ORGANIC LETTERS

2009
Vol. 11, No. 8
1845−1847

Indium-Catalyzed [1 + *n*] Annulation Reaction between *β*-Ketoester and α,*ω*-Diyne

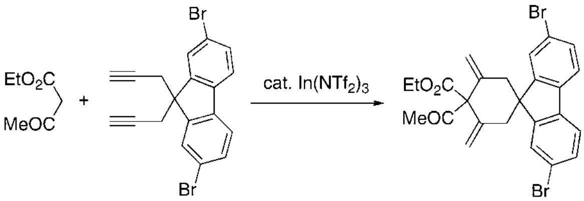
Hayato Tsuji,* Iku Tanaka, Kohei Endo,† Ken-ichi Yamagata, Masaharu Nakamura,‡ and Eiichi Nakamura*

Department of Chemistry, School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

nakamura@chem.s.u-tokyo.ac.jp

Received February 18, 2009

ABSTRACT



A catalytic amount of In(NTf$_2$)$_3$ effects the inter- and intramolecular addition of a *β*-ketoester to an α,*ω*-diyne to produce a 1,3-dimethylenecycloalkane derivative in a single step. This [1 + *n*] annulation reaction shows good functional group tolerance and allows the synthesis of five- to seven-membered carbo- and heterocyclic as well as spirocyclic structures in moderate to excellent yields.

Construction of ring systems through a quick assembly of multiple components continues to attract the interest of our group[1] and other researchers.[2,3] Focusing on the addition of metal enolates to unactivated alkenes[4] and alkynes,[5] we recently found that indium salts catalyzed the inter-[6] and intramolecular addition reactions[7] of a 1,3-dicarbonyl compound to an unactivated alkyne.[8,9] The efficiency of these reactions was found to be very high, particularly for the intramolecular reaction, which has been cross-checked independently by Hatakeyama.[8] Therefore, we conjectured

---

† Present address: Department of Chemistry and Biochemistry, School of Advanced Science and Engineering, Waseda University, Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan.

‡ Present address: International Research Center for Elements Science Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan.

(1) (a) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867–877. (b) Tsuji, H.; Yamagata, K.-i.; Fujimoto, T.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 7792–7793. See also ref 3.

(2) For reviews, see: (a) Lautens, M.; Kulte, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92. (b) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471–1499. (c) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101–4111.

(3) Kuninobu, Y.; Nishi, M.; Yudha, S. S.; Takai, K. *Org. Lett.* **2008**, *10*, 3009–3011.

(4) (a) Kubota, K.; Nakamura, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2491–2493. (b) Lorthiois, E.; Marek, I.; Normant, J. F. *J. Org. Chem.* **1998**, *63*, 566–574. (c) Rodriguez, A. L.; Bunlaksananusorn, T.; Knochel, P. *Org. Lett.* **2000**, *2*, 3285–3287. (d) Pei, T.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 11290–11291. (e) Yao, X.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 6884–6885. (f) Nakamura, M.; Hatakeyama, T.; Hara, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 6362–6363. (g) Nakamura, M.; Hatakeyama, T.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 11820–11825.

(5) (a) Nakamura, M.; Liang, C.; Nakamura, E. *Org. Lett.* **2004**, *6*, 2015–2017. (b) Nakamura, M.; Fujimoto, T.; Endo, K.; Nakamura, E. *Org. Lett.* **2004**, *6*, 4837–4840.

(6) (a) Nakamura, M.; Endo, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 13002–13003. (b) Nakamura, M.; Endo, K.; Nakamura, E. *Org. Lett.* **2005**, *7*, 3279–3281. (c) Nakamura, M.; Endo, K.; Nakamura, E. *Adv. Synth. Catal.* **2005**, *347*, 1681–1686. (d) Endo, K.; Hatakeyama, T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 5264–5271. (e) Tsuji, H.; Fujimoto, T.; Endo, K.; Nakamura, M.; Nakamura, E. *Org. Lett.* **2008**, *10*, 1219–1221. (f) Fujimoto, T.; Endo, K.; Tsuji, H.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 4492–4496.

