Tetrahedron Letters 53 (2012) 432–434

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Formal [4+2] cycloaddition of cyclobutanones bearing alkyne–cobalt complex at their 3-positions

Mizuki Kawano, Takaaki Kiuchi, Jun-ichi Matsuo *, Hiroyuki Ishibashi

School of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

ARTICLE INFO

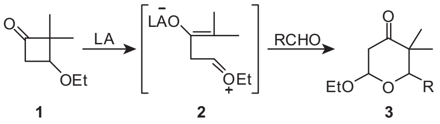
Article history:
Received 18 October 2011
Revised 11 November 2011
Accepted 14 November 2011
Available online 19 November 2011

Keywords:
[4+2] Cycloaddition
Alkyne–cobalt complex
Cyclobutanone
Lewis acid
Tetrahydropyrone

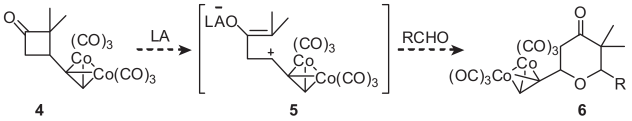
ABSTRACT

Cyclobutanones bearing an alkyne–cobalt complex at their 3-positions reacted with aldehydes to give formal [4+2] cycloadducts by using tin(IV) chloride as a Lewis acid. Highly substituted tetrahydropyrone derivatives were stereoselectively prepared by this method.

Cyclobutanones are important synthetic intermediates in organic synthesis.[1] We have recently reported that zwitterionic intermediate **2**, which was generated by Lewis acid-catalyzed ring cleavage of 3-ethoxycyclobutanone **1**, reacted with various aldehydes,[2a] allylsilanes,[2b] silyl enol ethers,[2c] and imines[2d] to afford the corresponding formal [4+2] cycloadducts (Eq. 1). We have also reported diastereoselective asymmetric [4+2] cycloaddition by using 3-alkoxycyclobutanone bearing L-ethyl lactate as a chiral auxiliary.[3] The generation of zwitterionic intermediate **2** was promoted by the alkoxy group at the 3-position of **1**. It was then thought that an alkyne–cobalt complex at the 3-position of cyclobutanone **4** would also promote the generation of zwitterionic intermediate **5** since an alkyne–cobalt complex stabilizes the α-cation (Eq. 2).[4] We report herein the formal [4+2] cycloaddition of cyclobutanones bearing an alkyne–cobalt complex at their 3-positions to afford tetrahydropyrones.



(1)



(2)

Cyclobutanones **11a**–**c** were prepared from amides **7a**–**c** by seven steps (Scheme 1). 3-Benzyloxymethylcyclobutanones **8a**–**c** were prepared by [2+2] cycloaddition with ketene iminium ions,[5] which were generated from amides **7a**–**c**, and allyl benzyl ether. Protection of the carbonyl group of **8a**–**c** with ethylene acetal, deprotection of the benzyl group of **9a**–**c**, and Swern oxidation[6] of the resulting primary alcohols gave aldehydes **10a**–**c**. Reaction of aldehydes **10a**–**c** with Bestmann–Ohira reagent[7] followed by the deprotection of acetal and complexation with $Co_2(CO)_8$ gave the desired cyclobutanones **11a**–**c**.

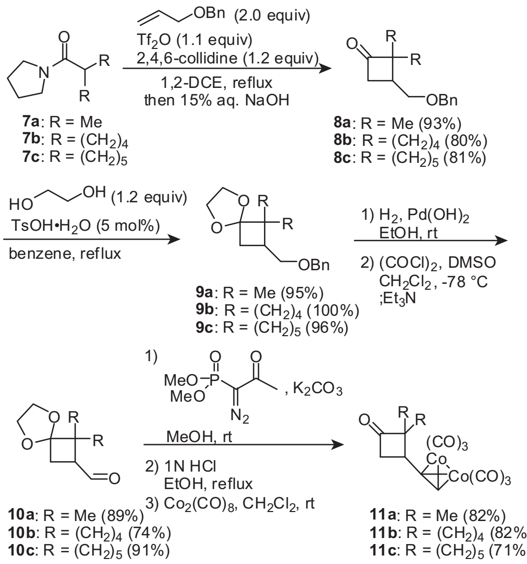
First, we explored a suitable Lewis acid for formal [4+2] cycloaddition between cyclobutanone **11a** and benzaldehyde **12** (Table 1). The desired product **13** was obtained in a 38% yield by using boron trifluoride etherate (entry 1). Catalysis with titanium(IV) chloride gave enone **14** in a 32% yield as the major product along with cycloadduct **13** (13%). Tin(IV) chloride was found to catalyze the desired [4+2] cycloaddition most effectively among the Lewis acids we tested, and **13** was obtained in an 82% yield with high *cis*-selectivity (*cis*/*trans* = 98:2) (entry 3). When ethylaluminum dichloride was employed, enone **14** was obtained in a 79% yield (entry 4).

