ORGANIC LETTERS

2002
Vol. 4, No. 6
1011−1013

Radical Cascade Reaction with 1,4-Dienes and 1,4-Enynes Using 2-(Iodomethyl)cyclopropane-1,1-dicarboxylate as a Homoallyl Radical Precursor: One-Step Synthesis of Bicyclo[3.3.0]octane Derivatives

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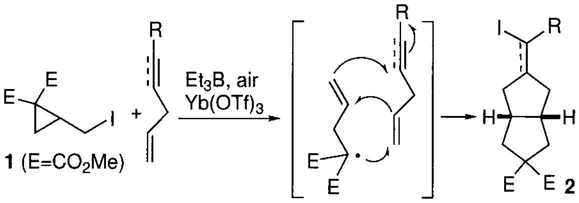
Received January 19, 2002

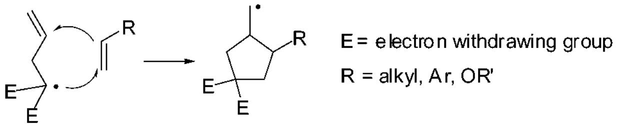
ABSTRACT



Radical cascade reaction with various 1,4-dienes and 1,4-enynes using dimethyl 2-(iodomethyl)cyclopropane-1,1-dicarboxylate as a homoallyl radical precursor smoothly proceeds through an iodine atom transfer mechanism to give functionalized bicyclo[3.3.0]octane derivatives in good yields.

The [3 + 2]-cycloaddition reaction with allylated active methine radicals (electrophilic homoallyl radicals) is well-known as a powerful means for one-step synthesis of a cyclopentanoid skeleton from simple alkenes (without any activating groups such as electron-withdrawing groups) (Scheme 1).[1,2]

Scheme 1



If this reaction is performed with 1,4-dienes, bicyclo[3.3.0]-octane derivatives would possibly be prepared in one step through [3 + 2]-cycloaddition and subsequent 5-*exo*-cyclization of the resulting (2-allylcyclopentyl)methyl radical. As far as we know, only one example of such a reaction has been reported by Snider et al.[2] However, in the Mn(OAc)$_3$-mediated reaction of allylmalonate with 2-methyl-1,4-pentadiene, the desired bicyclic product was merely obtained as a mixture of three isomers in poor yield (bicyclo[3.3.0]-octane, 12%; two kinds of bicyclo[3.4.0]nonene, 9%). This result may be due to the low reactivity of the homoallyl

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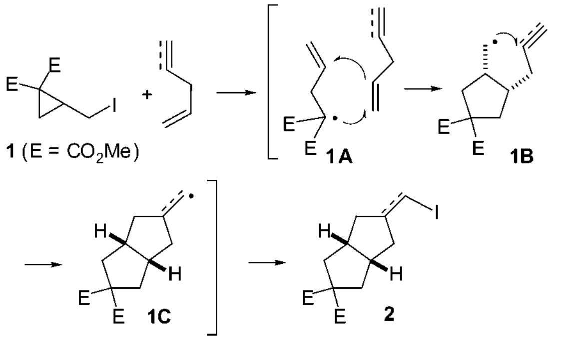
(1) (a) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300. (b) Miura, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5135. (c) Curran, D. P.; Chen, M.; Spletzer, E.; Seong, C. M.; Chang, C. *J. Am. Chem. Soc.* **1989**, *111*, 8872. (d) Singleton, D. A.; Church, K. M. *J. Org. Chem.* **1990**, *55*, 4780. (e) Maslak, V.; Cekovic, Z.; Saicic, R. N. *Synlett* **1998**, 1435. Examples of stepwise radical [3 + 2]-cycloaddition: (f) Curran, D. P.; Seong, C. *Tetrahedron* **1992**, *48*, 2157. (g) Curran, D. P.; Seong, C. *Tetrahedron* **1992**, *48*, 2175.

