Pergamon

Tetrahedron Letters, Vol. 36, No. 22, pp. 3785-3788, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00606-0

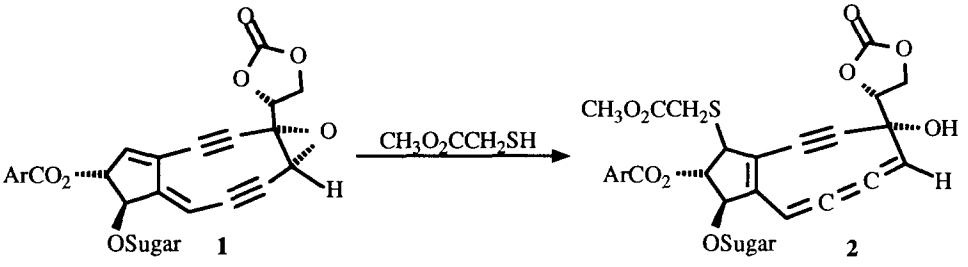
An Efficient Synthesis of Enyne[3]cumulenes

Kung K. Wang,* Bin Liu, and Yong-de Lu

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506.

Abstract: The $Pd(PPh_3)_4$-catalyzed cross coupling between **3** and terminal alkynes furnished enynyl aldehydes **4**, which were converted to **6** by condensation with **5**. Sequential treatment of **6** with *n*-butyllithium, methanesulfonyl chloride, and tetrabutylammonium fluoride (TBAF) afforded enyne[3]cumulenes **8**.

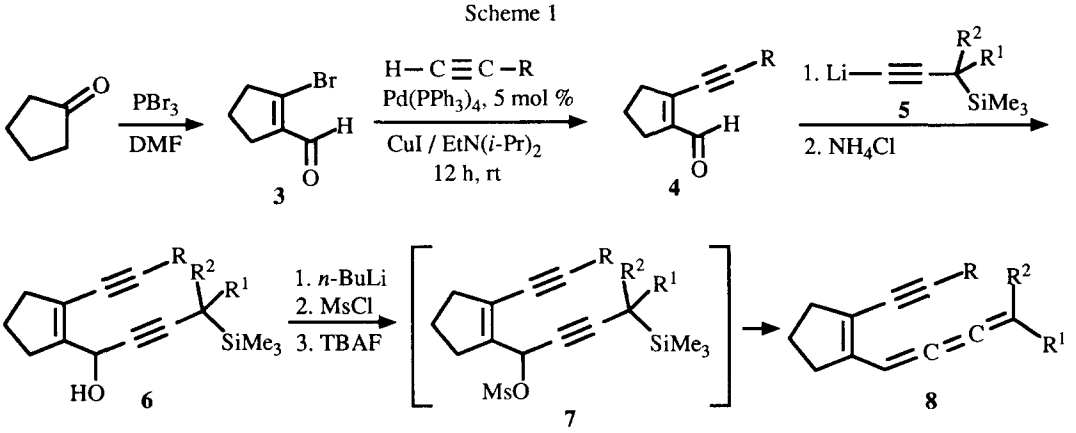
In recent years there has been a surge of interest in developing new synthetic routes to conjugated enyne[3]cumulenes.[1] This is due to the discovery that upon exposure to methyl thioglycolate the nonprotein chromophore of the antitumor antibiotic neocarzinostatin (NCS-Chrom, **1**) is transformed to the cyclic enyne[3]cumulene **2**, which serves as a key intermediate along the pathway of DNA cleavage.[2] Two general



routes have emerged for synthesis of enyne[3]cumulenes, one involving the use of various dienediyne derivatives as precursors[1a-f] and the other employing a Horner-Emmons type reaction of allenyldiphenylphosphine oxides with conjugated enynyl aldehydes.[1g] We recently reported a facile synthesis of [3]cumulenes via 1,4-elimination of hydroxytrimethylsilane from 4-(trimethylsilyl)-2-butyn-1-ols, readily obtained from condensation of terminal propargylic silanes with aldehydes and ketones.[3] We now have successfully extended this method to synthesis of enyne[3]cumulenes by using conjugated enynyl aldehydes for condensation.

