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journal or publication title	Chemical Communications
volume	46
number	6
page range	934-936
year	2010-01-01
URL	http://hdl.handle.net/2297/21295

doi: 10.1039/b919332d

Intramolecular formal [4 + 2] cycloaddition of 3-ethoxycyclobutanones and alkenes†‡

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Received (in XXX, XXX) Xth XXXXXXXXXX 200X, Accepted Xth XXXXXXXXXX 200X

First published on the web Xth XXXXXXXXXX 200X

DOI: 10.1039/b000000x

Intramolecular formal [4 + 2] cycloaddition between 3-ethoxycyclobutanones and a carbon-carbon double bond to the corresponding bicyclo[4.n.0]alkan-2-one derivatives proceeded effectively by using ethylaluminum dichloride.

Intramolecular cycloaddition is a powerful tool for efficient and stereoselective construction of complex molecules.¹ Especially, [4 + 2] cycloaddition reactions such as intramolecular Diels-Alder (IMDA) reaction have been successfully employed for the synthesis of biologically active compounds and natural products under the condition of a well-designed combination between diene and dienophile.² The utility of intramolecular [4 + 2] cycloaddition is expected to be enhanced by discovering a more potent and readily available C4 unit.

We have recently reported that intermolecular [4 + 2] cycloaddition between 3-alkoxycyclobutanone and aldehyde or ketone proceeds to afford tetrahydro- or dihydro- γ -pyrone derivatives by catalysis with boron trifluoride etherate.³ In the course of our study on this cycloaddition, we examined a reaction between 2,2-diallyl-3-ethoxycyclobutanone (**1a**) and benzaldehyde (Scheme 1). It was found that catalysis with boron trifluoride etherate gave expected adducts **2** and **3** in 67% and 13% yields, respectively, whereas the employment of ethylaluminum dichloride gave intramolecular cycloadduct **4a** as the major product (66% yield). The finding of unprecedented intramolecular cycloaddition of an allyl group into the C2-C3 bond of a cyclobutanone ring⁴⁻⁶ as well as the observed interesting chemoselectivity prompted us to investigate this intramolecular cycloaddition further. We report herein formal [4 + 2] cycloaddition between a cyclobutanone skeleton and carbon-carbon double bond of the alkenyl group at the 2-position of 3-ethoxycyclobutanones.

Scheme 1 Lewis acid (LA)-controlled chemoselectivity: intermolecular formal [4 + 2] cycloaddition between **1a** and benzaldehyde to **2** and **3** and intramolecular formal [4 + 2] cycloaddition of **1a** to **4a**

Table 1 Intramolecular formal [4 + 2] cycloaddition of 2-allyl-3-ethoxycyclobutanones **1** to **4**^a

entry	1 (R)	<i>cis</i> <i>trans</i> ^b	product (%yield) ^c	<i>cis/trans</i> ^b
1	1a (allyl)	—	4a (92)	84:16
2 ^d	1a (allyl)	—	4a (89), 5 (3)	27:73
3	1b (H)	30:70	4b (0), 6 (41)	—
4	1c (Me)	56:44	4c (72)	89:11
5	1d (Bn)	34:66	4d (81)	85:15
6	1e (<i>i</i> -Pr)	28:72	4e (88)	82:18
7	1f (Ph)	100:0	4f (0), 7 (70)	—
8	1f (Ph)	0:100	4f (0), 7 (74)	—

^a EtAlCl₂ (1.2 equiv) was employed. ^b The ratios were determined by ¹H NMR analysis. For determination of relative stereochemistry, see supporting information. ^c Isolated yield unless otherwise noted. ^d Conditions: Tin(IV) chloride (1.2 equiv), allyltriisopropylsilane (1.5 equiv), -45 to 0 °C, 80 min. Yield of **4a** was determined by ¹H NMR.

Among Lewis acids we tested,⁷ ethylaluminum dichloride most efficiently promoted intramolecular cycloaddition of **1a** to give *cis*- and *trans*-**4a** in 92% combined yield (*cis/trans* = 84:16, Table 1, entry 1).⁸ Neither regioisomeric cycloaddition nor elimination of ethanol from **4a** were observed. It is notable that the activation of **1a** with tin(IV) chloride in the presence of allyltriisopropylsilane inverted the ratio of *cis*- and *trans*-**4a** (*cis/trans* = 27:73), and intermolecular cycloadduct **5**⁹ was obtained in 3% yield (entry 2). Cycloaddition of several 2-alkyl-2-allyl-3-ethoxycyclobutanones **1b-e** was next performed in order to investigate stereospecificity as well as generality of the intramolecular reaction (entries 3-6). Treatment of a mixture of diastereomers (*cis/trans* = 30:70) of 2-allyl-3-ethoxycyclobutanone **1b** with ethylaluminum dichloride did not give a cycloadduct **4b**, but a self-cycloadduct **6** was obtained in 41% yield (entry 3).³ 2-Allylcyclobutanones **1c-e** gave the desired products **4c-e** in 72-88% yields, and the