(2) Snider, B. B.; Buckman, B. O. *Tetrahedron* **1989**, *45*, 6969.

10.1021/ol025583r CCC: $22.00

radical species toward alkyl-substituted alkenes. In this Letter, we report an efficient one-step synthesis of bicyclo-[3.3.0]octane derivatives by a radical iodine atom transfer cascade reaction with 1,4-dienes and 1,4-enynes using dimethyl 2-(iodomethyl)cyclopropane-1,1-dicarboxylate **1** as a homoallyl radical precursor (Scheme 2).

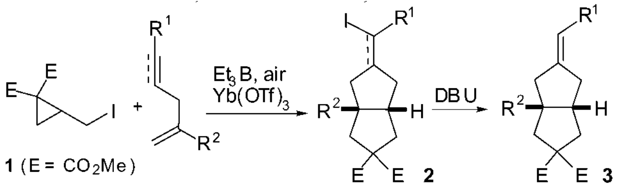
Scheme 2

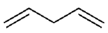
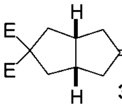
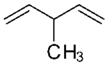
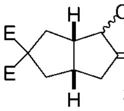
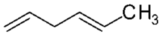
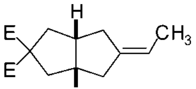
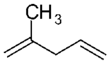
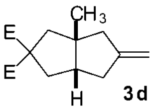
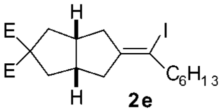
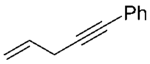
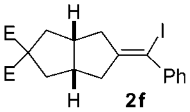
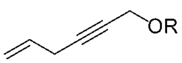
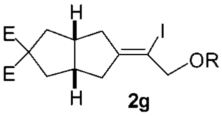


Among the three consecutive C−C bond formations in the reaction of homoallyl radical **1A** with 1,4-diene (Scheme 2), for the achievement of the third bond formation (corresponding to the second 5-*exo*-cyclization), stereoselective construction of *cis*-(2-allylcyclopentyl)methyl radical intermediates **1B** should be required. Although radical [3 + 2]-cycloadditions with alkenes using various electrophilic homoallyl radical precursors have been reported,[1,2] in the reaction with a monoalkyl-substituted alkene, moderate 1,2-*cis*-selectivity and chemical yield have been generally observed (with 1-hexene, 1-heptene, and 1-nonene: *cis/trans* = 2−5, 35−57% yield).[1b,c,e,2]

On the other hand, we recently found radical iodine atom transfer [3 + 2]-cycloaddition with various alkenes using (2-iodomethyl)cyclopropane-1,1-dicarboxylate **1** as a new homoallyl radical precursor.[3,4] This reaction which proceeds in the presence of Et$_3$B and Yb(OTf)$_3$ can be applied not only to reactive enol ethers and 1,1-disubstituted alkenes but also to less reactive 1-alkenes and 1,2-disubstituted alkenes. The success of the reaction is due to the formation of a more electronegative (more reactive) allylmalonate radical on the basis of bidentate coordination between the malonate carbonyl oxygen and Yb(OTf)$_3$.[5] Especially, in the reaction with 1-hexene, the product was obtained with high *cis*-selectivity (*cis/trans* = 11.2) in good yield (82%). This result prompted us to investigate the radical cascade reaction of **1** with various 1,4-diene and 1,4-enyne derivatives (Table 1).

Table 1. Iodine Atom Transfer Radical Cascade Reaction of **1** with Various 1,4-Dienes and 1,4-Eneynes[a]



entry	diene	2	3	yield (%)[b]
1		**2a** (*exo/endo* = 2.7)	 **3a**	78
2		**2b** (80 %)[c]	 **3b**	42 (*exo/endo* = 2.8)
3		**2c**	 **3c**	75
4		**2d**	 **3d**	51
5		 **2e**		74
6		 **2f**		71
7	 (R = TBDPS)	 **2g**		73

[a] Radical cascade reaction: **1** (0.5 mmol), diene or enyne (1 mmol), Et$_3$B (0.5 mmol), Yb(OTf)$_3$ (0.5 mmol) in CH$_2$Cl$_2$ (4 mL) at −15 °C. [b] Isolated yield of **3** in entries 1−4. Isolated yield of **2** in entries 5−7. [c] Isolated yield.

