ORGANIC LETTERS

2008
Vol. 10, No. 15
3267−3270

An Unexpected Phosphine-Catalyzed [3 + 2] Annulation. Synthesis of Highly Functionalized Cyclopentenes

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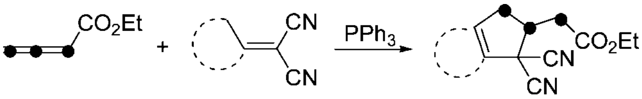
Received May 21, 2008

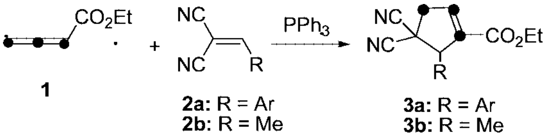
ABSTRACT



An unexpected phosphine-catalyzed [3 + 2] annulation from electron-deficient allenes and substituted alkylidenemalononitriles was realized in which the allylic moiety of the substituted alkylidenemalononitriles served as the three carbon unit of the cyclopentenes instead of the electron-deficient allenes.

The chemistry and biological properties of cyclopentenoids are of continual interest because of their occurrence in a wide range of natural products and drugs.[1] Effective methods to establish cyclopentene structure with substituents in different positions remain a continuing challenge.[2] Among them, phosphine-catalyzed [3 + 2] reaction of allenoates and alkenes is an efficient methodology in constructing cyclopentenes.[3] In the original discovery of this reaction,[3a] it was found that only terminal alkenes can be used as the two-carbon partner except those for the intramolecular annulation or dual-activated olefins (such as diethyl fumarate or diethyl maleate). A pair of regioisomers was also produced in almost every case.

Recently, the reaction was improved by the use of alkenes with strong electron-withdrawing groups (e.g., dinitriles[4a] or ketones[4b–d]) so that alkenes with β-substituents could react effectively. In the formed cyclopentenes (**3**), three carbon atoms come from the allenoate (**1**) and two carbon atoms are from the alkylidenemalononitrile (**2**).[4]



(eq 1)

The question arose if the reaction could still occur when another β-substituent was introduced into the alkenes. 2-(1′-Phenylbenzylidene)malononitrile was first chosen to test the reaction. To our disappointment, no reaction was observed

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(1) (a) Straus, D. S.; Glass, C. K. *Med. Res. Rev.* **2001**, *21*, 185. (b) Conti, M. *Anti-Cancer Drugs* **2006**, *17*, 1017.

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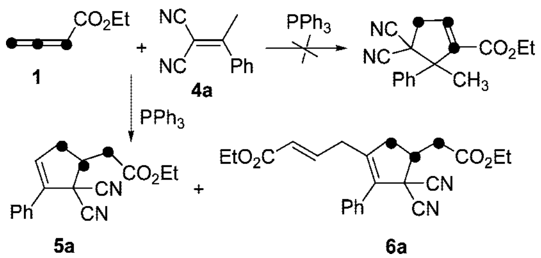
10.1021/ol8011452 CCC: $40.75 © 2008 American Chemical Society
Published on Web 07/03/2008

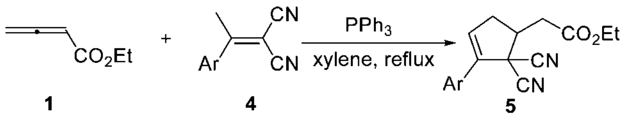
with allenoate in the presence of triphenylphosphine in toluene even under reflux. Isopropylidenemalononitrile gave a complicated mixture under the same reaction conditions. When 2-(1′-phenylethylidene)malononitrile (**4a**) was used, the reaction with allenoate (**1**) did occur in the presence of triphenylphosphine in toluene at 60 °C to give two products. Surprisingly, the result was not the one we expected since the signal of methyl group could not be found in the proposed products from the ^{1}H NMR spectra. One of the products was assigned as **5a** as confirmed by X-ray diffraction[5] and another product was **6a**. Unlike other reported phosphine-catalyzed annulation reaction of allenoates and alkenes,[3,4a] allenoate **1** here just acted as the two-carbon unit in this [3 + 2] reaction (Scheme 1).[6]

