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Highly site, regio-, and stereoselective multicomponent reaction of benzimidazole carbenes, isothiocyanates, and allenoates

Bo Wang, Jia-Qi Li, Ying Cheng *

Chemistry Department, Beijing Normal University, Beijing 100875, China

Abstract

The novel three-component reaction of benzimidazole carbenes with isothiocyanates and allenoates proceeded efficiently in a highly site, regio-, and stereoselective manner to produce predominantly spiro[benzimidazoline-2,3′-tetrahydrothiophene] derivatives. The reaction was proposed to occur via a tandem nucleophilic addition of carbenes to isothiocyanates followed by an unusual [3+2] cycloaddition to the less activated carbon–carbon double bond of allenoates.
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Multicomponent reactions (MCRs) have attracted considerable attention owing to high synthetic efficiency, and, in many cases, the facile construction of complex organic compounds.[1–5] For example, the three-component Passerini reaction[6,7] and four-component Ugi reaction[8] and their variants involving diverse isonitriles have provided expedient approaches to a wide range of drug-like compounds of biological and pharmaceutical interest.[4]

Nucleophilic carbenes are versatile and valuable intermediates not only as the ligands in organometallics[9,10] but also as organocatalysts[11–13] and unique building blocks in organic synthesis.[14–16] Although various reactions of nucleophilic carbenes have been investigated, the multicomponent reaction of nucleophilic carbenes has remained largely unexplored until recent years. Since 2000s, nucleophilic carbenes have emerged actively in the field of multicomponent reactions.[17–25] Most of the known MCRs participated by a carbene intermediate comprised of a nucleophilic carbene, an activated alkyne such as DMAD in most cases, and a carbonyl compound including aldehyde, ketone, anhydride, and ketene.[17–24] These three-component reactions generally led to the formation of furan derivatives. Although the known three-component reactions of carbenes are very successful, the examples of MCRs of nucleophilic carbenes are still rather limited. Moreover, except for electron-deficient alkynes and carbonyl compounds, the multicomponent reaction of the nucleophilic carbenes with other electrophiles has been scarcely investigated.[25]

Our interests in the reactivity of nucleophilic carbenes and their applications in organic synthesis[26–32] have led us to investigate multicomponent reactions involving nucleophilic carbenes. Nucleophilic carbenes have been reported to react with aryl isothiocyanates to form 1+1 1,3-dipolar adducts[33–36] or 1+2 cycloadducts[37,38] under different reaction conditions. On the other hand, the interaction of nucleophilic carbenes with allenoates was known to form 1+1 zwitterionic products.[39] We were intrigued by the three-component reactions among nucleophilic carbenes, isothiocyanates, and allenoates in terms of various selectivities, and envisioned that the reaction would lead to interesting multifunctional compounds. To our delight, this novel three-component reaction proceeded in highly site-, regio-, and stereoselective manners affording 2-amino-5-vinylspiro[benzimidazoline-2,3′-tetrahydrothiophenes] as

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* Corresponding author. Tel./fax: +86 10 58805558.
 *E-mail address:* ycheng2@bnu.edu.cn (Y. Cheng).

predominant products in moderate to good yields. We report herein our observations.

We started with the reaction of *N,N*′-diethylbenzimidazole carbene **2a**, butyl isothiocyanate **3a**, and methyl 4-benzylallenecarboxylate **4a**. The benzimidazole carbene was generated in situ by the deprotonation of the corresponding benzimidazolium salt **1a** using sodium hydride. Under a nitrogen atmosphere, the mixture of **1a**, **3a**, **4a**, and NaH in THF was refluxed for 2 h to produce a yellow-colored product **5a** in 72% yield. The generality of the three-component reaction was demonstrated by using benzimidazolium salts, isothiocyanates, and allenoates bearing different substituents (Scheme 1 and Table 1). In all cases examined, the reaction underwent efficiently to produce **5** as the major products in 42–82% yields. In addition to products **5**, three minor products **6**, **7**, and **8** were also detected (Table 1).

The structures of products were elucidated on the basis of spectroscopic data and microanalysis.[40] The NMR spectra, mass data, and elemental analyses indicated **5**, **6**, **7**, and **8** being isomeric products derived from 1+1+1 addition of carbene, isothiocyanate, and allenoate. To identify the isomers beyond doubt, the structures of **5i**, **7c**, and **8i** were determined unambiguously by single crystal X-ray diffraction analysis (Fig. 1).[41] It is worth noting that products

5, **6**, **7**, and **8** show distinctly different ^{13}C NMR and ^{1}H NMR spectra, and they can be used in turn as diagnostics to differentiate **5**, **6**, **7**, and **8**. For example, in ^{13}C NMR spectra, the 2-imino-thiophene products **5** and **6** gave their diagnostic C=N carbon signals at 158–167 ppm while C=S carbon signals of pyrrole-2-thiones **7** and **8** appeared at lower field around 197–211 ppm. On the other hand, the two isomeric 2-imino-thiophenes **5** and **6**, or pyrrole-2-thiones **7** and **8**, can be easily differentiated by their ^{1}H NMR spectra, because isomer **5** or **7** has a signal of vinyl proton but isomer **6** or **8** does not.