When **1** and 1,4-pentadiene (2 equiv) in CH$_2$Cl$_2$ were treated with Et$_3$B (1 equiv) and Yb(OTf)$_3$ (1 equiv) at −15 °C, three consecutive C−C bond formations by the reaction of the resulting allylmalonate radical with the diene and subsequent iodine atom transfer from **1** efficiently occurred to give (iodomethyl)bicyclo[3.3.0]octane derivative **2a** in good yield with a diastereomer ratio = 2.7 (entry 1).[6] Since the separation of the diastereomers *exo*-**2a** and *endo*-**2a** having *exo*- and *endo*-iodomethyl groups was difficult, **2a** was treated with DBU to obtain methylenebicyclooctane **3a** in 78% yield from **1** (entry 1). In this reaction, the formation of 3-allyl-4-(iodomethyl)cyclopentane-1,1-dicarboxylate, the radical iodine atom transfer [3 + 2]-cycloaddition product, was also observed as a minor side product (<10% yield). In the reaction with 3-methyl-1,4-pentadiene, the (iodomethyl)-

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(3) (a) Kitagawa, O.; Fujiwara, H.; Taguchi, T. *Tetrahedron Lett.* **2001**, *42*, 2165. (b) Kitagawa, O.; Yamada, Y.; Fujiwara, H.; Taguchi, T. *J. Org. Chem.* **2002**, *67*, 922.

(4) Similar radical [3 + 2]-cycloaddition using iodoaziridine derivatives: Kitagawa, O.; Yamada, Y.; Fujiwara, H.; Taguchi, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 3865.

(5) Typical reports in relation to Yb(OTf)$_3$-promoted radical reaction: (a) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779. (b) Mero, C. L.; Porter, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 5155. (c) Yang, D.; Ye, X.; Gu, S.; Xu, M. *J. Am. Chem. Soc.* **1999**, *121*, 5579. For reviews in relation to Lewis acid-mediated radical reaction, see: (d) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562. (e) Guindon, Y.; Jung, G.; Guerin, B.; Ogilvie, W. W. *Synlett* **1998**, 213.

(6) The use of a catalytic amount (0.1−0.3 equiv) of Yb(OTf)$_3$ brought about a considerable decrease in the chemical yield.

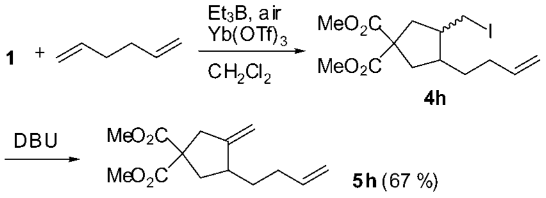
bicyclooctane **2b** was obtained in good yield (80%) as a mixture of the three possible diastereomers (entry 2). Although the conversion to methylene derivative **3b** was attempted by DBU treatment, the chemical yield was moderate (total 42% yield) (entry 2).[7]

The reactions with unsymmetrical 1,4-diene derivatives having different substituent patterns were further examined. In general, the reactivity of an allyl active methine radical toward alkyl-substituted alkenes is known to decrease in the order of 1,1-disubstituted, 1-substituted ,and 1,2-disubstituted alkenes.[1c,8] Accordingly, the reactions with 1,4-hexadiene and 2-methyl-1,4-pentadiene were expected to proceed in a regioselective manner. Indeed, the reaction of **1** with 1,4-hexadiene gave the product **2c** which resulted from attack of the malonate radical to the 1-alkene moiety, while the product from the attack of the malonate radical to the 1,2-disubstituted alkene moiety was not detected (entry 3). To avoid diastereomeric complications, iodide **2c** was converted to ethylidene derivative **3c** to be isolated in total 75% yield (entry 3). In the reaction with 2-methyl-1,4-pentadiene, the allylmalonate radical preferentially attacked the 1,1-disubstitued alkene moiety to give bicyclooctane derivative **3d** having an angular methyl group as a major product (total 51% yield) (entry 4).

