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Efficient One-Pot Synthesis of 2,3-Dihydropyrimidinthiones via Multicomponent Coupling of Terminal Alkynes, Elemental Sulfur, and Carbodiimides

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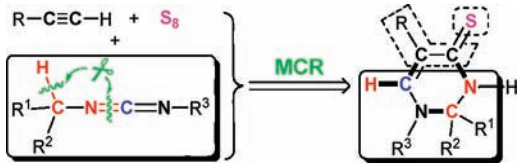
Multicomponent reactions (MCRs) have become very useful for fast and efficient construction of important molecules.[1] Utilization of common and readily available chemicals as their components and involvement of selective cleavage of chemical bonds such as C═N double bonds and C−H bonds should make an MCR much more attractive both fundamentally and synthetically.[2,3] Herein we report a novel organolithium-promoted MCR involving terminal alkynes, sulfur, and carbodiimides (Scheme 1) that affords 2,3-dihydropyrimidinthiones via C═N double bond cleavage and sp^3 C−H bond functionalization of the carbodiimide molecule. Formation and characterization of an η^3-S−C−N lithium species in the reaction process indicates that a molecule of carbodiimide is torn up into three fragments that are selectively incorporated into the 2,3-dihydropyrimidinthione skeleton, forming two C−N single bonds, one C═C double bond, and one C−H bond.

Scheme 1. MCR Synthesis of 2,3-Dihydropyrimidinthiones via C═N Cleavage and sp^3 C−H Bond Functionalization of Carbodiimides



Phenylethyne was first treated with *n*-BuLi in THF at −78 °C to afford phenylethynyllithium, to which 1 equiv of elemental sulfur was then added. After the mixture was stirred at room temperature for 2 h, *N*,*N*′-diisopropylcarbodiimide (^{i}PrN═C═N^{i}Pr) was added. The reaction mixture was then heated to 80 °C for 4 h. Hydrolysis of the reaction mixture with water afforded an unexpected product, 2,3-dihydropyrimidinthione **1a**, X-ray structural analysis of which revealed, to our surprise, that the C1 atom from ^{i}Pr is bonded to the two nitrogen atoms from the initial ^{i}PrN═C═N^{i}Pr (Figure 1). Three components, including phenylethyne, sulfur, and ^{i}PrN═C═N^{i}Pr, were incorporated into the new molecule, providing an efficient strategy for the construction of compounds containing sulfur from abundant elemental sulfur. Interestingly, the starting ^{i}PrN═C═N^{i}Pr underwent C═N double bond cleavage and sp^3 C−H bond functionalization to produce three different fragments that contributed to the formation of **1a** via the formation of two C−N single bonds, one C═C double bond, and one C−H bond. Carbodiimides for a long time have proved to be versatile reagents for organic synthesis, pharmaceutical chemistry, and organometallic chemistry.[4−8] As far as we are aware, this is the first example of carbodiimide rearrangement via C═N double bond cleavage and sp^3 C−H bond functionalization as well as the first example of an efficient preparation of well-defined 2,3-dihydropyrimidinthiones,[9] which are difficult to access by other means and might show unique biological activity.[10]

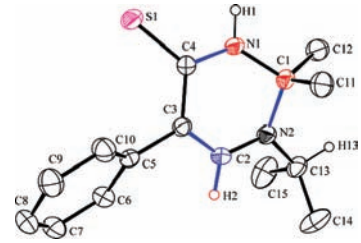
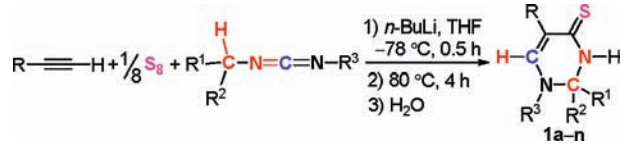


Figure 1. ORTEP drawing of **1a** with 30% thermal ellipsoids.

Table 1. Formation of Various 2,3-Dihydropyrimidinthiones[a]



entry	R	R^1	R^2	R^3	1 (% yield[b])
1	Ph	Me	Me	^{i}Pr	**1a** (83)
2	Ph	−(CH$_2$)$_5$−		Cy	**1b** (74)
3	Ph	−(CH$_2$)$_5$−		Ph	**1c** (80)
4	Ph	H	Ph	Ph	**1d** (52)
5	4-MeC$_6$H$_4$	Me	Me	^{i}Pr	**1e** (73)
6	4-MeOC$_6$H$_4$	Me	Me	^{i}Pr	**1f** (66)
7	3-MeOC$_6$H$_4$	Me	Me	^{i}Pr	**1g** (73)
8	4-ClC$_6$H$_4$	Me	Me	^{i}Pr	**1h** (71)
9	3-ClC$_6$H$_4$	Me	Me	^{i}Pr	**1i** (63)
10	3-thienyl	Me	Me	^{i}Pr	**1j** (53)
11	cyclohexyl	Me	Me	^{i}Pr	**1k** (77)
12	CH$_3$(CH$_2$)$_4$	Me	Me	^{i}Pr	**1l** (83)
13	−(1,4-C$_6$H$_4$)−	Me	Me	^{i}Pr	**1m** (71)[c]
14	−(CH$_2$)$_4$−	Me	Me	^{i}Pr	**1n** (73)[c]

[a] Conditions: terminal alkyne (1 mmol), carbodiimide (1 mmol), sulfur (1 mmol), THF (10 mL), unless otherwise noted. [b] Isolated yield. [c] Conditions: terminal diyne (1 mmol), carbodiimide (2 mmol), sulfur (2 mmol).