Scheme 1



With this unexpected result in hand, optimization of the reaction conditions was carried out. No product could be isolated when solvents with low boiling point (e.g., acetone, THF, and DCE) were used. In refluxing toluene or xylene, both the yield and the selectivity got better. Other tertiary phosphines were also tested as the catalyst, and triphenylphosphine gave the highest yield of **5a**. Finally, triphenylphosphine in refluxing xylene or toluene was chosen as the optimized condition of this reaction. Different substrates were studied as shown in Tables 1 and 2 and Scheme 2.

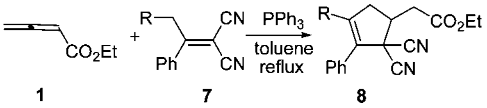
Table 1. Effect of Substituents of the Aryl Group on the Reaction[a]



entry	Ar	product	yield[b] (%)
1[c]	Ph (**4a**)	**5a**	70
2	*p*-ClC_6H_4 (**4b**)	**5b**	61
3	*p*-BrC_6H_4 (**4c**)	**5c**	64
4	*p*-MeC_6H_4 (**4d**)	**5d**	69
5	*p*-$MeOC_6H_4$ (**4e**)	**5e**	65
6	*p*-$NO_2C_6H_4$ (**4f**)	**5f**	disordered
7	*o*-MeC_6H_4 (**4g**)	**5g**	50

[a] **1** (0.45 mmol), **4** (0.36 mmol), and PPh_3 (0.036 mmol) in xylene (3 mL), reflux, 3 h. [b] Isolated yield. [c] Compound **6a** was isolated in 5% yield.

Table 2. Effect of Alkyl Substituents on the Reaction[a]

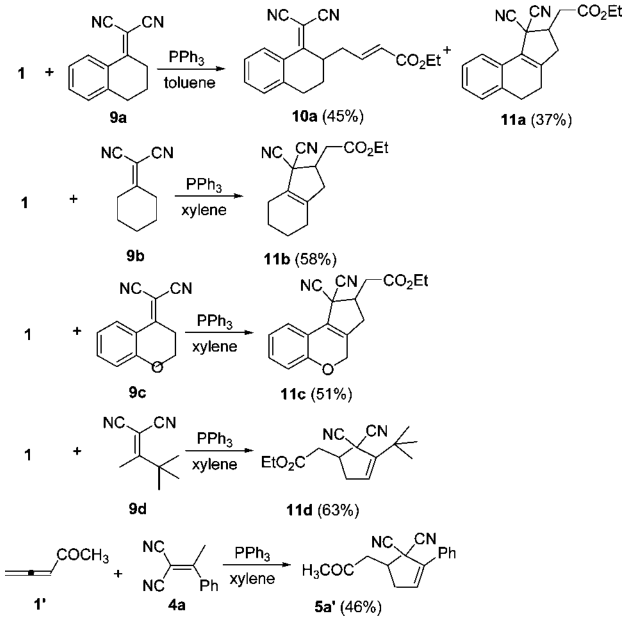


entry	R	product	yield[b] (%)
1	Me (**7a**)	**8a**	77
2	Et (**7b**)	**8b**	77
3	*i*-Pr (**7c**)	**8c**	56
4	Ph (**7d**)	**8d**	77
5	*p*-$NO_2C_6H_4$(**7e**)	**8e**	75
6	CO_2Et(**7f**)	**8f**	82
7	*n*-$C_{11}H_{23}$(**7g**)	**8g**	

[a] **1** (1.2 mmol), **7** (1 mmol), and PPh_3 (0.1 mmol) in toluene (3 mL), reflux, 15 h. [b] Isolated yield.