The formation of products **5**, **6**, **7**, and **8** can be best explained all by a tandem nucleophilic addition/[3+2] cycloaddition mechanism (Scheme 2). Nucleophilic addition of benzimidazole carbenes **2** to isothiocyanates **3** yielded 2-thiocarbamoyl benzimidazolium inner salts **9**. As the ambident 1,3-dipolar components, **9** acted as the C^+–C–S^- 1,3-dipoles to react with the C(2)–C(3) or C(1)–C(2) double bond of the allenoates **4** to produce spiro[benzimidazoline-2,3′-tetrahydrothiophenes] **5** or **10**, respectively. In turn, inner salts **9** behaved as the C^+–C–N^- 1,3-dipolar species to add to the C(2)–C(3) or C(1)–C(2) double bond of the allenoates giving rise to spiro[benzimidazoline-2,3′-tetrahydropyrroles] **7** or **11**. Under the reaction conditions, isomerization of the exocyclic double bond of inter-
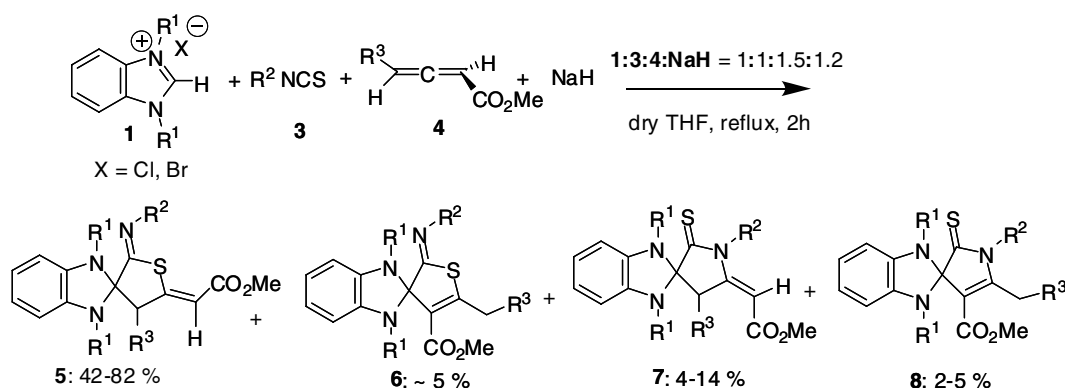
Scheme 1. Reaction of benzimidazolium salts, isothiocyanates, and allenoates in the presence of sodium hydride.

Table 1
Reaction of benzimidazolium salts, isothiocyanates, and allenoates in the presence of sodium hydride

Entry	Starting materials			Yield of product (%)			
	1: R^1	**3**: R^2	**4**: R^3	**5**	**6**	**7**	**8**
1	**1a**: Et	**3a**: *n*-Bu	**4a**: Bz	**5a** 72	—[a]	—	—
2	**1a**: Et	**3b**: *i*-Pr	**4a**: Bz	**5b** 60	—	—	—
3	**1a**: Et	**3c**: Bz	**4a**: Bz	**5c** 42	**6c** 5	**7c** 13	**8c** 2
4	**1a**: Et	**3d**: Ph	**4a**: Bz	**5d** 78	—	—	—
5	**1a**: Et	**3b**: *i*-Pr	**4b**: Me	**5e** 52	—	—	—
6	**1b**: *n*-Bu	**3c**: Bz	**4b**: Me	**5f** 56	—	**7f** 5	—
7	**1b**: *n*-Bu	**3c**: Bz	**4a**: Bz	**5g** 62	—	**7g** 14	—
8	**1b**: *n*-Bu	**3d**: Ph	**4a**: Bz	**5h** 82	—	—	—
9	**1c**: Bz	**3a**: *n*-Bu	**4a**: Bz	**5i** 61	—	**7i** 2	**8i** 7
10	**1c**: Bz	**3d**: Ph	**4a**: Bz	**5j** 76	—	—	—
11	**1c**: Bz	**3e**: *p*-C$_6$H$_4$OMe	**4a**: Bz	**5k** 60	—	—	—
12	**1c**: Bz	**3f**: *p*-C$_6$H$_4$Cl	**4a**: Bz	**5l** 77	—	—	—

