Entry	Solvent[a]	Time (h)	Yields (%)[b]
1	CH_3CN	2	25
2	H_2O (100 °C)	2	18
3	—	2	0
4	CH_3OH,	2	50
5	DMF (100 °C)	2	Trace
6	THF	2	40
7	EtOH	1	75
8	EtOH	2	89
9	EtOH	3	90

Note. Reagents and conditions: thiazolidine-2,4-dione (1 mmol), 4-chlorobenzaldehyde (1 mmol), malononitrile (1 mmol), cyclopropylamine (1.2 mmol), and EtOH (8 mL).

[a]Unless explicitly stated, the reaction was conducted under reflux conditions.

[b]Isolated products.

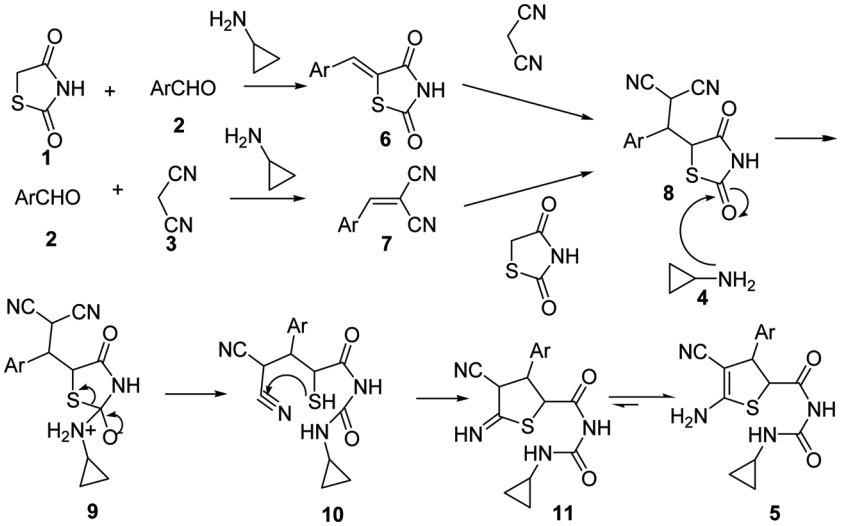


Scheme 2. Synthesis of 3-aryl-2,3-dihydrothiophene-2-carboxamide.

Table 2. Results of synthesis of 3-aryl-2,3-dihydrothiophene-2-carboxamide

Entry	Ar	Product	Yields (%)
1	C_6H_5	**5a**	85
2	4-FC_6H_4	**5b**	89
3	4-ClC_6H_4	**5c**	90
4	3-BrC_6H_4	**5d**	82
5	4-BrC_6H_4	**5e**	83
6	2,4-$Cl_2C_6H_3$	**5f**	91
7	3,4-$Cl_2C_6H_3$	**5g**	84
8	4-$CH_3C_6H_4$	**5h**	80
9	2-$CH_3OC_6H_4$	**5i**	81
10	4-$CH_3OC_6H_4$	**5j**	87
11	3,4-$(CH_3O)_2C_6H_3$	**5k**	92

Cyclopropylamine reacted with **8** and intermediate **9** could be gained. Intermediate **9** took place with ring opening to give **10**. The intramolecular cyclization reaction of intermediate **10** was taken place to give **11**. At last, the product **5** was obtained by the tautomerization of **11**.



Scheme 3. Probable mechanisms of the reaction.

All the products were characterized by infrared (IR), ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrometry (HRMS). The structures of the products could be explained as follows, using example **5a**: In ^{1}H NMR shows a singlet at δ 0.52 (2H), multiple at δ 0.64–0.69 (2H), and two doublets at δ 2.63 (1H) due to the five aliphatic hydrogen protons of cyclopropyl. A singlet at δ 4.07 (1H) and a doublet at δ 4.53 (1H) are two protons on the thiofuran ring. Multiple at δ 7.28–7.31(3H) and triplet at δ 7.33 (2H) are five protons on the benzene ring. A singlet at δ 7.21 of two protons is the NH_2 and the singlet at δ 8.17 and 10.40 are due to the NH protons. In ^{13}C NMR, the chemical shifts of 16 carbon atoms show at 172.10, 162.15, 154.15, 141.90, 141.88, 129.17, 127.94, 127.89, 127.52, 118.64, 70.67, 55.62, 55.59, 22.78, 6.63, and 6.50. In HRMS spectrum, the calculated m/z for $C_{16}H_{16}N_4O_2S$ [M + Na] is 351.0892, and we found m/z is 351.0877.

CONCLUSION

In summary, we have developed a simple and efficient method for the synthesis of 5-amino-4-cyano-*N*-(cyclopropylcarbamoyl)-3-aryl-2,3-dihydrothiophene-2-carboxamide derivatives via a one-pot, four-component reaction of thiazolidine-2,4-dione, aromatic aldehydes, malononitrile, and cyclopropylamine without use of any other catalysts. Eleven new compounds were successfully synthesized using our reported method. The advantages of the present procedure are experimental simplicity, good yields, and mild reaction conditions. In addition, the purification of the products is very simple.

EXPERIMENTAL

All reagents were purchased from the Merck and Aldrich chemical companies and used without further purification. Melting points were determined on an XT-5 microscopic melting-point apparatus and were uncorrected. IR spectra were recorded on a Fourier transform (FT) Bruker Tensor 27 spectrometer. ^{1}H NMR spectra and ^{13}C NMR spectra were obtained from solution in dimethylsulfoxide (DMSO-d_6) with Me_4Si as internal standard using a Bruker-400 spectrometer. HRMS spectra were obtained with a Bruker Micro-TOF-Q 134 instrument.

Thiazolidine-2,4-dione (1 mmol), aromatic aldehyde (1 mmol), malononitrile (1 mmol), cyclopropylamine (1.2 mmol), and anhydrous EtOH (8 mL) were put in a reaction flask and left at 75 °C for about 2 h. After completing the reactions, the mixture was cooled under room temperature. The precipitate could be brought out, filtered, and dried, and **5** could be gained without further purification.

Complete experimental details are available online in the Supplemental Material.

ACKNOWLEDGMENTS

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