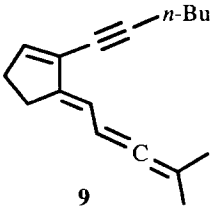
The $Pd(PPh_3)_4$-catalyzed cross coupling of various terminal acetylenes with 1-(2-bromo-1-cyclopentenyl)carboxaldehyde (**3**), readily obtained from reaction of cyclopentanone with PBr_3 and DMF in 68% yield,[4] proceeded smoothly and furnished the conjugated enynyl aldehydes **4**[1g] (Scheme 1) in excellent isolated yields (Table 1). Treatment of **4** with 1-lithio-1-alkynes **5**, derived from corresponding propargylic silanes[5] and *n*-butyllithium, afforded condensation adducts **6** in a straightforward and highly efficient manner. Essentially equal amounts of two diastereomers were formed in the cases of **6c**, **6d**, and **6f**. Conversion of **6** to enyne[3]cumulenes **8** was carried out by treating **6** with *n*-butyllithium, methanesulfonyl chloride, and TBAF in a sequence as described previously.[3] Again, enyne[3]cumulenes **8c**, **8d**, and **8f** were essentially 1:1 mixtures of the *E* and the *Z* isomers. It is worth noting that the mildness of the reaction condition for the 1,4-elimination step through methanesulfonates **7** is ideally suited for the synthesis of thermally labile enyne[3]cumulenes. By selecting different combinations of various fragments to produce **6** as precursors, enyne[3]cumulenes with diverse structures could thus be synthesized.

Scheme 1



Enyne[3]cumulenes **8a** and **8b** were stable enough to allow isolation and purification by HPLC without extensive decomposition. A small fraction of pure **8f** was also isolated by HPLC. The efficiency of conversion from **6** to **8** was determined by comparison of the integrated peak areas of the ^{1}H NMR signals of the crude reaction products using 1,4-dinitrobenzene as the internal standard as described previously.[3]

In addition to **8b**, the ^{1}H NMR signals at δ (C_6D_6) 6.62 (1 H, dt, J = 10.8 and 2 Hz), 6.17 (1 H, t, J = 2.8 Hz), and 5.98 (1 H, d of septet, J = 11.0 and 2.7 Hz), attributable to the formation of a substantial amount of **9** (**8b** : **9** = 1:1), were also observed when the elimination step was carried out at 0 °C. Presumably, **9** was



produced from a competing 1,4-elimination by deprotonation of one of the allylic hydrogens on the five-membered ring and protodesilylation of the propargylsilane moiety.[6] The geometry of the exocyclic double bond is tentatively assigned the *E* geometry on the basis of less steric interaction. Fortunately by conducting 1,4-elimination at -78 °C, the amount of **9** was reduced (**8b** : **9** = 5:1). Similar results were also observed in other cases. Although all of the starting alcohol in the case of **6e** was consumed, we were unable to detect the formation of **8e**. This is presumably because of the presence of a very labile monosubstituted [3]cumulene moiety[7] in **8e**, making it too unstable under the reaction condition as observed previously.[3]

The following procedure for the synthesis of **8b**[1g] is representative. To a degassed solution containing 0.867 g of $Pd(PPh_3)_4$ (0.75 mmol), 0.29 g of CuI (1.5 mmol), 2.63 g of **3** (15 mmol), and 5.82 g of diisopropylethylamine (45 mmol) in 20 mL of DMF was added via cannula a degassed solution of 1.89 g of 1-hexyne (23 mmol) in 10 mL of DMF. After 12 h of stirring at rt, the reaction mixture was poured into a flask containing 200 mL of a saturated NH_4Cl solution and 200 mL of pentane. After filtration, the organic layer was separated, washed with water (3 x 30 mL), dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel / 5% diethyl ether in hexanes) to afford 2.50 g of **4b**[1g] (14.2 mmol, 95%) as a yellow liquid: IR (neat) 2211, 1668, 1596 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.01 (1 H, s), 2.66 (2 H, tt, J = 7.7 and 2 Hz), 2.57 (2 H, t, J = 7.6 Hz), 2.43 (2 H, t, J = 6.9 Hz), 1.92 (2 H, quintet, J = 7.5 Hz), 1.6-1.4 (4 H, m), 0.92 (3 H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 189.23, 146.94, 144.71, 103.24, 74.99, 39.21, 30.42, 29.28, 21.99, 21,96, 19.51, 13.54; MS m/e 176 (M^+), 175, 161, 147, 134, 105, 91.