This regioselective radical cascade reaction can also be applied to 1,4-enyne derivatives. We have previously confirmed that radical [3 + 2]-cycloaddition of **1** with 1-alkyne did not proceeded to a significant extent even in the presence of Yb(OTf)$_3$. Thus, in the reaction with 1,4-enyne, the (iodomethylene)bicyclooctane derivative should be obtained through [3 + 2]-cycloaddition to the alkene moiety and subsequent 5-*exo*-cyclization to the alkyne moiety. As expected, under the same conditions, the reaction with 1,4-undecaeneyne gave the iodomethylene product **2e** in good yield (74%) with complete regioselectivity (entry 5). Similarly, the reactions with 1,4-enyne derivatives having a phenyl or siloxymethyl group also proceeded in a regioselective manner to give the products **2f** and **2g** in 71% and 73% yields, respectively (entries 6 and 7).

Unfortunately, one-step synthesis of a bicyclo[3.4.0]nonane derivative through the reaction of **1** with 1,5-hexadiene failed. In this reaction, iodomethylcyclopentane derivative **4h** was obtained as a major product together with a trace amount of the desired bicyclononane derivative (Scheme 3). This result indicates that an iodine transfer process to the resulting (2-homoallyl)cyclopentylmethyl radical from **1** occurs prior to 6-*exo*-cyclization because of the slower rate than that of 5-*exo*-cyclization.

Scheme 3



In conclusion, we have succeeded in the development of a radical iodine atom transfer cascade reaction with 1,4-dienes and 1,4-enynes using dimethyl 2-(iodomethyl)cyclopropane-1,1-dicarboxylate **1** as a homoallyl radical precursor. The present reaction should provide useful methodology for the one-step synthesis of various bicyclo[3.3.0]octane derivatives from 1,4-dienes (commercially available) and 1,4-enynes (can be easily prepared in short steps). In addition, most of the reported syntheses of polycyclic compounds using the radical cascade reaction consist of consecutive intramolecular cyclization,[9] and a limited number of reactions initiated from intermolecular radical addition have thus far been reported.[10] Thus, the present radical cascade reaction involving an intermolecular addition followed by two intramolecular cyclizations is be also noteworthy from the viewpoint of basic radical chemistry.

Supporting Information Available: Experimental procedures and characterization data for products **3a**−**3d**, **2e**−**2g**, and **5h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Although elimination reactions with other reagents were attempted (PhSeNa−H$_2$O$_2$, NaH, *t*-BuOK), an increase in the chemical yield of **3b** was not observed.

(8) Riemenschneider, K.; Bartels, H. M.; Dornow, R.; Dreschel-Grau, E.; Eichel, W.; Luthe, H.; Matter, Y. M.; Michaelis, W.; Boldt, P. *J. Org. Chem*. **1987**, *52*, 205.

(9) For reviews in relation to radical cascade reactions, see: (a) Jasperse, C. P.; Curran D. P.; Fevig, T. L. *Chem. Rev*. **1991**, *91*, 1237. (b) Malacria, M. *Chem. Rev*. **1996**, *96*, 289. (c) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed*. **2001**, *40*, 2224.

(10) For recent examples in relation to the synthesis of polycyclic compounds through a radical cascade reaction which is started from intermolecular addition, see: (a) Jung, M. E.; Rayle, H. L. *J. Org. Chem*. **1997**, *62*, 4601. (b) Sibi, M. P.; Chen, J.; Rheault, T. R. *Org. Lett*. **2001**, *3*, 3679. These reactions using a cyclic homoallyl radical involve two consecutive C−C bond formations.