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Multicomponent Domino Reactions of Hydrazinecarbodithioates: A Concise Access to 3-Substituted 5-Thiol-1,3,4-Thiadiazolines

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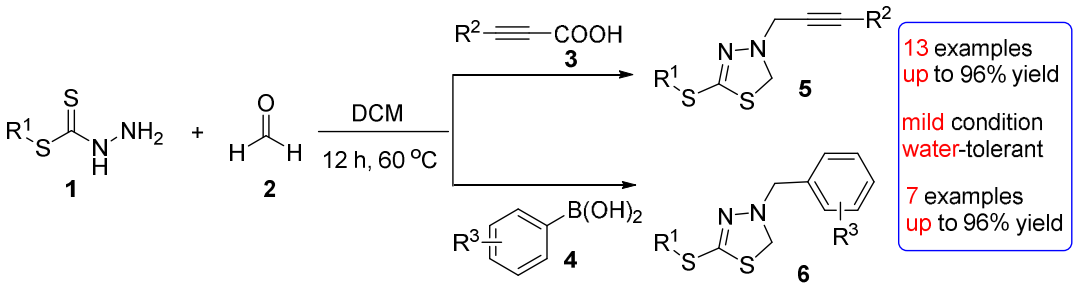
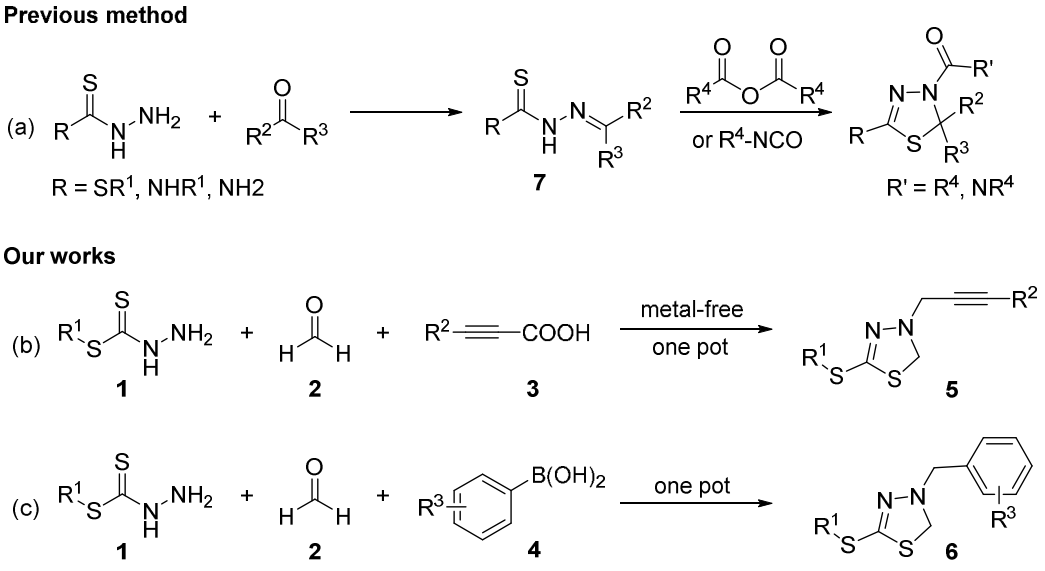


ABSTRACT

Two classes of addition/cycloaddition cascade reactions of hydrazinecarbodithioate (**1**) have been developed under mild reaction conditions. Reaction of hydrazinecarbodithioate (**1**) with formaldehyde solution (**2**) and propiolic acid (**3**) gives 3-propargyl-5-thiol-2,3-dihydro-1,3,4-thiadiazoles (**5**) via a decarboxylative coupling/cycloaddition domino sequence. When propiolic acid (**3**) is switched to phenyl boronic acid (**4**), a Petasis/cycloaddition domino reaction is instead observed, in which 3-benzyl-5-thiol-2,3-dihydro-1,3,4-thiadiazoles (**6**) are obtained. Both of these two reactions show a wide range of functional-group compatibility for propiolic acids and aryl boronic acids, and give the corresponding products in moderate to good yields.

