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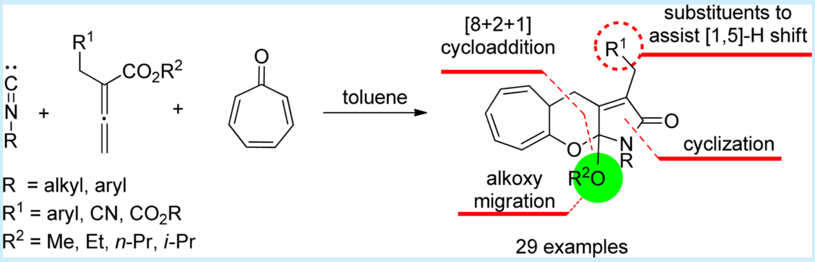
Multicomponent Cascade Cycloaddition Involving Tropone, Allenoate, and Isocyanide: A Rapid Access to a 7,6,5-Fused Tricyclic Skeleton

Shuanglong Jia,[†] Shikuan Su,[†] Chunju Li,[†] Xueshun Jia,*[,†,‡] and Jian Li*[,†]

[†]Department of Chemistry, Innovative Drug Research Center, Shanghai University, 99 Shangda Road, Shanghai 200444, P. R. China
[‡]Key Laboratory of Synthetic Organic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China

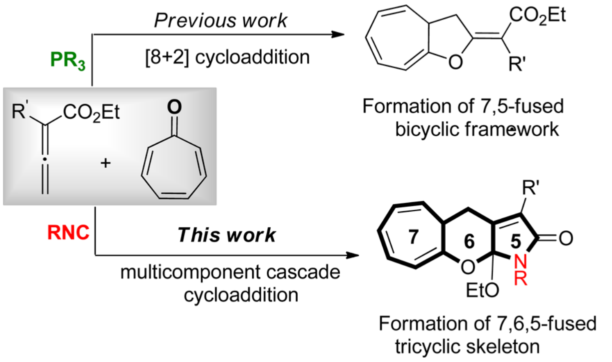
Ⓢ *Supporting Information*



ABSTRACT: Multicomponent cascade cycloaddition of tropone, allenoate, and isocyanide has been disclosed. This method allows for the rapid construction of a highly unusual tricyclic skeleton in an efficient manner. The proposed transformation proceeds through [8 + 2 + 1] cycloaddition, [1,5]-H shift, and cyclization followed by an alkoxy group migration process.

Tropone and its derivatives represent highly valuable building blocks and have been extensively used in organic synthesis and mechanistic studies.[1] Moreover, troponoids have also found application in syntheses of natural products[2] since the tropolone moieties are frequently present in some alkaloids.[3] In particular, they are proven to be a versatile cycloaddition partner in a variety of high-order cycloadditions. It is therefore not surprising that many impressive cycloadditions have been extensively reported using tropone as four-,[4] six-,[5] and eight-membered[6] building blocks, respectively. Recently, reactions involving tropone and 1,3-dipoles have attracted much attention from organic chemists. Early works include the reactions of tropone and 1,3-dipoles derivated from allenoate and modified allylic compounds in the presence of a phosphine catalyst (Scheme 1).[7] The palladium-complex-catalyzed [6 + 3] cycloaddition constitutes another representative example.[8] Following these pioneering works, Ni- and $SnCl_4$-catalyzed [8 + 3] cycloadditions of tropone and dipoles *in situ* generated from 1,1-cyclopropane derivatives have also been achieved.[9] More recently, the metal-catalyzed [6 + 3] cycloaddition of tropone with azomethine ylide has been reported to approach bicyclic heterocycles.[10] Yet, to our knowledge, whereas the traditional cycloadditions involving tropone can serve as highly efficient protocols for the syntheses of bicyclic frameworks, examples in the construction of a more complex tricyclic skeleton are still very rare.