Next, the scope and limitations of tin(IV) chloride-catalyzed [4+2] cycloaddition of cyclobutanone **11a** were investigated by using various aldehydes **15a**–**l** (Table 2). 4-Methyl and 4-methoxybenzaldehydes reacted with **11a** to give the corresponding [4+2] cycloadducts in 57% and 31% yields, respectively (entries 1 and 2). The use of halogen-substituted benzaldehydes **15c**–**e** afforded the desired products **16c**–**e** in high yields (entries 3–5). These results suggest that electrophilic aldehydes reacted smoothly. In comparison with 2-naphtaldehyde **15g**, which gave cycloadduct **16g** in a 45% yield (entry 7), the reaction with 1-naphtaldehyde

---

* Corresponding author.
E-mail address: jimatsuo@p.kanazawa-u.ac.jp (J. Matsuo).

doi:10.1016/j.tetlet.2011.11.067



Scheme 1. Preparation of cyclobutanone **11a**–**c**.

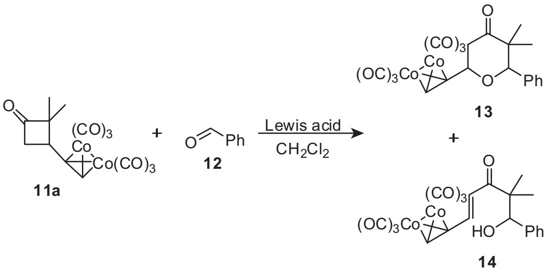
15f gave the desired adduct **16f** in a lower yield (entry 6). Aliphatic aldehydes **15h**–**k** gave the corresponding tetrahydropyrones **16h**–**k** (entries 8–12). Longer reaction time was required for sterically hindered aldehydes. In all of the examples described above, cycloadducts **16a**–**l** were obtained with high *cis*-selectivity.

Reactions of spirocyclobutanones **11b** and **11c** also gave the corresponding cycloadducts **17b** and **17c** in 64% and 58% yields, respectively, as a single diastereomer (Table 3).

Decomplexation of alkyne–cobalt complex **13** with cerium(IV) diammonium nitrate afforded tetrahydropyrone **18** in a 75% yield (Scheme 2). Reaction of cyclobutanone **19** with benzaldehyde catalyzed by tin(IV) chloride did not proceed. Therefore, the stabilization of α-cation by the alkyne–cobalt complex was important for these cycloaddition reactions.

In summary, we have developed tin(IV) chloride-mediated intermolecular [4+2] cycloaddition of cyclobutanones bearing an alkyne–cobalt complex at their 3-positions. This formal [4+2] cycloaddition showed *cis*-stereoselectivity.

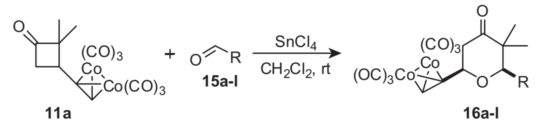
Table 1
Effects of Lewis acids[a]



Entry	Lewis acid	Conditions	Yield[b] (%)	
			13	**14**
1	BF_3-OEt_2	rt, 12 h	38	nd[c]
2	$TiCl_4$	−20 °C, 15 min	13	32
3	$SnCl_4$	rt, 4 h	82[d]	Trace
4	$EtAlCl_2$	−20 °C to 0 °C, 1 h	Trace	79

[a] PhCHO (**12**, 1.0 equiv), cyclobutanone **11a** (1.5 equiv) and Lewis acid (2.0 equiv) were employed.
[b] Isolated yield (%).
[c] nd = Not detected.
[d] *Cis*/*trans* = 98:2. The stereochemistry was determined by ^{1}H NMR spectra.

