

Tetrahedron Letters 42 (2001) 4353-4355

TETRAHEDRON LETTERS

# Stereocontrolled synthesis of branched enyne by stepwise cross-coupling reactions of 1,1-dibromo-1-alkenes

Jun'ichi Uenishi\* and Katsuaki Matsui

Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607-8412, Japan Received 2 April 2001; revised 1 May 2001; accepted 2 May 2001

Abstract—Geometrically pure alkynyl, alkenyl and alkyl substituted branched enynes were prepared by the Sonogashira coupling followed by Sonogashira, Suzuki–Miyaura, and Kumada–Tamao–Corriu coupling reactions. © 2001 Elsevier Science Ltd. All rights reserved.

Enyne is an important structural unit for biologically active organic compounds, including anticancer antibiotics,<sup>1</sup> and other natural products,<sup>2</sup> and also for new functional materials.<sup>3</sup> The functional unit has been prepared by the cross-coupling reaction of haloalkene with terminal alkyne,<sup>4</sup> Wittig olefination of aldehyde with alkynylmethylidene ylide,<sup>5</sup> or homologation of enal to terminal enyne.<sup>6</sup> However, such synthetic methods are sometimes not so effective for the stereoselective preparation of branched enynes, **I–III** and there have been few efforts made to develop a general method for the synthesis of branched enynes (Fig. 1).<sup>7</sup>



Figure 1.



## Scheme 1.

0040-4039/01/\$ - see front matter @ 2001 Elsevier Science Ltd. All rights reserved. PII: \$0040-4039(01)00749-3

A differentiation of two carbon-halogen bonds of 1,1dihalo-1-alkene under metal-catalyzed reactions has been successfully performed in Kumada-Tamao-Corriu coupling,<sup>8</sup> Suzuki coupling,<sup>9</sup> Stille coupling,<sup>10</sup> and hydrogenolysis<sup>11</sup> (Scheme 1). However, a few stereoselective Sonogashira couplings of 1,1-dibromo-1-alkene were reported, in which a combination of  $Pd(PPh_3)_4$ and alkynyl metals were employed.<sup>12</sup> The couplings using free terminal alkyne were poorly chemoselective,<sup>13</sup> and the next cross coupling reaction of the resultant trisubstituted bromoenyne (Scheme 2) has not been examined. If the second cross-coupling reaction of the resultant bromoenyne occurs with alkynyl, alkenyl and alkyl reagents under Sonogashira, Suzuki-Miyaura and Kumada-Tamao-Corriu conditions,<sup>4,14</sup> a variety of branched enynes will be obtained.



#### Scheme 2.

In this paper, we describe the synthesis of some branched (E)- and (Z)-enynes in geometrically pure form by stereoselective Sonogashira coupling reaction of 1,1-dibromo-1-alkenes using terminal alkyne, and the successive cross-coupling reaction of the resultant bromoenyne.

Sonogashira coupling of 1,1-dibromo-1-alkene 1 with (trimethylsilyl)acetylene in the presence of a

Keywords: enyne; cross coupling; stereocontrolled synthesis.

<sup>\*</sup> Corresponding author. Fax: +81-75-595-4763; e-mail: juenishi @mb.kyoto-phu.ac.jp

PdCl<sub>2</sub>(dppf) catalyst, copper iodide and diisopropylamine gave enyne **2** in 87% yield stereoselectively along with 1,1-dialkynyl-1-alkene in less than 10% yield.<sup>15</sup> The same coupling reaction of 1,1-dibromo-1,3-diene **3** also proceeded very well to give dienyne **4** in 79% yield and dialkynyldiene in 15% yield. Since the Sonogashira reaction of 1,1-dibromo-1-alkene gave a mixture of 1-alkynyl-1-bromo-1-alkene, 1,1-dialkynyl-1-alkene and some recovery of starting material<sup>13</sup> under typical conditions,<sup>16</sup> the use of PdCl<sub>2</sub>(dppf) largely improved the chemoselective formation of bromoenyne **2** or **4**. In fact, Pd catalysts such as Pd(PPh<sub>3</sub>)<sub>4</sub>, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, Pd(dppe)<sub>2</sub> and other commercial catalysts provided a mixture of bromoenyne, enediyne and the starting dibromoalkene with poor selectivity (Scheme 3).