(7) (a) Tsuji, H.; Yamagata, K.-i.; Itoh, Y.; Endo, K.; Nakamura, M.; Nakamura, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 8060–8062. (b) Itoh, Y.; Tsuji, H.; Yamagata, K.-i.; Endo, K.; Tanaka, I.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 17161–17167.

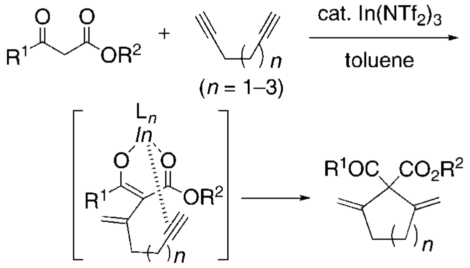
(8) Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6244–6246.

(9) An example of inter- and intramolecular addition of a *β*-dicarbonyl moiety to an alkyne catalyzed by a Re complex: Kuninobu, Y.; Kawata, A.; Takai, K. *Org. Lett.* **2005**, *7*, 4823–4825.

10.1021/ol9003542 CCC: $40.75

that it is possible to apply this indium catalysis to the one-pot [1 + *n*] synthesis of carbocyclic and heterocyclic rings. Herein, we report that the In(NTf$_2$)$_3$-catalyzed reaction of β-ketoesters and α,ω-diynes takes place smoothly to afford the expected [1 + *n*] annulation products, 1,3-dimethylenecycloalkane derivatives (Scheme 1). This reaction, usually carried out in a 0.2 M toluene solution with 1 mol % of catalyst loading at 150 °C, gives an excellent yield and produces five- and six-membered rings with a simple structure and a moderate yield in the synthesis of seven-membered rings and of five- and six-membered rings with a relatively complex structure.

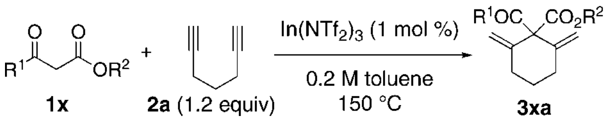
Scheme 1

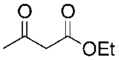
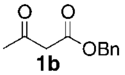
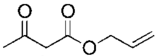
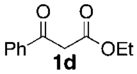
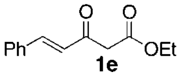


A typical procedure for the formation of six-membered rings as performed on a gram scale is as follows. A mixture of ethyl acetoacetate **1a** (1.06 g) and 1,6-heptadiyne **2a** (0.86 g) in toluene (38 mL) was heated at 150 °C for a period of 3 h in the presence of 1 mol % of In(NTf$_2$)$_3$, which was found to be the most effective catalyst for intermolecular cyclization in our previous studies.[7] After being cooled to ambient temperature, the resulting mixture was passed through a pad of Celite to remove the catalyst. After evaporation, bulb-to-bulb distillation afforded 1.41 g of the product **3aa** (90% yield, Table 1, entry 1, in parentheses). When this reaction was carried out on a 0.5 mmol scale, and the resulting mixture was purified using silica gel column chromatography, the expected 1,3-dimethylenecyclohexane product **3aa** was obtained in a 98% isolated yield (Table 1, entry 1). The structure of the product was fully characterized from the NMR spectra, mass spectrometry data, and elemental analysis.