Nitrogen-containing heterocycles have received intense attention due to their wide applications in medicinal chemistry, agro-chemistry, and so on. 1,3,4-Thiadiazoles and their derivatives are very important heterocycles as they display a broad spectrum of biological activities, including anti-tuberculosis,[1] anti-cancer,[2] anti-microbial,[3] anti-HIV,[4] anti-inflammatory,[5] and anti-hypertensive[6] activities. Furthermore, their synthetic importance has prompted considerable interest to develop "ideal" protocols for the formation of various substituted derivatives. One of the most widely used and reliable procedure for the construction of 1,3,4-thiadiazolines is the cycloaddition of intermediate **7** prepared from aldehydes and ketones under acylation conditions, usually employing a base (Figure 1a).[7] In such a case, functional groups introduced to the 3-position of 1,3,4-thiadiazole are limited to acyl derivatives. Therefore, we undertook an investigation aimed at developing efficient approaches to the synthesis of various non-acyl 3-substituted 5-thiol-2,3-dihydro-1,3,4-thiadiazole derivatives from easily accessible starting materials.

Figure 1. Synthesis of 3-Substituted 2,3-Dihydro- 1,3,4-thiadiazole



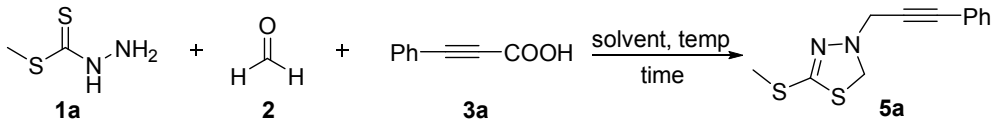
Recently, transition metal catalyzed decarboxylative coupling reactions have been well established owing to widely available starting materials, simple operation, and excellent atom economy (only producing CO_2 as a byproduct).[8,9] In light of the recent

demands for an environmentally benign and economically feasible "ideal" chemistry, development of metal-free decarboxylative reaction has been a continuing challenge in modern organic synthesis.[10] One such reaction is that of propiolic acids with paraformaldehyde and secondary amines to give propargylamines, previously reported by Lee et al.[11] We recently reported the reaction of propiolic acids with primary amines, formaldehyde solution, and boronic acids as part of our ongoing program related to the formation of propargylamines via metal-free decarboxylative coupling.[12] Given our interest in developing metal-free decarboxylative reactions and multicomponent domino reactions,[13] we envisioned a facile and a selective approach to 3-propargyl-5-thiol-2,3-dihydro-1,3,4-thiadiazoles generated by metal-free decarboxylative coupling and cyclization domino reactions (Figure 1b). Moreover, a one pot tandem combination of Petasis reaction[14] and cycloaddition was also designed for the generation of 3-benzyl-5-thiol-2,3-dihydro- 1,3,4-thiadiazoles (Figure 1c).

We initiated our studies by evaluating the reaction between methyl hydrazinecarbodithioate (**1a)**, formaldehyde solution (**2)**, and phenylpropiolic acid (**3a)** in toluene at 60 ° C for 12 h (Table 1). The reaction underwent smooth transformation to afford the desired product (**4a**) in 53% yield. Switching the solvent to ethanol, water, and tetrahydrofuran (THF) did not affect the reaction outcome (Table 1, entries 2−4), but the use of 1,2-dichloroethane (DCE) or dichloromethane (DCM) significantly enhanced the reactivity even further, both affording **4a** in 71% yield (Table 1, entries 5 and 6). When acetonitrile was used (Table 1, entry 7), only 58% of the product was isolated, which is much lower than the case using DCE or DCM. Although the solvent DCE could also promote the reaction well, its environmental friendliness and cost effectiveness were worse than DCM. So DCM was chosen as the solvent to further optimize the reaction conditions. Next, different reaction temperatures and time were tested, but these did not give much improvement of the yield (Table 1, entries 8−11). To our delight, a 77% yield was obtained by changing the **1a**/**3a** ratio from 1.0 : 1.0 to 1.0 : 0.8 (Table 1, entry 13). Eventually, a variety of additives such as L-proline, $PhCO_2H$, DABCO, and PPh_3 were examined; and no

enhancement was observed (Table 1, entries 14-17).