The second coupling reactions of 2 can take place stereospecifically to give the corresponding substituted envnes. Thus, 1,1-dialkynyl-1-alkene 5 was obtained as a single stereoisomer in 95% yield by the second Sonogashira coupling of 2 with hexyne. Suzuki-Miyaura coupling of 2 with 1-hexenylboronic acid provided dienyne 6E exclusively in 82% yield, though the terminal trimethylsilyl group was removed under the reaction conditions. On the other hand, Kumada-Tamao-Corriu coupling with ethylmagnesium bromide in the presence of NiCl<sub>2</sub>(dppp) gave (E)-alkene 7a exclusively in 71% yield. The coupling reaction of 2 with trimethylsilylmethyl Grignard reagent gave the corresponding coupling products 7b in 53% yields. These three sp-,  $sp^2$ - and  $sp^3$ -carbon coupling reactions occur to give a single stereoisomer with retention of the configuration, respectively (Scheme 4).

Pd-catalyzed cross-coupling reaction of 1 with 1-hexenylboronic acid took place smoothly to give bromodiene 8 stereoselectively in 85% yield.<sup>9</sup> Although Roush et al. noted that 2-bromo-1,3-diene was poorly reactive for the second Suzuki coupling reactions,<sup>9a</sup> Sonogashira coupling of 8 with trimethylsilylacetylene in the presence of PdCl<sub>2</sub>(dppf), CuI and diisopropylamine at 65°C in benzene gave dienyne in 81% yield. Desilylation of the product by Bu<sub>4</sub>NF afforded dienyne **6***Z* quantitatively, corresponding to the stereoisomer of **6***E*, which was obtained in Suzuki coupling of **2** with hexynylboronic acid shown in Scheme 4. Combinations of Sonogashira and Suzuki cross-coupling reactions in either order can provide either **6***Z* or **6***E* in stereochemically pure form (Scheme 5).

We have demonstrated this methodology for the synthesis of (2E,4Z)-3-ethyl-5-iodopentadienyl silyl ether **12**. This iododiene is a C11–C15 part of a 13-ethyl substituted analogue of (11Z)-retinal, which is an important chromophore for the visual system. A silyl ether of 3-hydroxy-1,1-dibromo-1-propene **9**<sup>17</sup> having a protected hydroxymethyl group, which can be transformed to other functional groups and elongate a carbon chain in a later stage, was first coupled with (trimethylsilyl)acetylene to give **10** in 81% yield. The coupling reaction of **10** with ethylmagnesium bromide followed by desilylation with Bu<sub>4</sub>NF gave branched



Scheme 3.



Scheme 4.





enyne 11 in 58% yield. Manipulation of the terminal enyne to (Z,E)-iododiene was performed in two steps. First, iodination with iodine in the presence of morpholine and then *cis*-reduction of the idodoalkyne with diimide eventually gave 12 in 58% yield.<sup>18</sup> Since there have been no reports on the synthesis of 13-substituted derivatives for (11Z)-retinal, this method should be valuable for the stereocontrolled preparation of the corresponding fragment (Scheme 6).

In conclusion, we have demonstrated a novel and efficient preparation of geometrically pure branched enynes from 1,1-dibromo-1-alkene by Pd- or Ni-catalyzed cross-coupling reactions.



Scheme 6. Reagents and conditions: (a) (trimethylsilyl)acetylene, cat.  $PdCl_2(dppf)$ , CuI,  $Pr_2^iNH$ , benzene, rt; (b) ethylmagnesium bromide, cat.  $NiCl_2$  (dppp), THF, rt; (c)  $Bu_4NF$ , THF, -20°C; (d) iodine, morpholine, benzene, 50°C; (e) diimide, THF, rt.

#### Acknowledgements

This work was financially supported by the Grant-in-Aid for Scientific Research on Priority Areas (A) from the Ministry of Education, Science, Sports and Culture, Japan, and a Special Grant for Cooperative Research administered by the Japan Private School Promotion Foundation.