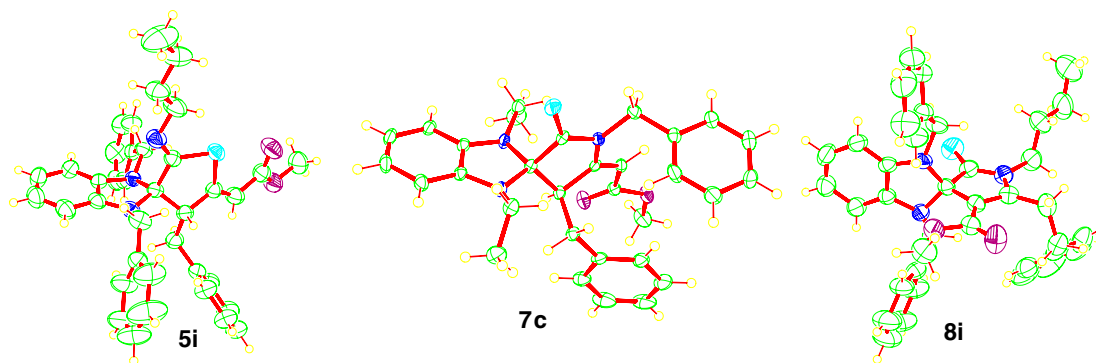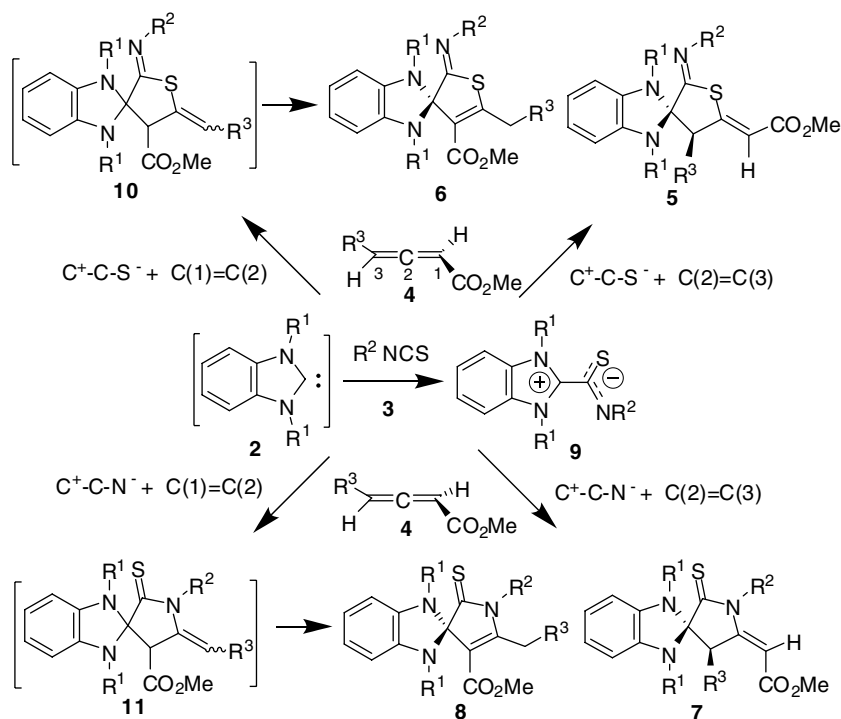[a] A tiny amount of minor product was observed.

Fig. 1. The ORTEP drawings of single-crystal structures of compounds **5i**, **7c**, and **8i** (50% probability was chosen for the ellipsoids).

Scheme 2. The proposed mechanisms for the formation of products **5**, **6**, **7**, and **8**.

mediates **10** and **11** to the endocyclic double bond gave the thermodynamically more stable conjugated products **6** and **8**.

In addition to the synthetic value of the present three-component reaction, wherein polyfunctionalized spiro-[benzimidazoline-2,3'-tetrahydrothiophene] derivatives are easily accessed, several intriguing features deserve comment. First, the reaction exhibits high site selectivity. The benzimidazolium salts **9** act predominantly as the C–C–S dipolar components rather than as the C–C–N ones. Second, the cycloaddition of allenoates **4** with the C–C–S dipolar function of **9** is regioselective, with the inactivated double bond of the allenoates being involved. Finally, the reaction appears highly stereoselectivity because only *Z*-configured 5-vinyltetrahydrothiophenes **5** and *E*-configured 5-vinyltetrahydropyrroles **7** were obtained.