Scheme 1. Selective Cycloaddition Involving Tropone and Allenoate



Isocyanide-based multicomponent reactions (IMCRs) have been widely investigated in organic synthesis owing to their inherent features such as atom and step economy, convergence, and diversity.[11,12] Remarkably, IMCRs enjoy unique superiority over traditional methods for the rapid and efficient generation of structurally complex molecules.[13] As a result, the past decades have witnessed a rapid increase in the application of isocyanide-based multicomponent reactions.[14] In 2011, we developed the first example of a multicomponent reaction involving isocyanide and allenoate, thus providing a quick access to spirooxindole.[15] The system was subsequently proven to be an efficient strategy to construct other five-membered carbocycles and heterocycles.[16a,b] More recently, we have also

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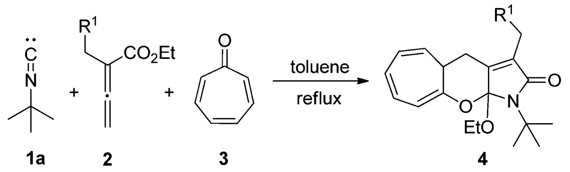
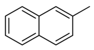
found that this MCR method can also be used to synthesize more complex fused derivatives by using substituted allenoate.[16d] Taking the high reactivity of tropone into consideration, we assume that the tropone may react with isocyanide and allenoate to give new results. As a continuation of our previous research,[16] herein we wish to report the multicomponent cascade cycloaddition from readily available isocyanide, allenoate, and tropone (Scheme 1).

In order to test our hypothesis, we initially selected *tert*-butyl isocyanide **1a**, allenoate **2a**, and tropone **3** as model substrates. Upon heating the mixture in toluene for 20 h, the reaction gave rise to 7,6,5-fused tricyclic adduct **4a** in 61% yield (Table 1, entry 1). The structure of compound **4a** was unambiguously confirmed by single-crystal X-ray analysis (Figure 1).[17] In this process, reactions to see the effect of different solvents and temperature were also conducted. However, only toluene under reflux was found to be the best conditions. Encouraged by this result, we then turned our attention to investigate the scope of allenoate with different substitution patterns. Pleasingly, allenoate bearing electron-deficient (Table 1, entries 2−7) and electron-rich substituents (Table 1, entries 8−11) on the aromatic ring all worked well under the standard conditions to afford the desired compounds **4**. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. Notably, the structure of compound **4d** was also confirmed by single-crystal X-ray analysis.[18] These results also implied that varying the substituents on the aromatic rings did not have any major impact on the yield of product **4**. Remarkably, the nature of the substituent R^1 in allenoate **2** played an important role in the present transformation. As shown in Table 1, a complex mixture was observed when allenoate with a methyl substitution was used (Table 1, entry 13), whereas substrates **2** bearing the CN and CO_2Me group proceeded smoothly to produce the products **4m** and **4n** (Table 1, entries 14−15). These results might indicate that the presence of an anion-stabilizing group such as an aryl, CN group is indispensible. It was also worthy to note that the allenoates **2** were used as four carbon (C4) building blocks to form the rings, which is less common.[19] In our previous works, the multicomponent reactions involving isocyanide and allenoate were usually used for the syntheses of five-membered rings.[15,16] In contrast, the first step in the present IMCRs essentially involved the formation of a six-membered ring, thus offering a new opportunity for the construction of structurally unusual skeletons with diversity.

Table 1. Multicomponent Cascade Cycloaddition to Synthesize 7,6,5-Fused Tricyclic Derivatives with Isocyanide 1a, Allenoate 2, and Tropone 3[a]



entry	R^1	product	yield (%)[b]
1	C_6H_5	**4a**	61
2	$3\text{-}ClC_6H_4$	**4b**	43
3	$4\text{-}BrC_6H_4$	**4c**	51
4	$4\text{-}NO_2C_6H_4$	**4d**	52
5	$3\text{-}NO_2C_6H_4$	**4e**	37
6	$2\text{-}NO_2C_6H_4$	**4f**	70
7	$4\text{-}CNC_6H_4$	**4g**	48
8	$4\text{-}MeC_6H_4$	**4h**	50
9	$3\text{-}MeC_6H_4$	**4i**	49
10	$2\text{-}MeC_6H_4$	**4j**	66
11	$4\text{-}MeOC_6H_4$	**4k**	38
12		**4l**	51
13	H	-	-[c]
14	CO_2Me	**4m**	54
15	CN	**4n**	65

[a] Reaction conditions: isocyanide **1a** (0.5 mmol), allenoate **2** (0.6 mmol), and tropone **3** (0.5 mmol) in 5 mL of toluene and heated under reflux. [b] Yield of product after silica gel chromatography. [c] In this case, a very complex mixture was observed.