Table 1. Synthesis of **4**, **6**, and Enyne[3]cumulenes **8**

enynyl aldehydes **4**,[a] isolated yield, %	alcohols **6**,[a] isolated yield, %	enyne[3]cumulenes, **8** yield, %[b] (isolated yield, %)
4a, 97 R = $SiMe_3$	**6a**, 93 R = $SiMe_3$, $R^1 = R^2$ = Me	**8a**, 62 (30) R = H, $R^1 = R^2$ = Me
4b, 95 R = *n*-Bu	**6b**, 93 R = *n*-Bu, $R^1 = R^2$ = Me	**8b**, 54 (35) R = *n*-Bu, $R^1 = R^2$ = Me
	6c, 93 R = *n*-Bu, R^1 = H, R^2 = *n*-Bu	**8c**, 51 R = *n*-Bu, R^1 = H, R^2 = *n*-Bu
4c, 98 R = 1-(1-cyclohexenyl)	**6d**, 91 R = 1-(1-cyclohexenyl), R^1 = H, R^2 = *n*-Bu	**8d**, 41 R = 1-(1-cyclohexenyl), R^1 = H, R^2 = *n*-Bu
	6e, 91 R = 1-(1-cyclohexenyl), R^1 = H, R^2 = H	**8e**, - R = 1-(1-cyclohexenyl), R^1 = H, R^2 = H
4d, 86 R = Ph	**6f**, 82 R = Ph, R^1 = H, R^2 = Ph	**8f**, 44 R = Ph, R^1 = H, R^2 = Ph

[a]The isolated products were characterized by IR, ^1H (270 MHz) and ^{13}C (67.9 MHz) NMR,[8] and/or MS.
[b]The yield of the reaction was determined by comparison of the integrated peak areas of the ^1H NMR signals using 1,4-dinitrobenzene as the internal standard.

To a solution of 0.35 g of 3-methyl-3-(trimethylsilyl)-1-butyne (2.5 mmol) in 10 mL of dry THF was added 0.96 mL of a 2.5 M solution of *n*-butyllithium (2.4 mmol) in hexanes at -30 °C. After 20 min of stirring, 0.387 g of **4b** (2.2 mmol) in 5 mL of THF was added via cannula, and the reaction mixture was allowed to warm to 0 °C. After 1.5 h, 5 mL of a dilute NH_4Cl solution and 60 mL of pentane were introduced. The organic layer was separated, washed with water (2 x 20 mL), dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel / 5% diethyl ether in hexanes) to give 0.65 g of **6b** (2.06 mmol, 93%) as a light yellow liquid: IR (neat) 3431, 2216, 1457, 1249, 840 cm^{-1}; ^1H NMR (C_6D_6) δ 5.71 (1 H, s), 2.65 (2 H, t, *J* = 7.5 Hz), 2.41 (2 H, t, *J* = 7 Hz), 2.11 (2 H, t, *J* = 6.6 Hz), 2.07 (1 H, s, OH), 1.66 (2 H, quintet, *J* = 7 Hz), 1.3-1.2 (4 H, m), 1.09 (3 H, s), 1.08 (3 H, s), 0.76 (3 H, t, *J* = 7.1 Hz), 0.03 (9 H, s); ^{13}C (C_6D_6) δ 148.41, 120.80, 96.12, 92.61, 80.30, 76.63, 60.57, 37.50, 31.31, 31.14, 24.09, 22.46, 22.20, 19.51, 17.36, 13.71, -4.43.