Table 2 EtAlCl₂-catalyzed intramolecular formal [4 + 2] cycloaddition of various 2-alkenyl-3-ethoxycyclobutanones **8**^a

entry	cyclobutanone	major product (% yield ^b)	d.r.
1			>99:1
2			>99:1
3			—
4			two isomers 65:35
5			two isomers 95:5
6			>99:1

^a Conditions: see Table 1. ^b Combined yield of diastereomers. ^c A mixture of diastereomers (53:47). ^d A mixture of four diastereomers was treated at −45 to 0 °C.

reactions were found to proceed nonstereospecifically since *cis/trans* ratios of **1c–e** did not correspond to the efficiency of the cycloaddition nor *cis/trans* ratios of **4c–e**. Also, cyclobutanones bearing a bulky alkyl group tended to give the cycloadducts more efficiently (entries 4–6). On the other hand, both isolated diastereomers of 2-allyl-3-ethoxy-2-phenylcyclobutanones **1f** gave no [4 + 2] cycloadduct **4f** but afforded 1-allyl-2-naphthol **7** (entries 7 and 8). These results suggest that cyclization of the phenyl group¹⁰ followed by aromatization to the 2-naphthol derivative **7** took place selectively rather than insertion of the allyl group.

Preparation of bicyclic or tricyclic compounds other than bicyclo[4.1.0]heptan-2-ones **4** was next investigated (Table 2). Cyclobutanones **8a,b** having a 3-butenyl or 4-pentenyl group at the 2-position gave the corresponding cycloadducts **9a** and **9b** in 18% and 86% yields, respectively, as a single diastereomer (entries 1 and 2). Cyclobutanone **8c** bearing a 5-hexenyl group did not give a cycloadduct **9c** (entry 3), whereas the reaction of 2-(*o*-allylbenzyl)cyclobutanone **8d** gave two products, **9d** and its 4-epimer **9d'** (**9d** : **9d'** = 65:35) in 67% combined yield (entry 4). Restricted conformation of the *o*-allylbenzyl group might help the successful cycloaddition of **8d**. Intramolecular cycloaddition of spirocyclobutanones **8e,f** proceeded smoothly to afford the corresponding tricyclic compounds **9e,f** in good yields (entries 5 and 6), and stereochemical convergence was observed. That is, treatment of a mixture of four diastereomers of **8f** with

ethylaluminum dichloride gave **9f** as a single diastereomer.¹¹

A plausible mechanism for the present intramolecular cycloaddition is shown in Scheme 2. A zwitterionic intermediate **11** is regioselectively formed by EtAlCl₂-catalyzed ring cleavage of cyclobutanone **10**,³ and [4 + 2] cycloaddition of a terminal alkenyl group proceeds to give an adduct **12**.

Scheme 2. Plausible mechanism for EtAlCl₂-catalyzed [4 + 2] cycloaddition of 2-alkenyl-3-ethoxycyclobutanones **10** to 4-ethoxybicyclo[4.*n*.0]alkan-2-ones **12**.

In summary, we have developed ethylaluminum dichloride-promoted intramolecular insertion of a carbon-carbon double bond into 3-ethoxycyclobutanones. This intramolecular [4 + 2] cycloaddition shows high regioselectivity and stereoselectivity. Studies on the nature of zwitterionic intermediates generated by activation of 3-ethoxycyclobutanones and the reaction mechanism for the present intramolecular cycloaddition is currently underway.

The authors thank Prof. Shuhei Fujinami (Kanazawa University) for X-ray crystallographic analysis. This study was supported by a SUMBOR grant and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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† Electronic Supplementary Information (ESI) available: Experimental details and spectral data. See DOI: 10.1039/b000000x/

‡ CCDC 735720 for **9d**, CCDC735721 for **9d'**, and CCDC 735722 for a derivative of **9f** contain the supplementary crystallographic data. 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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Graphical contents entry

Intramolecular [4+2] cycloaddition of 3-ethoxycyclobutanones and alkenes proceeded regioselectively and stereoselectively by using ethyl aluminumdichloride as a Lewis acid.