3,4-Pentadien-2-one (**1′**) reacted similarly with **4a** giving **5a′** in 46% yield (Scheme 2).[4e] Compound **2b** reacted with **1** giving the normal [3 + 2] reaction product **3b** (eq 1).[4e] The results that reactions of the allenoate **1** with **9a−d** in toluene or xylene gave the addition products **11a−d** (Scheme 2) indicated that this [3 + 2] reaction of alkylidenemalononitriles could proceed even without the aryl group; thus, a rather broad class of compounds can be used as the substrates. These results also showed that a *β*,*β*-disubstituted olefin with one methyl substituent is necessary for this kind

Scheme 2



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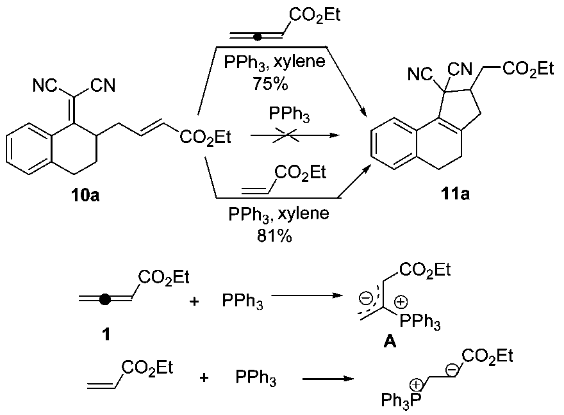
[5] For a CIF file of **5a**, see the Supporting Information.

[6] For other examples that allenoates acted as two-carbon unit in the [3 + 2] reactions, see: (a) Zhu, X. F.; Henry, C. E.; Wang, J.; Dudding, T.; Kwon, O. *Org. Lett.* **2005**, *7*, 1387. (b) Henry, C. E.; Kwon, O. *Org. Lett.* **2007**, *9*, 3069.

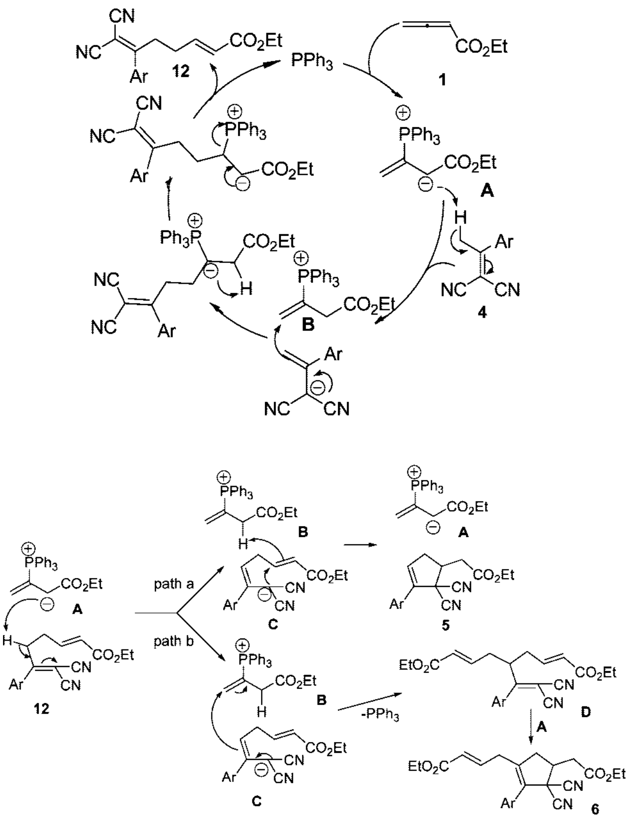
of new [3 + 2] reaction. The products dinitriles can be easily converted to the cyclopentene derivatives which are useful in natural products and drug synthesis.[7]