Table1. Optimization of Metal-Free Conditions for the Synthesis of 3a[a]



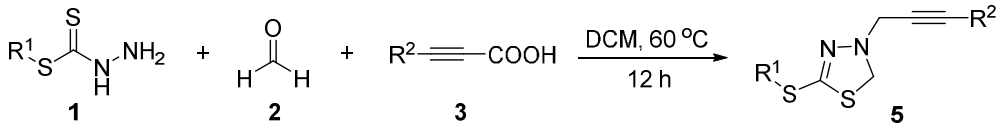
entry	ratio	solvent	additive	Temp [°C]	*t* [h]	Yield [%][b]
1	1.0/3.2/1.0	Toluene		60	12	53
2	1.0/3.2/1.0	EtOH		60	12	25
3	1.0/3.2/1.0	H_2O		60	12	26
4	1.0/3.2/1.0	THF		60	12	5
5	1.0/3.2/1.0	DCE		60	12	71
6	1.0/3.2/1.0	DCM		60	12	71
7	1.0/3.2/1.0	CH_3CN		60	12	58
8	1.0/3.2/1.0	DCM		80	12	64
9	1.0/3.2/1.0	DCM		40	12	60
10	1.0/3.2/1.0	DCM		60	6	62
11	1.0/3.2/1.0	DCM		60	18	68
12	1.0/3.2/1.2	DCM		60	12	57
13	**1.0/3.2/0.8**	**DCM**		**60**	**12**	**77**
14	1.0/3.2/0.8	DCM	L-Proline	60	12	45
15	1.0/3.2/0.8	DCM	$PhCO_2H$	60	12	64
16	1.0/3.2/0.8	DCM	DABCO	60	12	11
17	1.0/3.2/0.8	DCM	PPh_3	60	12	18

[a]Reactions conditions: **1a** (0.5 mmol), formaldehyde solution (37 wt% in water) (0.6-1.6 mmol), **3a** (0.4mmol) and solvent (1.0 mL) in a sealed tube. [b]Isolated yield. [c]Additive (1.0 mmol).

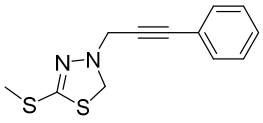
Having established the optimal reaction conditions, we explored a variety of propiolic acids (**3**) in the reaction with methyl hydrazinecarbodithioate and formaldehyde solution to examine the substrate scope. Phenylpropiolic acids, bearing both electron-donating and -withdrawing groups, gave the corresponding products **5b**−**h** in good to high yields ranging from 66% to 90% (Table 2, entries 2−8). In addition, alkyl propiolic acids were also suitable substrates for this reaction to generate the desired products in moderate yields (38−42%, Table 2, entries 9 and 10). However, 3-(pyridin-2-yl)propiolic acid only produced a trace amount of **5k** (Table 2, entry 11). We next examined the reactions of various hydrazinecarbodithioates (**1**) to explore the substrate scope of our protocol. As expected, substitutions on the thiol group did not

largely affect the efficiency of the reaction, affording the desired products **5l**−**m** in good yields (Table 2, entries 12−14).