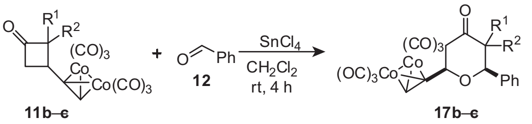
Table 2
Tin(IV) chloride-catalyzed formal [4+2] cycloaddition of cyclobutanone **11a** to various aldehydes **15a**–**l**[a]



Entry	**15** (R)	Time (h)	Yield[b] (%)	*Cis*/*trans*[c]
1	**15a** (4-MeC_6H_4)	4	57	>99:1
2	**15b** (4-$MeOC_6H_4$)	10	31	>99:1
3	**15c** (4-FC_6H_4)	4	77	99:1
4	**15d** (4-ClC_6H_4)	4	83	93:7
5	**15e** (4-BrC_6H_4)	4	87	91:9
6	**15f** (1-naphthyl)	22	27	>99:1
7	**15g** (2-naphthyl)	8	45	>99:1
8	**15h** ($PhCH_2CH_2$)	6	76	96:4
9	**15i** (*n*-heptyl)	6	68	91:9
10	**15j** (*i*-Bu)	9	42	94:6
11	**15k** (*i*-Pr)	18	61	97:3
12	**15l** (*t*-Bu)	12	11	98:2

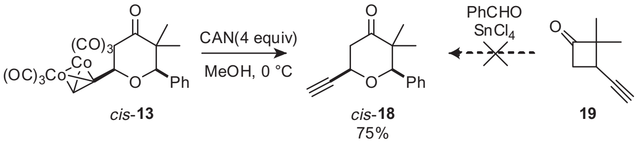
[a] For reaction conditions, see Table 1.
[b] Isolated yield (%).
[c] The stereochemistry was determined by ^{1}H NMR spectra.

Table 3
Tin(IV) chloride-catalyzed formal [4+2] cycloaddition of 2,2-dialkylcyclobutanones **11b** and **11c** to benzaldehyde[a]



Entry	Cyclobutanone **11**	Yield[b] (%)	*Cis*/*trans*[c]
1	R^1, R^2 = $(CH_2)_4$ (**11b**)	64	>99:1
2	R^1, R^2 = $(CH_2)_5$ (**11c**)	58	>99:1

[a] For reaction conditions, see Table 1.
[b] Isolated yield (%).
[c] The stereochemistry was determined by ^{1}H NMR spectra.



Scheme 2. Decomplexation of alkyne–cobalt complex **13**.

Acknowledgment

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.067.

References and notes

1. (a) Conia, J. M.; Robson, M. J. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 473; (b) Belluš, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 797; (c) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449; (d) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485.
2. (a) Matsuo, J.; Sasaki, S.; Tanaka, H.; Ishibashi, H. *J. Am. Chem. Soc.* **2008**, *130*, 11600; (b) Matsuo, J.; Sasaki, S.; Hoshikawa, T.; Ishibashi, H. *Org. Lett.* **2009**, *11*, 3822; (c) Matsuo, J.; Negishi, S.; Ishibashi, H. *Tetrahedron Lett.* **2009**, *50*, 5831; (d) Matsuo, J.; Okado, R.; Ishibashi, H. *Org. Lett.* **2010**, *12*, 3266.
3. Negishi, S.; Ishibashi, H.; Matsuo, J. *Org. Lett.* **2010**, *12*, 4984.
4. (a) Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133; (b) Allart, E. A.; Christie, S. D. R.; Pritchard, G. J.; Elsegood, M. R. J. *Chem. Commun.* **2009**, 7339.
5. (a) Houge, C.; Frisque-Hesbain, A. M.; Mockel, A.; Ghosez, L. *J. Am. Chem. Soc.* **1982**, *104*, 2920; (b) Markó, I.; Ronsmans, B.; Frisque-Hesbain, A. M.; Dumas, S.; Ghosez, L. *J. Am. Chem. Soc.* **1985**, *107*, 2192.
6. (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165; (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.
7. (a) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521; (b) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59; (c) Pietruszka, J.; Witt, A. *Synthesis* **2006**, 4266.