ORGANIC LETTERS

2008
Vol. 10, No. 12
2441−2444

Efficient Synthetic Method of Multisubstituted Allenes from the Reactions of Allylindium Reagents with 3°-Propargyl Alcohols

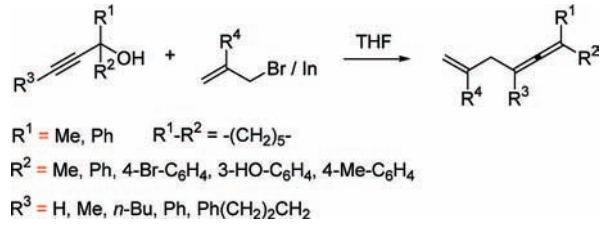
Kooyeon Lee and Phil Ho Lee*

National Research Laboratory for Catalytic Organic Reaction, Department of Chemistry and Institute for Molecular Science & Fusion Technology, Kangwon National University, Chunchon 200-701, Republic of Korea

phlee@kangwon.ac.kr

Received March 31, 2008

ABSTRACT



An efficient synthetic method of tri- and tetra-substituted allenes having an allyl and methallyl group was developed by the reactions of allylindium reagents generated in situ from indium and allyl bromides with 3°-propargyl alcohols.

Development of efficient and practical synthetic methods for multisubstituted allenes is highly desirable because these compounds are versatile building blocks for organic synthesis.[1] In general, allene compounds can be prepared by alkylation of allenylmethyl halides with appropriate carbanionic species,[1e] an S_N2'-type selective displacement of propargyl alcohol derivatives with organocopper reagents,[2] intramolecular regio- and stereoselective reduction of an acetylenic substrate,[3] 1,4-addition to enynes,[4]and 1,6-addition reactions to acceptor-substituted enynes.[5] Synthesis of allenes by means of metal-catalyzed cross-coupling reactions would be an alternative method.[6] Among these, allene preparation through S_N2' nucleophilic substitutions of propargylic electrophiles using organocopper reagents has developed into one of the most versatile and popular protocols. In these cases, propargyl acetates and benzoates,[7] carbonates,[8] sulfonates,[9] ethers and acetals,[10] halides,[11] oxiranes,[12] and even aziri-

(1) (a) Rossi, R.; Diversi, P. *Synthesis* **1973**, 25. (b) *The Chemistry of Ketenes, Allenes, and Related Compounds*; Patai, S., Ed.; Wiley: New York, 1980. (c) Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier: Amsterdam, 1981. (d) *The Chemistry of Allenes*; Landor, S. R., Ed.; Academic Press: London, 1982. (e) Coppola, G. M.; Schuster, H. F. *Allenes in Organic Synthesis*; Wiley: New York, 1984. (f) *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004. (g) Urabe, H.; Takeda, T.; Hideura, D.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 11295. (h) Funami, H.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 909. (i) Lee, J. H.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 912.

(2) (a) Rona, P.; Crabbe, P. *J. Am. Chem. Soc.* **1968**, *90*, 4733. (b) Fleming, I.; Terrett, N. K. J. *Organomet. Chem.* **1984**, *264*, 99. (c) Trost, B. M.; Urabe, H. *J. Am. Chem. Soc.* **1990**, *112*, 4982. (d) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *J. Am. Chem. Soc.* **1990**, *112*, 8042. (e) Borzilleri, R. M.; Weinreb, S. M.; Parvez, M. *J. Am. Chem. Soc.* **1995**, *117*, 10905. (f) Jansen, A.; Krause, N. *Inorg. Chim. Acta* **2006**, *359*, 1761.

(3) (a) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492. (b) Shepard, M. S.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 2597.

(4) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 186.

(5) Krause, N.; Thorand, S. *Inorg. Chim. Acta* **1999**, *296*, 1.

(6) Lee, K.; Seomoon, D.; Lee, P. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3901.