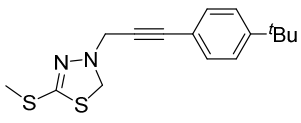
Table 2. Reactions of Hydrazinecarbodithioates with Propiolic acids[a]



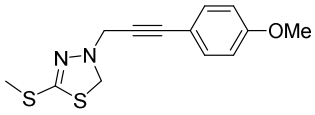
1 **2** **3** **5**



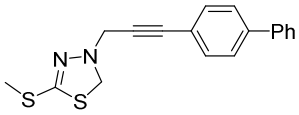
5a 77%



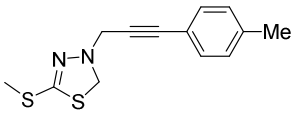
5b 77%



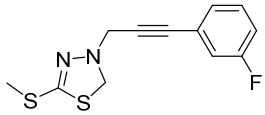
5c 70%



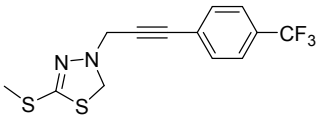
5d 71%



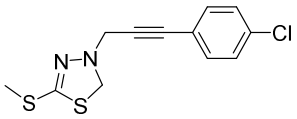
5e 90%



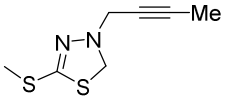
5f 75%



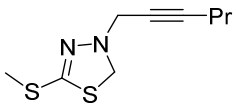
5g 66%



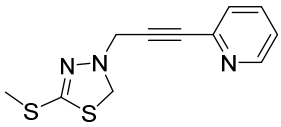
5h 87%



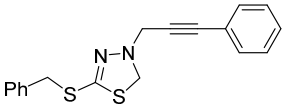
5i 38%



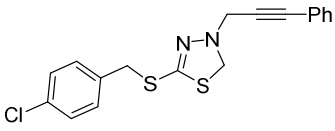
5j 42%



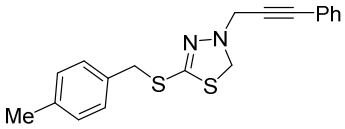
5k trace



5l 61%



5m 68%



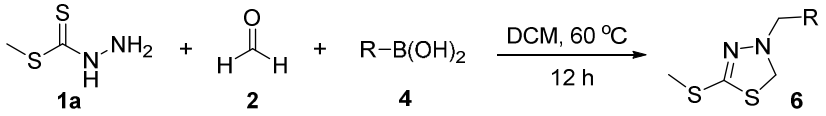
5n 47%

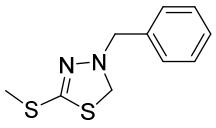
[a]A mixture of hydrazinecarbodithioates (0.5 mmol), formaldehyde solution (37 wt% in water) (1.6 mmol), propiolic acid (0.4 mmol) in DCM in a sealed tube at a temperature of 60 °C for 12 h.

Subsequently, in another set of experiments, we evaluated boronic acid (**4**) as the nucleophile in this one pot process (Table 3). As in the case of propiolic acids, no metal was required. When R was a phenyl group, different electronic properties (electron-neutral, -rich, or -deficient) were tolerated and the desired products **6a**–**6g** were produced in good yields (Table 3, entries 1−7). However, the steric properties of the R groups strongly affected the reaction yield. For instance, substrate **4d**–**4f** with a

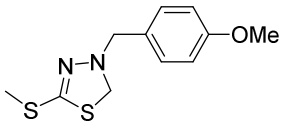
2-position substituent afforded the corresponding product **6d**–**6f** in much lower yield (Table 3, entries 4−6). Unfortunately, when (4-nitrophenyl)boronic acid **4h** and ethylboronic acid **4i** were used to the reaction, the corresponding products **6h** and **6i** were not found. Instead bis(5-(methylthio)-1,3,4-thiadiazol-3(2H)-yl)methane **7** was obtained in 66% yield after cycloaddition.

Table 3. Reactions of Methyl Hydrazinecarbodithioate with Boronic acids[a]

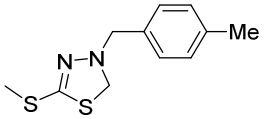




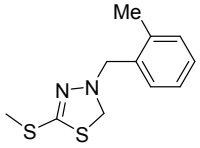
6a 79%



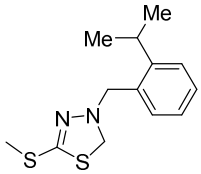
6b 91%



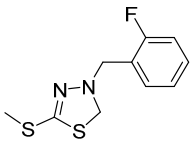
6c 64%



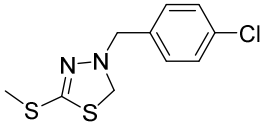
6d 54%



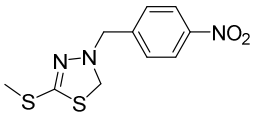
6e 40%



6f 23%



6g 61%



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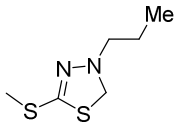