Other examples of the reaction of β-ketoesters with 1,6-heptadiyne **2a** are shown in Table 1. Benzyl and allyl acetates that may be moderately acid-sensitive gave the cyclized products in 97% (2 h) and 90% yields (12 h), respectively (entries 2 and 3). We can ascribe the lower reactivity of the allyl acetate **1c** compared to **1a** and **1b** to the competitive coordination of the alkene moiety of the allyl group and the alkyne to the indium atom. The reactions of benzoyl- and cinnamoylacetate, which produced some uncharacterizable side products, afforded the cyclized products in lower yields (entries 4 and 5). Other active methylene compounds, such as β-ketoamide and malonic ester, did not participate well in the reaction. β-Diketone (2,4-pentanedione) gave the corresponding six-membered ring product in a high yield as a mixture of 1,3-dimethylenecyclohexane and its olefin isomer, a 1-methyl-5-methylenecyclohex-1-ene derivative (see the Supporting Information).

Table 1. Reaction of β-Ketoesters with 1,6-Heptadiyne[a]



entry	substrate	time	product	yield[b]
1	 **1a**	(3 h) 2 h	**3aa**	(90%)[c] 98%
2	 **1b**	2 h	**3ba**	97%
3	 **1c**	12 h	**3ca**	90%
4	 **1d**	19 h	**3da**	77%
5	 **1e**	2 h	**3ea**	78%

[a] The data were obtained from reactions on a 0.2 mmol scale unless otherwise noted. [b] Isolated yield. [c] The reaction time and yield in parentheses are for the 1 g scale reaction.

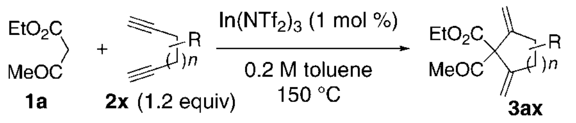
Next, we examined the reactions of ethyl acetoacetate **1a** with various other α,ω-diynes **2b−i** (Table 2). The formation of the simplest five-membered ring by the reaction with 1,5-hexadiyne was performed at 100 °C to obtain a 1,3-dimethylenecyclopentane product **3ab** in a 79% isolated yield (72 h, entry 1). We did not detect any of the initial monoaddition product (i.e., without cyclization), as opposed to the case of the seven-membered ring formation (vide infra), where the second intramolecular cyclization was found to be slow. The 1,2-diethynylbenzene afforded an indane derivative **3ac** in a 30% yield (at 100 °C after 48 h, entry 2). When these reactions were performed at 150 °C, the yield of the desired product decreased (28% and trace amounts of **3ab** and **3ac**, respectively), while the amount of unidentified product increased. Such a reactivity in the formation of five membered-rings is presumably due to the ring strain of the resulting dimethylenecyclopentane products.

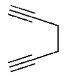
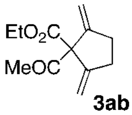
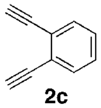
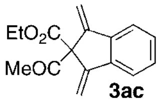
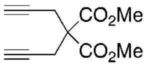
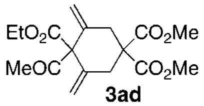
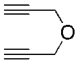
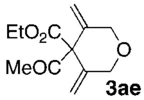
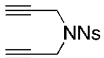
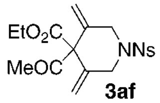
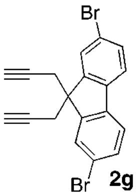
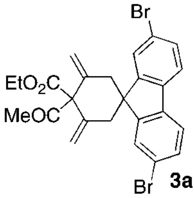
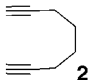
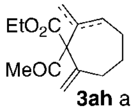
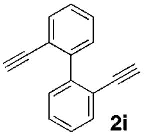
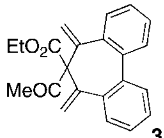
In agreement with the results shown in Table 1, the synthesis of six-membered rings took place in higher yields. Thus, an α,α-dipropargyl malonate **2d** afforded the expected cyclized product **3ad** in 78% yield (entry 3) and the dipropargyl ether **2e** gave the dimethylenetetrahydropyrane derivative **3ae** in a 70% yield (entry 4). The reaction of 2-nitrobenzensulfonyl (Ns)[10] dipropargylamine **2f** was complete after 8 h at 150 °C and gave the cyclic amine **3af** in 90% yield (entry 5). The reaction with 2,7-dibromo-9,9′-

---

(10) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353–359.