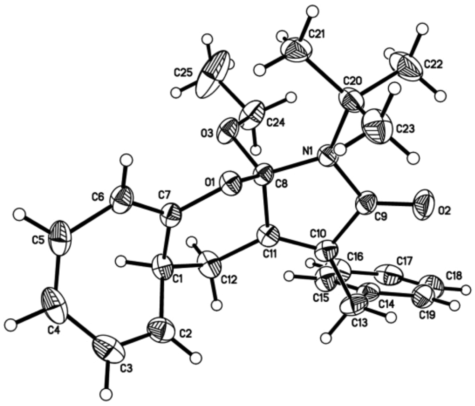


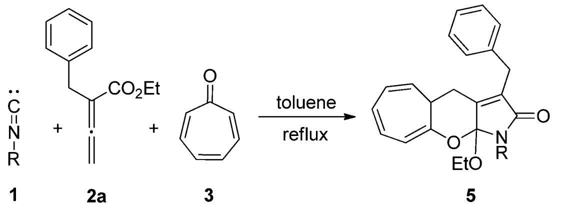
Figure 1. Single crystal X-ray structure for **4a**.

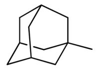
To further demonstrate the scope and limitation of the present reaction, a series of aliphatic and aromatic isocyanides were used to undergo the standard conditions. To our delight, all isocyanides used worked well to give the products **5**. For instance, the employment of cyclohexyl isocyanide essentially led to the formation of **5d** in 80% yield (Table 2, entry 4). Sterically hindered admantyl isocyanide **1f** was also found to be compatible with the present cascade cycloaddition protocol (Table 2, entry 6). To our surprise, the less reactive 4-bromophenyl isocyanide also showed high performance to afford **5g** in good yield (Table 2, entry 7).

Based on the experimental results, a mechanistic proposal is outlined in Scheme 2. The beginning of the cascade cycloaddition involves the formation of resonance-stabilized species, which are very reactive and exist as form **A**↔**B**. Then, nucleophilic attack takes place to produce intermediate **C**. The following [1,5]-H shift[20] step is believed to be the key step in the whole transformation, which is facilitated by the presence of a functional group such as an aryl or another electron-withdrawing group. Further cyclization and the second [1,5]-H shift essentially result in the formation of intermediate **G**. The last step comprises the elimination of the ethoxy group and nucleophilic addition, thus furnishing a formal ethoxy group migration.

Subsequently, experiments varying the alkyl group in allenoate were also conducted (Scheme 3). In this stage,

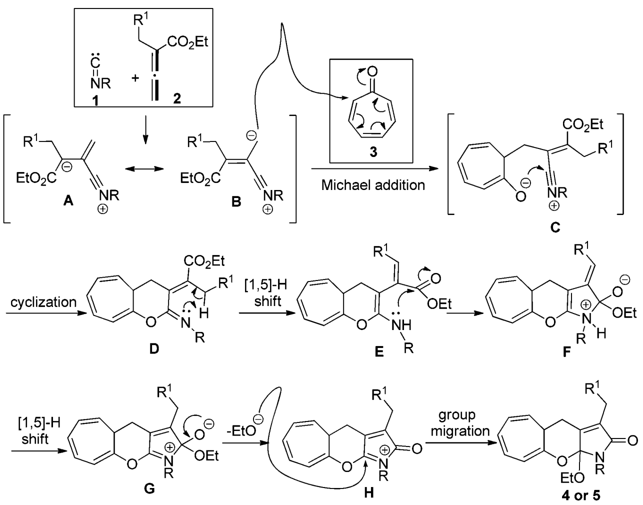
Table 2. Multicomponent Cascade Cycloaddition To Synthesize 7,6,5-Fused Tricyclic Derivatives with Isocyanide 1, Allenoate 2a, and Tropone 3[a]



entry	R	product	yield (%)[b]
1	*iso*-propyl	**5a**	57
2	*n*-butyl	**5b**	39
3	1,1,3,3,-tetramethylbutyl	**5c**	54
4	cyclohexyl	**5d**	80
5	benzyl	**5e**	44
6		**5f**	50
7	4-bromophenyl	**5g**	61
8	4-methoxyphenyl	**5h**	41
9	2,4-dimethoxyphenyl	**5i**	69