In the reaction of the allenoate **1** with **9a**, a noncyclized product **10a** was also isolated. Compound **10a** could not be transformed to **11a** in toluene using triphenylphosphine only as the catalyst, but the reaction did occur in the presence of both **1** and triphenylphosphine. This might be due to the formation of the intermediate A from **1** and triphenylphosphine (Scheme 3) which could act as a base in the next intramolecular conjugate addition step (Scheme 4).[8] When ethyl acrylate, which could also react with triphenylphosphine to produce a basic intermediate like A[9] (Scheme 3), was used instead of **1**, the reaction proceeded similarly. These results indicated that the reaction proceeded first with the formation of **10a** followed by the intramolecular conjugate addition to form **11a**.

Scheme 3

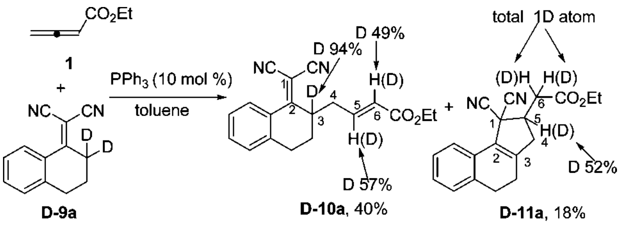


Scheme 4



Thus, a plausible mechanism is shown in Scheme 4. The methyl group of **4** is believed to be deprotonated by the zwitterion **A** first to form the carbanion because of its acidic property (Scheme 4).[7b,10] The formed carbanion could react with other substrates via the γ-addition[10] in phosphine-catalyzed reactions. The first cycle is the γ-addition of compound **4** to the allenoate **1** to give the diene **12** under the catalysis of PPh_3.[3a,b,11] Cyclization of intermediate **12** in the presence of **A** gives compound **5** (path a in Scheme 4). Another possible pathway is the addition of the diene **12** to another molecule of the dipole intermediate **B** to give the triene intermediate **D**, followed by cyclization under the action of **A** to yield compound **6** (path b).To obtain more information of this reaction, a PPh_3-catalyzed reaction of deuterium labeled **D-9a** and **1** in toluene was carried out to give products **D-10a** and **D-11a** (Scheme 5). In the γ-addition product **D-10a**, nearly total hydrogen was deuteriated on carbon 3, and half was deuteriated on both carbon 5 and 6. In product **D-11a**, nearly half was deuteriated on carbon 5, and totally half was deuteriated for the two hydrogen atoms

Scheme 5



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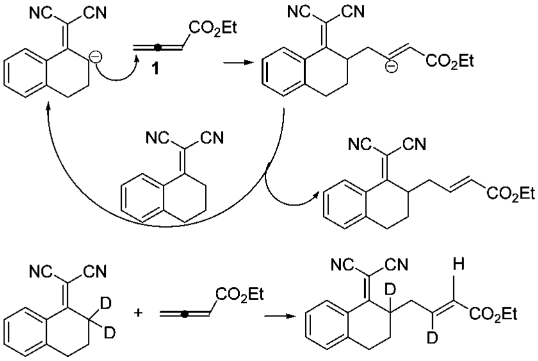
on carbon 6. These results are in compatible with our proposed mechanism.

The results of deuteriated experiments also exclude the possibility of direct addition of the anion of **D-9a** to allenoate **1** in which a different deuteriated product will be obtained (Scheme 6).

Scheme 6



In summary, we developed a highly efficient method for synthesizing substituted cyclopentenes from allenoates and substituted alkylidenemalononitriles via an unexpected method of phosphine-catalyzed [3 + 2] annulation, in which allenoate **1** acted as the two-carbon unit in the formed cyclopentenes. This strategy offers a convenient method for constructing cyclopenenoids under neutral conditions with high atom economy.

Acknowledgment. We thank the National Natural Science Foundation of China (20572121) and Chinese Academy of Sciences for financial support.

Supporting Information Available: Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8011452