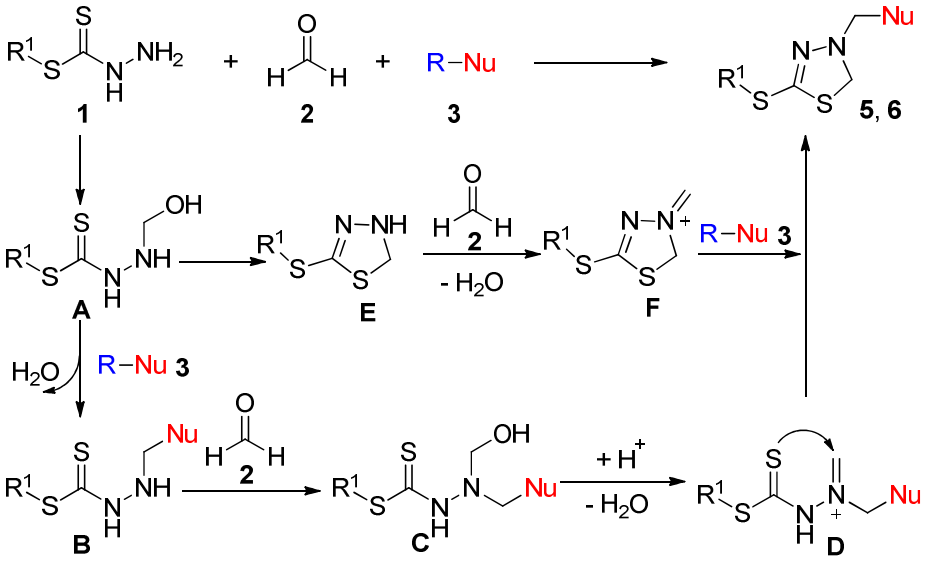
6i 0%

[a]A mixture of hydrazinecarbodithioates (0.5 mmol), formaldehyde solution (37 wt% in water) (1.6 mmol), boronic acid (0.4 mmol) in DCM in a sealed tube at a temperature of 60 °C for 12 h.

A plausible mechanism for the generation of the 5-thiol-2,3-dihydro-1,3,4-thiadiazoles from formaldehyde solution, and nucleophiles is depicted in Figure 2. Initially, the transformation is proceed through condensation of hydrazinecarbodithioate **1** and formaldehyde solution **2** to form an intermediate **A**, followed by nucleophilic attack to produce an intermediate **B**. Then, this intermediate **B** reacts with another formaldehyde solution **2** to produce an iminium intermediate **C**, which in the presence of a proton results in the formation of iminium salt **D**. Subsequent cycloaddition of **D** affords the desired products. If the cycloaddition of **A**

takes precedence over nucleophilic attack, another pathway involves cycloaddition of **A** resulting in the formation of intermediate **E**, followed by condensation with formaldehyde solution to provide **F**, and subsequently react with nucleophiles to give desired products.

Figure 2. Proposed Mechanism for the Formation of 5-Thiol-2,3-Dihydro-1,3,4-Thiadiazoles



In summary, we have developed a useful method for the synthesis of 3-substituted 5-thiol-2,3-dihydro-1,3,4-thiadiazoles by either a domino reaction of hydrazinecarbodithioates with formaldehyde followed by metal-free decarboxylative coupling, or Petasis reaction. Notably, the 5-methylthio substituent on the products can serve as a versatile group for further transformation. We believe that application of these protocols will offer an opportunity for rapid generation of molecular diversity.

ACKNOWLEDGMENTS

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