[a] All reactions were carried out with 0.5 mmol of isocyanide **1**, 0.6 mmol of allenoate **2a**, and 0.5 mmol of tropone **3** in 5 mL of toluene under reflux unless otherwise noted. [b] Yield of product after silica gel chromatography.

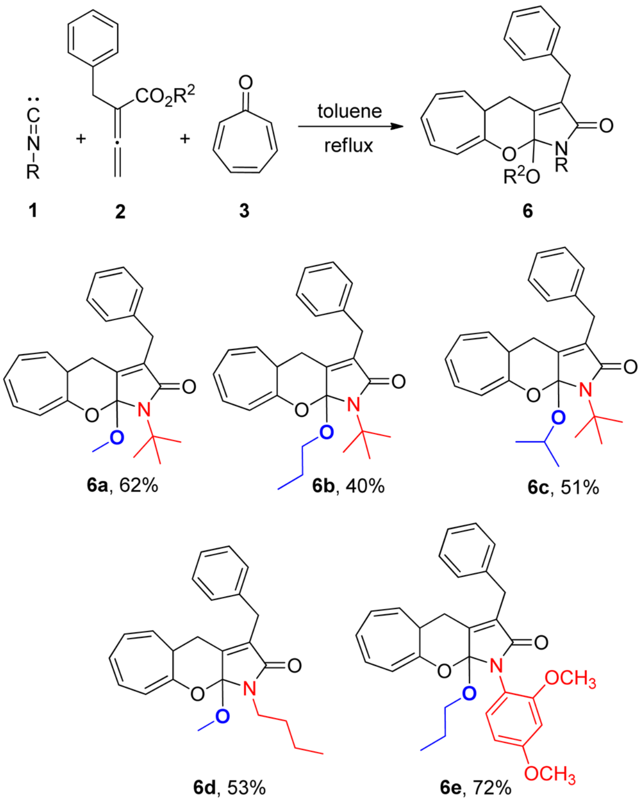
Scheme 2. Proposed Mechanism



allenoate bearing both linear groups and alkyl substitution with a side chain proceeded readily to yield the corresponding adducts **6a**, **6b**, and **6c**. In addition, experiments with isocyanides other than *tert*-butyl ones were also tested. In this case, 2,6-dimethoxyphenyl isocyanide gave a good yield of product **6e**.

In conclusion, we have disclosed an unprecedented multicomponent cascade cycloaddition reaction from readily available isocyanide, allenoate, and tropone. The present strategy provides a new opportunity to access 7,6,5-fused tricyclic skeletons, which are difficult to synthesize with traditional methods. The reaction mechanism is believed to experience unusual [8 + 2 + 1] cycloaddition, sequential [1,5]-H shift, cyclization, and group migration. Remarkably, the present reaction also demonstrates very high synthetic efficiency since the allenoate is used as a C4 component to form the rings. This protocol is also featured by excellent atom economy and mild conditions. As a result, the present reaction has potential to be further applied in organic synthesis.

Scheme 3. Expanded Reactions by Changing the Alkoxy Group in Allenoate



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experiment procedures and full characterization of all compounds, spectral data, ^{1}H and ^{13}C NMR spectra for all products, and X-ray crystal structure data (CIF) for compounds **4a** and **4d**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: xsjia@mail.shu.edu.cn.
*E-mail: lijian@shu.edu.cn.

Notes

The authors declare no competing financial interest.

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(17) CCDC 1020163 for compound **4a** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

(18) CCDC 1020164 for compound **4d** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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