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Efficient synthesis of benzothiophenes by [4+1] cycloaddition of 2-mercaptobenzaldehyde derivatives with isocyanides

Takahiro Soeta *, Saori Shitaya, Takumi Okuno, Shuhei Fujinami, Yutaka Ukaji *

Division of Material Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Kanazawa 920-1192, Japan

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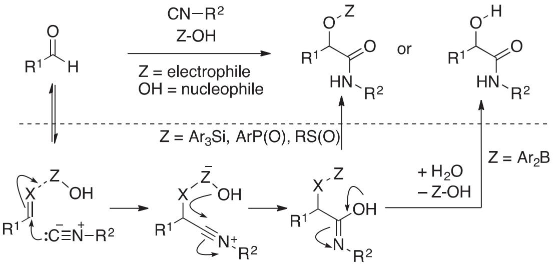
ABSTRACT

We developed a [4+1] cycloaddition reaction of isocyanides with 2-mercaptobenzaldehydes and/or their disulfide derivatives, promoted by LiI·$2H_2O$, to afford benzothiophene derivatives in moderate to good yields. Isocyanides, 2-mercaptobenzaldehydes and disulfide derivatives of various types were used successfully in the reaction.

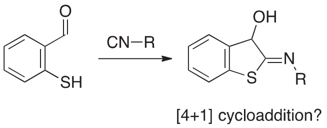
1. Introduction

The Passerini reaction is one of the oldest multicomponent reactions, and has been found to be useful in the construction of multifunctional α-acyloxyamides.[1] It is probably the best method for producing α-acyloxyamide in a highly convergent manner, and a large number of biologically active substances can be accessed quickly in this way.[2] The Passerini reaction generally requires a carboxylic acid, which activates an aldehyde and traps a nitrilium cation to form an acyloxylated intermediate; subsequent acyl transfer leads to the corresponding α-acyloxy amides. The requirement for a carboxylic acid limits the application of this reaction to the construction of a particular range of molecules. To overcome this limitation, we reasoned that a compound Z–X, composed of an electrophile Z and a nucleophilic group X, could essentially perform the same function as the carboxylic acid in the Passerini reaction. Based on this hypothesis, we previously developed *O*-silylative, *O*-phosphinative, and *O*-sulfinative Passerini reactions as well as borinic acid-catalyzed α-addition of isocyanide (Scheme 1).[3] In addition, we expanded this concept to intramolecular trapping of a nitrilium intermediate in an Ugi-type reaction. Thus, when a molecule contains both an electrophile (such as C=N) and a potential nucleophilic group (Nu^-), intramolecular trapping of the nitrilium intermediate should be readily achieved in a manner similar to the intermolecular version of the reaction.[4]

Based on these investigations, we focused on the utility of 2-mercaptobenzaldehyde for effective synthesis of benzothiophene derivatives (Scheme 2).



Scheme 1. *O*-Silylative Passerini reaction, *O*-phosphinative Passerini reaction, *O*-sulfinative Passerini reaction, and borinic-acid-catalyzed α-addition of an isocyanide.



Scheme 2. Working hypothesis.

Benzothiophene derivatives have been the subject of much attention and are frequently found in pharmaceuticals.[5] They are also useful as building blocks in materials science.[6] Owing to these unique properties, various methods of synthesizing benzothiophene derivatives have been investigated, and a number of

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* Corresponding authors. E-mail addresses: soeta@se.kanazawa-u.ac.jp (T. Soeta), ukaji@staff.kanazawa-u.ac.jp (Y. Ukaji).

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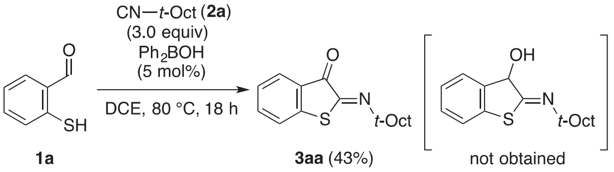
combinatorial techniques have recently been developed, including one using Friedel–Crafts type aroylation,[7] and an electrophilic cyclization.[8] These methods can only be used with a limited number of substrates; however, benzothiophene derivatives are not readily accessed through existing preparative methods. To address this deficiency, we herein report [4+1] cycloaddition of isocyanides to 2-mercaptobenzaldehyde derivatives promoted by a lithium iodide to afford various benzothiophene derivatives.

2. Results and discussion

First, we examined whether 2-mercaptobenzaldehyde (**1a**) was capable of participating in a Passerini-type reaction to afford the corresponding benzothiophene derivatives. For this, we used a combination of 2-mercaptobenzaldehyde (**1a**) and *tert*-octyl isocyanide (**2a**, 3.0 equiv) in the presence of a catalytic amount of phenylborinic acid, which has been shown to be useful in catalyzing α-addition of isocyanide,[3d] in dichloroethane (DCE) at 80 °C. Once the starting material had been consumed after 18 h, the reaction mixture was purified and characterized. ^1H NMR, ^{13}C NMR, IR and HRMS spectroscopies revealed that the structure of the product was different from what was expected: the hydroxy group had been oxidized during the reaction, giving the benzothiophene-3(2*H*)-one derivative **3aa** (Eq. 1).