(7) (a) Keinan, E.; Bosch, E. *J. Org. Chem.* **1986**, *51*, 4006. (b) Corriu, R. J. P.; Huyn, V.; Iqbal, J.; Moreau, J. J. E.; Vernhet, C. *Tetrahedron* **1992**, *48*, 6231. (c) Spino, C.; Thibault, C.; Gingras, S. *J. Org. Chem.* **1998**, *63*, 5283. (d) Riveiros, R.; Rodriguez, D.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **2006**, *8*, 1403.

10.1021/ol800719g CCC: $40.75
Published on Web 05/14/2008

dines[13] have been successfully employed as substrates. Although the synthetic utility of allylallenes is very useful in thermal aromatization,[14] radical cyclization,[15] gold-mediated cyclization,[16] and preparation of bicyclo[3.1.0]hexanone,[17] (*E*)-vinyl azides, and polysubstituted pyrroles,[18] synthesis of tri- and tetra-substituted allylallenes is tedious. In addition, as far as we are aware, there is no report that propargyl alcohol itself instead of propargyl alcohol derivatives has been used as an electrophile in S_N2' nucleophilic substitution reactions. It is presumably due to the basicity of a variety of organometallic reagents which act as nucleophiles. Therefore, there is still a strong need for a highly efficient synthesis of multisubstituted allenes despite the recent progress of allene synthesis.[19] Recently, allylindiums and propargylindiums generated in situ from the reactions of indium with allyl halides and propargyl halides could participate as nucleophiles in Pd-catalyzed substitution reactions of allyl carbonates to produce 1,5-dienes and 1,5-enynes in good yields.[20] In continuation of our studies directed toward the development of efficient indium-mediated reactions, we describe herein an efficient synthetic method of multisubstituted allenes containing allyl groups from the reactions of allylindiums with 3°-propargyl alcohols (Scheme 1).

Our initial study focused on reaction of 2-phenyl-3-butyn-2-ol (**1a**) with allylindium generated in situ from indium and allyl halides. The results are summarized in Table 1. Allylindium obtained from indium (1.0 equiv) and allyl bromide (1.5 equiv) gave allylallene **2a** in 51% yield (entry 1). The use of indium (1.5 equiv) with allyl bromide (1.5 equiv) afforded the desired product in 50% yield (entry 2). Of the reactions screened, the best results were obtained with allylindium generated in situ from the reaction of indium (1.5 equiv) with allyl bromide (2.25 equiv) in THF at 35 °C for 4 h under a nitrogen atmosphere, producing allylallene **2a** in 87% yield with complete regioselectivity (entry 7). There is no propargylic substitution product (**3**) through S_N-reaction nor carboindation products (**4** and **5**) through addition of allylindium to triple bond formed in this reaction (see Figure 1). The present method worked equally well with allyl iodide (entry 8). However, 1-phenyl-2-propyn-1-ol, which is a 2°-propargyl alcohol, did not react with allylindium reagent. Also, when **1a** was used, 2-phenyl-1-buten-3-yne was not obtained. These results indicate that the present reactions proceeded through an *S_N1* like mechanism. The use of indium in less than 1.5 equiv and allyl bromide in less than 2.25 equiv resulted in sluggish reactions and gave lower yields (entries 1−3). The use of indium (2.0 equiv) and allyl

Scheme 1. Reactions of Allylindiums with 3°-Propargyl Alcohols

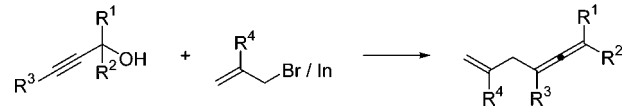
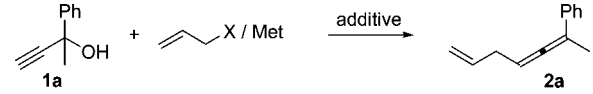