### References

- (a) Maier, M. E. Synlett 1995, 13; (b) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. Tetrahedron 1996, 52, 6453; (c) Nicolaou, K. C.; Smith, A. L. Acc. Chem. Res. 1992, 25, 497.
- (a) Kuhnt, D.; Anke, T.; Besl, H.; Bross, M.; Herrmann, R.; Mocek, U.; Steffan, B.; Steglich, W. J. Antibiot. 1990, 43, 1413; (b) Kusumi, T.; Ohtani, I.; Nishiyama, K.; Kakisawa, H. Tetrahedron Lett. 1987, 28, 3981; (c) Ohta, T.; Uwai, K.; Kikuchi, R.; Nozoe, S.; Oshima, Y.; Sasaki, K.; Yoshizaki, F. Tetrahedron 1999, 55, 12087; (d) Trowitsch-Kienast, W.; Forche, E.; Wray, V.; Riechenbach, H.; Hunsmann, G.; Höfle, G. Liebigs Ann. Chem. 1992, 659.
- (a) Boldi, A. M.; Anthony, J.; Gramlich, V.; Knobler, C. B.; Boudon, C.; Gisselbrecht, J.-P.; Gross, M.; Diederich, F. Helv. Chim. Acta 1995, 78, 779; (b) Hynd, G.; Jones, G. B.; Plourde, II, G. W.; Wright, J. M. Tetrahedron Lett. 1999, 40, 4481; (c) Shimada, S.; Masaki, A.; Hayamizu, K.; Matsuda, H.; Okada, S.; Nakanishi, H. Chem. Lett. 2000, 11, 1128; (d) Ciulei, S. C.; Tykwinski, R. R. Org. Lett. 2000, 2, 3607.

- Metal-Catalyzed Cross-Coupling Reactions; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.
- 5. Ogawa, H.; Mukae, J. Tetrahedron Lett. 1978, 4929.
- Michel, P.; Gennet, D.; Rassat, A. *Tetrahedron Lett.* 1999, 40, 8575.
- (a) Ikeda, S. Acc. Chem. Res. 2000, 33, 511; (b) Hara, R.; Liu, Y.; Sun, W.-H.; Takahashi, T. Tetrahedron Lett. 1997, 38, 4103; (c) Trost, B. M.; McIntosh, M. C. Tetrahedron Lett. 1997, 38, 3207.
- (a) Minato, A.; Suzuki, K.; Tamao, K. J. Am. Chem. Soc. 1987, 109, 1257; (b) Minato, A. J. Org. Chem. 1991, 56, 4052.
- (a) Roush, W. R.; Moriarty, K. J.; Brown, B. B. Tetrahedron Lett. 1990, 31, 6509; (b) Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. J. Am. Chem. Soc. 1996, 118, 7502.
- 10. Shen, W.; Wang, L. J. Org. Chem. 1999, 64, 8873.
- (a) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. J. Org. Chem. 1996, 61, 5716; (b) Uenishi, J.; Kawahama, R.; Shiga, T.; Yonemitsu, O.; Tsuji, J. Tetrahedron Lett. 1996, 37, 6759.
- (a) Neidlein et al. reported the reaction using alkynylmagnesium bromide in which dibromoalkene was recovered in all the cases, see: Bryant-Friedrich, A.; Neidlein, R. Synthesis 1995, 1506; (b) The reaction using alkynylzinc chloride was recently reported by Hayashi et al, see: Ogasawara, M.; Ikeda, H.; Ohtsuki, K.; Hayashi, T. Chem. Lett. 2000, 776.
- Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. J. Org. Chem. 1998, 63, 8965. Exceptionally, Meyers recently reported selective alkynylation in specific substrate: Meyers, A. G.; Goldberg, S. D. Angew. Chem., Int. Ed. 2000, 39, 2732.
- Comprehensive Organic Synthesis; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, by Sonogashira, K. p. 521, by Knight, D. W., p. 481 and by Tamao, K., p. 435.
- 15. General procedure: To a mixture of 1,1-dibromo-1-alkene (2 mmol) and trimethylsilylacetylene (3 mmol) in anhydrous benzene (20 mL) were added PdCl<sub>2</sub>(dppf)·CH<sub>2</sub>Cl<sub>2</sub> (5 mol%), CuI (0.08 mmol), and EtNPr<sup>i</sup><sub>2</sub> (4–6 mmol), and the mixture was stirred for 10–20 min at rt. After a work up, purification by flash column chromatography (eluted with hexane for 1 and 3) gave the corresponding bromoenyne.
- Sonogashira, K.; Tohda, Y.; Hagiwaha, N. Tetrahedron Lett. 1975, 4756.
- Francesch, A.; Alvarez, R.; Löpez, S.; De Lera, A. R. J. Org. Chem. 1997, 62, 310.
- The corresponding 13-methyl derivative was used for the synthesis of (11Z)-9-demethylretinal. De Lera, A. R.; Torrado, A.; Iglesias, B.; Löpez, S. *Tetrahedron Lett.* 1992, 33, 6205.