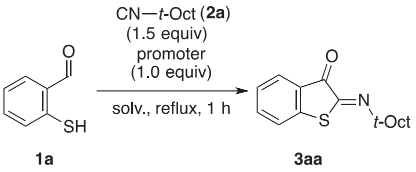


(1)

Based on these results, we optimized the reaction conditions (Table 1). When 2-mercaptobenzaldehyde (**1a**) was refluxed in dioxane with *tert*-octyl isocyanide (**2a**) (1.5 equiv), the starting material **1a** was consumed after 1 h and the desired **3aa** was obtained in 62% yield (entry 1). Chlorotrimethylsilane (TMSCl) and diphenylborinic acid, which are useful Lewis acids for the isocyanide-based reactions,[3d,4d] were not effective in this reaction, affording the product in lower yields (entries 2 and 3). $LiI\cdot 2H_2O$ was found to be a good promotor in this reaction system, giving the product in 72% yield (entry 4). Anhydrous LiI was less effective (entry 5), but NaI and KI were relatively effective (entries 6 and 7). In the case of LiBr and LiCl, the reactions proceeded at much lower rate, affording the product in 60% and 46% yields, respectively (entries 8 and 9). Since it was evident that the solvent influenced the efficiency of the reaction, we next examined $LiI\cdot 2H_2O$-promoted [4+1] cycloaddition using different solvents. When toluene was used as a solvent, the reaction proceeded smoothly to afford the product **3aa** in 74% yield, although the reaction system has slightly complicated compared with the use of dioxane as a solvent (entry 10). Dichloroethane (DCE) and propionitrile were not particularly effective, affording the product only in moderate yields (entries 11 and 12).

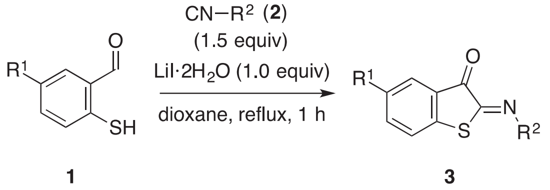
Next, we attempted to expand the range of isocyanides **2** and 2-mercaptobenzaldehyde derivatives **1** that can be used in the Passerini-type [4+1] cycloaddition reaction with $LiI\cdot 2H_2O$ as a promoter, as detailed in Table 2. The reaction of aliphatic isocyanides **2a** and **2b** (R^2=*t*-Oct and *t*-Bu) with **1a** in the presence of $LiI\cdot 2H_2O$ gave the products in good yields (entries 1 and 2), while the secondary and primary aliphatic isocyanides **2c** and **2d** were not applicable to the reaction (entries 3 and 4). However, isocyanides **2e**–**2h** reacted with **1a** to afford the desired products (entries 5–8). We also investigated substituted 2-mercaptobenzaldehyde derivatives bearing an electron-donating or an electron-withdrawing group on the aromatic ring (entries 9–11). The reactions proceeded to afford the corresponding benzothiophene derivatives **3ba**–**3da** in moderate to good yields. The structure of the product was confirmed by X-ray crystallographic analysis of a single crystal of **3af**. The structure of **3af** is shown in Fig. 1.

Table 1
Results of Passerini-type [4+1] cycloaddition reaction using 2-mercaptobenzaldehyde under various conditions



entry	promoter	solv.	yield/%
1	—	dioxane	62
2	TMSCl	dioxane	22
3	Ph_2BOH	dioxane	48
4	$LiI\cdot 2H_2O$	dioxane	72
5	LiI	dioxane	41
6	NaI	dioxane	69
7	KI	dioxane	64
8	LiBr	dioxane	60
9	LiCl	dioxane	46
10	$LiI\cdot 2H_2O$	toluene	74
11	$LiI\cdot 2H_2O$	DCE	50
12	$LiI\cdot 2H_2O$	propionitrile	59

Table 2
Range of isocyanides and 2-mercaptobenzaldehyde derivatives applicable to the Passerini-type [4+1] cycloaddition reaction



entry	R^1	R^2	yield/%
1	H (**1a**)	*t*-Oct (**2a**)	72 (**3aa**)
2	H (**1a**)	*t*-Bu (**2b**)	54 (**3ab**)
3	H (**1a**)	*c*-Hex (**2c**)	—[a]
4	H (**1a**)	Bn (**2d**)	—[a]
5	H (**1a**)	Ph (**2e**)	51 (**3ae**)
6[b]	H (**1a**)	$4\text{-}MeOC_6H_4$ (**2f**)	27 (**3af**)
7	H (**1a**)	$4\text{-}Me_2NC_6H_4$ (**2g**)	66 (**3ag**)
8	H (**1a**)	$4\text{-}BrC_6H_4$ (**2h**)	31 (**3ah**)
9	*t*-Bu (**1b**)	*t*-Oct (**2a**)	77 (**3ba**)
10	MeO (**1c**)	*t*-Oct (**2a**)	47 (**3ca**)
11	Cl (**1d**)	*t*-Oct (**2a**)	51 (**3da**)

[a] Complex mixture.
[b] The reaction was quenched after 20 h.

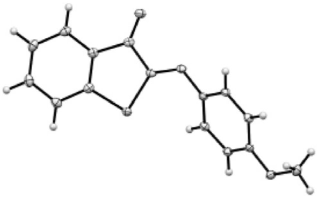


Fig. 1. X-ray structure of **3af**.