Table 1. Reaction Optimization of Allylindium with 3°-Propargyl Alcohol[a]



entry	X	Met	additive	solvent	temp (°C)	time (h)	yield (%)[b]
1[c]	Br	In		THF	70	3	51
2[d]	Br	In		THF	70	7	50
3[e]	Br	In		THF	70	7	40
4[c]	Br	In	LiI	THF	70	20	0
5[c]	Br	In	LI	THF	70	20	10
6[f]	Br	In		THF	35	3	88
7	**Br**	**In**		**THF**	**35**	**4**	**87**
8	I	In		THF	35	3	87
9	Br	In		DMF	100	20	0
10	Br	In		H_2O	100	20	0
11	Br	In		Wet-THF	70	20	9
12	Cl	In		THF	70	20	0
13	Br	In		THF-H_2O	70	20	0
14	Br	In		THF-NH_4Cl	70	20	0
15	Br	Zn		THF	70	5	0
16	Br	Mg		THF	70	5	0

[a] Reactions were carried out with **1a** (1 equiv), indium (1.5 equiv) and allyl halide (2.25 equiv) unless otherwise noted. [b] Isolated yield. [c] **1a**:In:allyl halide = 1:1:1.5. [d] **1a**:In:allyl halide = 1:1.5:1.5. [e] **1a**:In:allyl halide = 1:1.5:1. [f] **1a**:In:allyl halide = 1:2:3.

(8) (a) Darcel, C.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1994**, 1845. (b) Dixneuf, P. H.; Guyot, T.; Ness, M. D.; Robert, S. M. *Chem. Commun.* **1997**, 2083. (c) Ishikura, M.; Matsuzaki, Y.; Agata, I.; Katagiri, N. *Tetrahedron* **1998**, *54*, 13929.

(9) (a) Agami, C.; Couty, F.; Evano, G.; Mathieu, H. *Tetrahedron* **2000**, *56*, 367. (b) Ohno, H.; Anzai, M.; Toda, A.; Ohishi, S.; Fujii, N.; Tanaka, T.; Takemoto, Y.; Ibuka, T. *J. Org. Chem.* **2001**, *66*, 4904.

(10) A1exakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *J. Am. Chem. Soc.* **1990**, *112*, 8042.

(11) (a) Pasto, D. J.; Hennion, G. F.; Shults, R. H.; Waterhouse, A.; Chou, S.-K. *J. Org. Chem.* **1976**, *41*, 3496. (b) Jeffery-Luong, T.; Linstrumelle, G. *Tetrahedron Lett.* **1980**, *21*, 5019. (c) Yus, M.; Gomis, J. *Eur. J. Org. Chem.* **2003**, 2043.

(12) (a) A1exakis, A. *Pure Appl. Chem.* **1992**, *64*, 387. (b) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180. (c) Spino, C.; Frechette, S. *Tetrahedron Lett.* **2000**, *41*, 8033.

(13) (a) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **1999**, *40*, 349. (b) Ohno, H.; Toda, A.; Fujii, N.; Takemoto, Y.; Tanaka, T.; Ibuka, T. *Tetrahedron* **2000**, *56*, 2811.

(14) Huntsman, W. D.; Chen, J. P.; Yelekci, K.; Yin, T.-K.; Zhang, L. J. *J. Org. Chem.* **1988**, *53*, 4357.

(15) El Gueddari, F.; Grimaldi, J. R.; Hatem, J. M. *Tetrahedron Lett.* **1995**, *36*, 6685.

(16) Lemiere, G.; Gandon, V.; Cariou, K.; Fukuyama, T.; Dhimane, A.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2007**, *9*, 2207.

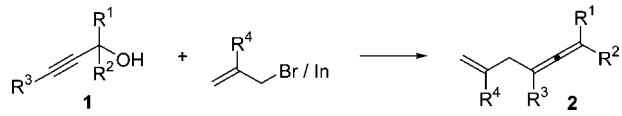
(17) Grimaldi, J.; Malacria, M.; Bertrand, M. *Tetrahedron Lett.* **1974**, 275.