Table 2. Reaction of Ethyl Acetoacetate with α,ω-Diynes



entry	diyne	time	product	yield[a]
1	 **2b**	72 h[b]	 **3ab**	79%
2	 **2c**	48 h[b]	 **3ac**	30%
3	 **2d**	20 h	 **3ad**	78%
4	 **2e**	8 h	 **3ae**	70%
5	 **2f**	8 h	 **3af**	90%
6	 **2g**	43 h	 **3ag**	57%
7	 **2h**	72 h	 **3ah** and **3ah'**	45%[c,d]
8	 **2i**	36 h	 **3ai**	71%[d]

[a] Isolated yield. [b] Reaction temperature was 100 °C. [c] *exo*-Olefin (**3ah**): *endo*-olefin (**3ah′**) = 2:1. The α-alkynylidene compound was also obtained in 10% yield. See the Supporting Information. [d] Concentration was 0.05 M.

dipropargylfluorene **2g** required a longer reaction time and afforded a structurally intriguing spirofluorene compound **3ag** in 57% yield (entry 8). Note that the bromine atoms in the starting material survived the reaction conditions, and the dibromide product may serve as a useful starting material for further development of organoelectronic materials.[11] Seven-membered ring formation by the reaction of **1a** with 1,7-octadiyne (**2h**) took place slowly in a lower yield (entry 7) and produced an inseparable mixture of a 1,3-dimethylenecycloheptane **3ah** and its olefin isomer, the 1-methyl-6-methylenecyclohept-1-ene derivative, **3ah′** in 30% and 15% yields, respectively. The uncyclized monoaddition product (as an α-alkylydene compound **4**,[5b] see the Supporting Information) also formed in a 10% yield, indicating that the intramolecular addition is slow. The reaction of 2,2′-diethynylbiphenyl **2i** took place much faster than 1,7-octadiyne (**2h**) to afford dibenzocycloheptane **3ai** in a 71% yield (entry 8) either because of the higher reactivity of the arylacetylene structure or because of the lower degree of freedom of the starting material. Attempts to form rings larger than eight-membered rings have so far been unsuccessful.

The single-crystal X-ray structure of the spirofluorene compound **3ag** is shown in Figure 1. The 1,3-dimethylenecyclohexane moiety is in a chair conformation, which places the ester group flanked by the two *exo*-methylene groups.

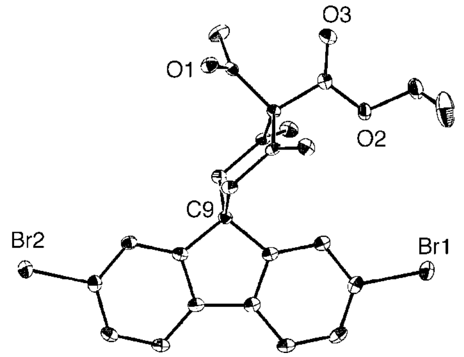


Figure 1. ORTEP drawing of the spirocyclic compound **3ag** (50% probability for thermal ellipsoids). Hydrogen atoms are omitted for clarity.

In summary, we have shown that In(NTf$_2$)$_3$ catalyzes the double addition of a β-ketoester to an α,ω-diyne to promote the [1 + *n*] cyclization reaction. This reaction produces densely functionalized cyclic compounds with minimal effort and, hence, will be useful in further synthetic applications.

Acknowledgment. This research was supported by KAKENHI provided by MEXT/JSPS (to E.N., Grant No. 18105004) and the Global COE Program for Chemistry Innovation through Cooperation of Science and Engineering.

Supporting Information Available: Detailed experimental procedure and properties of compounds. CIF file of compound **3ag**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9003542

---

(11) For a recent example, see: Tsuji, H.; Mitsui, C.; Ilies, L.; Sato, Y.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 11902–11903.