The highly site selective reaction of C–C–S dipolar system of benzimidazolium inner salts **9** toward allenoates is in agreement with our recent discovery on the ambident reactivity of 2-arylthiocarbamoyl benzimidazolium salts toward different electron-deficient alkynes.[29,30] Our experimental and theoretical studies have shown that the reactivity and site selectivity of the cycloaddition reaction of 2-arylthiocarbamoyl benzimidazolium salts were regulated by both electronic and steric effects of 1,3-dipolarophiles.[30,32] In general, sterically hindered and strong electronic 1,3-dipolarphiles prefer to react with the C–C–S dipolar component, whereas the dipolarophiles with less steric hindrance favor the reaction with C–C–N moiety. In the current three-component reaction, the steric hindrance between the N-substituents of intermediates **9** and the substituents of the allenes probably disfavor the C–C–N cycloaddition pathway. The much higher reactivity

of C(2)–C(3) double bond of the allenoates toward C–C–S 1,3-diploar components was remarkable and intriguing. The 1,3-dipolar cycloadditions of various dipoles, such as nitrones, diazoalkanes, and nitrile oxide, with electron-deficient allenes have been investigated.[42–46] According to the literature, in most reactions, it was the activated C(1)–C(2) double bond that underwent 1,3-dipolar cycloaddition reaction, since the electron-withdrawing group caused lowering of the LUMO energy level of allenes, which favored the dipole HOMO–dipolarophile LUMO interaction. Our recent study also indicated that dipoles **9** preferred to react with more electron-deficient dipolarophiles.[30] However, we now observed an opposite selectivity of the relatively less activated C(2)–C(3) bond of allenoates in the C–C–S cycloaddition reaction. The exact reason for the reversed double bond selectivity remains unclear at this stage, although we may ascribe it to the formation of more stable conjugated product. The stereoselective formation of *Z*-configured isomer of **5** and *E*-configured isomer of **7** was most probably due to the thermodynamic factors, as the substituents on the double bond and on the thiophene or pyrrole ring tend to keep far away to avoid steric strains.

In conclusion, we have developed a novel three-component reaction of benzimidazole carbenes with isothiocyanates and allenoates. The simple and efficient reaction proceeded in a highly site selective, regioselective, and stereospecific manner to produce predominantly spiro[benzimidazoline-2,3′-tetrahydrothiophene] derivatives. The reaction was proposed via a tandem nucleophilic addition of carbenes to isothiocyanates followed by an unusual [3+2] cycloaddition to the less activated carbon–carbon double bond of allenoates. The novel spiro products are not easily prepared by other synthetic methods and are potentially amenable to further transformations. The systematic study on the detailed mechanism and the regioselectivity of the reactions between various nucleophilic carbenes, isothiocyanates, and allenes are actively pursued in our laboratory.

Acknowledgments

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.095.

References and notes

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40. *Spectral data of selected compound*: (*Z*)-Methyl 1,3-diethyl-2′-benzylimino-4′-benzylspiro[benzimidazoline-2,3′-tetrahydrothien-5′-ylidene]acetate **5c**: 42%, mp 119–120 °C; IR *v* (cm⁻¹) 1704, 1654, 1616, 1506; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.29–7.34 (m, 5H), 7.22–7.27 (m, 5H), 6.61 (t, *J* = 4.1 Hz, 2H), 6.31 (dd, *J* = 6.0, 4.0 Hz, 1H), 6.28 (dd, *J* = 6.0, 4.0 Hz, 1H), 6.13 (d, *J* = 2.5 Hz, 1H), 4.64 (d, *J* = 16.0 Hz, 1H), 4.60 (d, *J* = 16.0 Hz, 1H), 3.76 (s, 3H), 3.51 (d, *J* = 15.9 Hz, 1H), 3.44 (d, *J* = 9.1 Hz, 1H), 3.32–3.40 (m, 2H), 3.11–3.18 (m, 1H), 3.01–3.07 (m, 1H), 2.96 (dd, *J* = 16.0, 9.1 Hz, 1H), 1.11–1.15 (m, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 166.5, 163.2, 158.1, 140.6, 139.3, 138.8, 138.5, 128.8, 128.3, 128.1, 127.6, 126.9,

126.4, 117.9, 117.5, 111.1, 103.0, 102.7, 97.8, 60.5, 51.6, 51.5, 40.0, 38.9, 32.8, 14.6, 12.8; MS (MALDI-TOF): 512 (M+1). Anal. Calcd for $C_{31}H_{33}N_3O_2S$: C, 72.77; H, 6.50; N, 8.21. Found: C, 72.76; H, 6.52; N, 8.09.

41. CCDC 642031, 642032, and 642033 (**5i**, **7c**, and **8i**) contain the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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