(18) Huang, X.; Shen, R.; Zhang, T. *J. Org. Chem.* **2007**, *72*, 1534.

(19) (a) Russel, C. E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1983**, *105*, 943. (b) Keinan, E.; Peretz, M. *J. Org. Chem.* **1983**, *48*, 5302. (c) Tsuji, J.; Sugiura, T.; Minami, I. *Synthesis* **1987**, 603. (d) Mandai, T.; Kunitomi, H.; Higashi, K.; Kawada, M.; Tsuji, J. *Synlett* **1991**, 697. (e) Bouyssi, D.; Gore, J.; Balme, G.; Louis, D.; Wallach, J. *Tetrahedron Lett.* **1993**, *34*, 3129. (f) Aidhen, I. S.; Braslau, R. *Synth. Commun.* **1994**, *24*, 789. (g) Badone, D.; Cardamone, R.; Guzzi, U. *Tetrahedron Lett.* **1994**, *35*, 5477. (h) Ma, S.; Zhang, A. *J. Org. Chem.* **1998**, *63*, 9601. (i) Ma, S.; Zhang, A.; Yu, Y.; Xia, W. *J. Org. Chem.* **2000**, *65*, 2287.

(20) (a) Lee, P. H.; Sung, S.-Y.; Lee, K.; Chang, S. *Synlett* **2002**, 146. (b) Lee, P. H.; Shim, E.; Lee, K.; Seomoon, D.; Kim, S. *Bull. Korean Chem. Soc.* **2005**, *26*, 157.

Table 2. Reactions of Allylindium with 3°-Propargyl Alcohols[a]



entry	reactant	R^1	R^2	R^3	R^4	time (h)	product	yield (%)[b]
1	**1a**	Ph	Me	H	Me	4	**2b**	75
2	**1b**	Ph	Me	Me	H	4	**2c**	86
3	**1b**	Ph	Me	Me	Me	4	**2d**	85
4	**1c**	Ph	Me	*n*-Bu	H	7	**2e**	75[c]
5	**1c**	Ph	Me	*n*-Bu	Me	6	**2f**	80
6	**1d**	Ph	Me	Ph	H	6	**2g**	80
7	**1d**	Ph	Me	Ph	Me	6	**2h**	71
8	**1e**	4-Br-C_6H_4	Me	H	H	7	**2i**	71
9	**1e**	4-Br-C_6H_4	Me	H	Me	7	**2j**	70
10	**1f**	3-HO-C_6H_4	Me	H	H	7	**2k**	75
11	**1f**	3-HO-C_6H_4	Me	H	Me	8	**2l**	74
12	**1g**	4-Me-C_6H_4	Me	H	H	6	**2m**	84
13	**1g**	4-MeC_6H_4	Me	H	Me	6	**2n**	86
14	**1h**	Ph	Ph	H	H	7	**2o**	85
15	**1h**	Ph	Ph	H	Me	7	**2p**	83
16	**1i**	Me	Me	$PhCH_2CH_2CH_2$	H	8	**2q**	74[c]
17	**1i**	Me	Me	$PhCH_2CH_2CH_2$	Me	8	**2r**	76[c]
18[d]	**1j**	$-(CH_2)_5-$		$PhCH_2CH_2CH_2$	H	8	**2s**	80[c]
19[d]	**1j**	$-(CH_2)_5-$		$PhCH_2CH_2CH_2$	Me	9	**2t**	83[c]

[a] Alcohol:In:allyl halide = 1:1.5:2.25. Reactions proceeded at 35 °C. [b] Isolated yield. [c] Reactions proceeded at 70 °C. [d] Alcohol:In:allyl halide = 1:2:3.

bromide (3.0 equiv) provided a similar result to entry 7 (entry 6). THF was the best solvent among several reaction media (DMF, THF, H_2O, DMF-H_2O, and THF-H_2O) that were examined (entries 7−14). The use of LiI and KI as an additive did not give the desired product at 70 °C for 20 h (entries 4 and 5). Treatment of **1a** with allylzinc bromide and allylmagnesium bromide (1 or 2 equiv) in THF did not give trisubstituted allene **2a** (entries 15 and 16), indicating that allylindium is essential to produce multisubstituted allylallenes.