Summarized in Table 1 are representative results obtained from *n*-BuLi-mediated reactions among terminal alkynes, sulfur, and carbodiimides. In the presence of 1 equiv of *n*-BuLi, the reactions of phenylethyne with carbodiimides having at least one α-H-neighboring nitrogen atom, such as ^{i}PrN═C═N^{i}Pr, CyN═C═NCy, PhN═C═NCy, and PhN═C═NBn, were carried out at 80 °C for 4 h to yield the corresponding 2,3-dihydropyrimidinthiones **1a**−**d** in moderate to high isolated yields (entries 1−4). Aromatic terminal alkynes with either electron-withdrawing or -donating substituents

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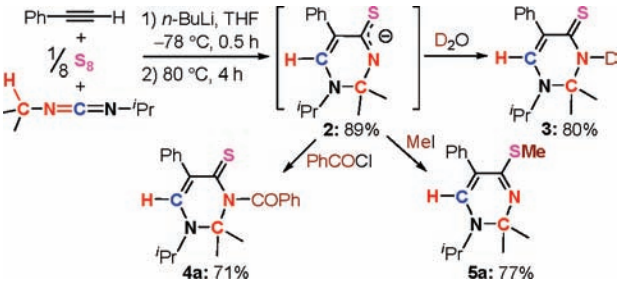
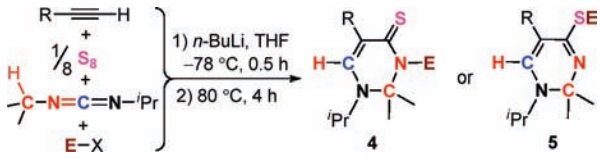
on the phenyl ring all afforded their corresponding 2,3-dihydropyrimidinthiones **1e**−**i** in good isolated yields (entries 5−9). It is noteworthy that halogen tolerance was also observed, as aromatic C−Cl bonds survived under the present conditions to selectively yield the corresponding chloro-substituted 2,3-dihydropyrimidinthiones **1h** and **1i** (entries 8 and 9). Aromatic terminal alkynes with ortho substituents, such as 2-methoxy- and 2-chloroethynylbenzene, were not suitable for this reaction, probably because of their steric hindrance. Heteroatom-containing alkynes, such as 3-ethynylthiophene (entry 10), were also applicable. In addition, aliphatic alkynes could be also applied (entries 11 and 12). Furthermore the diynes 1,4-diethynylbenzene and 1,7-octadiyne reacted with 2 equiv of elemental sulfur and ^{i}PrN=C=N^{i}Pr to afford the corresponding bis(2,3-dihydropyrimidinthione) compounds **1m** and **1n** in 71 and 73% isolated yield, respectively (entries 13 and 14).

Scheme 2. Isolation and Trapping Experiments on Intermediate **2**

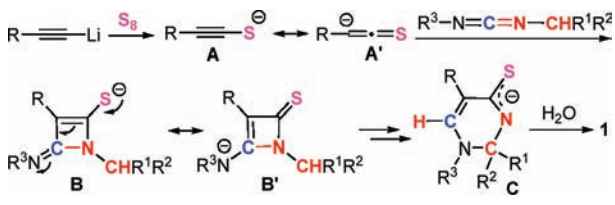


Scheme 3. One-Pot 4CR for the Formation of **4** or **5**



Successful isolation and characterization of an η^3-S−C−N lithium species **2** from the reaction mixture of PhC≡CLi, sulfur, and ^{i}PrN=C=N^{i}Pr before quenching were achieved, and this was very useful for understanding the reaction mechanism (Scheme 2; for details, see the Supporting Information). The intermediate **2** was further confirmed by trapping with various electrophiles such as D_2O, benzoyl chloride, and iodomethane (Scheme 2), yielding 2,3-dihydropyrimidinthione derivatives **3** and **4a** and 1,2-dihydrothiopyrimidine derivative **5a**, respectively. Thus, as a whole, either 2,3-dihydropyrimidinthione **4** or 1,2-dihydrothiopyrimidine **5** could be readily obtained in a one-pot four-component reaction (4CR) process involving terminal alkynes, elemental sulfur, ^{i}PrN=C=N^{i}Pr, and electrophiles (Scheme 3).

Scheme 4. Possible Mechanism for the Formation of **1**



Scheme 4 shows a possible route for the formation of dihydropyrimidinthione derivatives **1**. The reaction between a lithium acetylide[11] and sulfur should yield lithium alkynethiolate **A** and/or **A′**. Next, a four-membered-ring intermediate **B** and/or **B′** might be formed via cyclization after nucleophilic attack by **A′** on a carbodiimide.[12] It is not clear yet how the final η^3-S−C−N lithium species **C** is formed from the four-membered-ring intermediate **B** and/or **B′** (see the Supporting Information for more discussion).

In summary, an organolithium-promoted MCR involving terminal alkynes, elemental sulfur, and carbodiimides has been achieved for the first time and offers a straightforward route to 2,3-dihydropyrimidinthiones that may have important biological activity. Moreover, the results observed in this work demonstrate that carbodiimides can undergo interesting and useful C=N double bond cleavage and an sp^3 C−H bond functionalization. Studies of mechanistic aspects and reaction applications are in progress.

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Supporting Information Available: Experimental details, X-ray data for **1a** (CIF), and scanned NMR spectra of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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