To demonstrate the efficiency and scope of the present method, we applied the above reaction system to a variety of propargyl alcohols and allyl halides. The results are summarized in Table 2. Compound **1a** was treated with methallylindium obtained from indium and methallyl bromide to afford **2b** in 75% yield (entry 1). 3°-Propargyl alcohols possessing an internal triple bond turned out to be compatible with the reaction conditions (entries 2−7 and 16−19). Reaction of 2-phenyl-3-pentyn-2-ol (**1b**) with methallylindium provided tetrasubstituted allene (**2d**) in 85% yield (entry 3). Allylindium reacted with 2-phenyl-3-octyn-2-ol (**1c**) and 2,4-diphenyl-3-butyn-2-ol (**1d**) to give tetrasubstituted allenes **2e** and **2g** in 75% and 80% yields, respectively (entries 4 and 6). The presence of various substituents such as bromide, hydroxyl, and methyl group on the aromatic ring in propargyl alcohol showed minor effects on the efficiency of reactions (entries 8−13). It is noteworthy that protection of hydroxyl groups on the substrates is not necessary as demonstrated by reaction of 2-(3-hydroxyphenyl)-3-butyn-2-ol (**1f**) with allylindiums (entries 10 and 11). Subjecting 1,1-diphenyl-2-propyn-1-ol (**1h**) to allylindium and methallylindium produced trisubstituted allenes **2o** and **2p** in 85% and 83% yields, respectively (entries 14−15). 3°-Propargyl alcohols possessing alkyl groups instead of phenyl group at the propargylic position worked equally well with the present conditions. Exposure of compound **1i**, having dimethyl groups, to allylindium and methallylindium gave tetrasubstituted allene **2q** and **2r** in good yields (entries 16−17). Treatment of compound **1j** obtained from cyclohexanone and 5-phenyl-1-pentyne with indium reagents afforded allenes **2s** and **2t** possessing four substituents (entries 18−19). No propargylic substitution products through S_N-type selective displacement and carboindation products through addition of allylindiums to triple bonds are formed in any reactions. Failure of reactions of **1a** with a variety of allylindiums obtained from cinnamyl bromide, crotyl bromide, cyclohexenyl bromide, and prenyl bromide is presumably due to solvent incompatibility for formation of allylindium in THF and steric

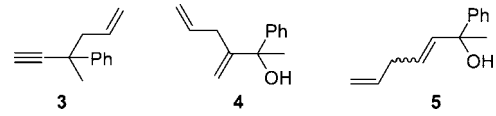
hindrance related to attack of the γ-position of allylindium in the substitution reaction of propargyl alcohol.

In summary, we have developed an efficient synthetic method to prepare tri- and tetra-substituted allenes having an allyl and methallyl group from the reactions of allylindiums generated in situ from indium and allyl halides with 3°-propargyl alcohols. It is worth noting because propargyl alcohols possessing surplus hydroxyl groups can react with allylindiums without protection. The present method complements the existing synthetic methods due to direct substitution of 3°-propargyl alcohols without activation and some advantageous properties of allylindiums over organometallics such as availability, ease of preparation and handling, high reactivity and selectivity, and operational simplicity.

Acknowledgment. This work was supported by the Korea Science and Engineering Foundation (KOSEF) through the National Research Laboratory Program funded by the Ministry of Science and Technology (No. M10600000203-06J0000-20310) and by KOSEF (R01-2006-000-11283-0). The NMR data were obtained from the central instrumental facility in Kangwon National University. Dr. Sung Hong Kim at the KBSI (Daegu) is thanked for obtaining the MS data.

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

OL800719G



3 4 5

Figure 1. Propargylic Substitution and Carboindation Products.