To a solution of 0.474 g of **6b** (1.50 mmol) in 10 mL of dry THF was added by a syringe 0.64 mL of a 2.5 M solution of *n*-butyllithium (1.6 mmol) in hexanes at -50 °C. After 20 min, 0.183 g of methanesulfonyl chloride (1.60 mmol) in 6 mL of dry THF was introduced via cannula. The reaction mixture was stirred at -50 °C for 2 h and then was cooled to -78 °C before 4.5 mL of a 1.0 M solution of TBAF in THF was added by a syringe. After 1 h at -78 °C, the reaction mixture was allowed to warm to -20 °C and was transferred via cannula to a separatory funnel containing 40 mL of a degassed aqueous solution of Na_2CO_3 and 60 mL of pentane under a nitrogen atmosphere. The aqueous layer was separated, and the organic layer was washed with 30 mL of a degassed aqueous solution of Na_2CO_3 and then was transferred via cannula to a flask under a nitrogen atmosphere. The organic solvent was evaporated under reduced pressure at 0 °C, and a solution of 0.081 g of 1,4-dinitrobenzene in 1 mL of C_6D_6 and 1.8 mL of THF was introduced. The yield of **8b**[1g] (54%) was determined by comparison of the integrated peak areas of the ^1H NMR signals of 1,4-dinitrobenzene at δ

8.05 and the vinylic hydrogen of **8b** at δ 6.37.[9] In a second run by starting from 0.221 g of **6b** (0.70 mmol), the reaction mixture containing **8b** was concentrated to ca. 2 mL and was passed through a column (Florisil, 100-200 mesh, Fisher F-101, pentane) at 0 °C under a nitrogen atmosphere. The fractions containing **8b** were combined and concentrated under reduced pressure at 0 °C to ca. 0.3 mL and were further purified by HPLC (silica / hexanes) to afford 0.055 g of **8b** (35%) as a yellow solid: ^{1}H NMR (C_6D_6) δ 6.97 (1 H, s), 2.59 (4 H, q, J = 7 Hz), 2.22 (2 H, t, J = 6.5 Hz), 1.74 (3 H, s), 1.68 (3 H, s), 1.63 (2 H, quintet, J = 7.7 Hz), 1.4-1.2 (4 H, m), 0.76 (3 H, t); ^{13}C (C_6D_6) δ 158.10, 153.02, 146.42, 123.27, 116.06, 100.34, 98.36, 78.24, 38.04, 33.41, 31.27, 24.93, 24.01, 22.61, 22.20, 19.81, 13.68.

Acknowledgment. We thank the National Science Foundation (CHE-9307994) for financial support.

References and Notes

1. (a) Hirama, M; Fujiwara, K.; Shigematu, K.; Fukazawa, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4120-4122. (b) Fujiwara, K.; Sakai, H.; Hirama, M. *J. Org. Chem.* **1991**, *56*, 1688-1689. (c) Doi, T.; Takahashi, T. *J. Org. Chem.* **1991**, *56*, 3465-3467. (d) Myers, A. G.; Finney, N. S. *J. Am. Chem. Soc.* **1992**, *114*, 10986-10987. (e) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1993**, *115*, 7021-7022. (f) Scheuplein, S. W.; Machinek, R.; Suffert, J.; Bruckner, R. *Tetrahedron Lett.* **1993**, *34*, 6549-6552. (g) Saito, I.; Yamaguchi, K.; Nagata, R.; Murahashi, E. *Tetrahedron Lett.* **1990**, *31*, 7469-7472.
2. (a) Myers, A. G. *Tetrahedron Lett.* **1987**, *28*, 4493-4496. (b) Myers, A. G.; Proteau, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 1146-1147. (c) Goldberg, I. H. *Acc. Chem. Res.* **1991**, *24*, 191-198. (d) Hensens, O. D.; Helms, G. L.; Zink, D. L.; Chin, D.-H.; Kappen, L. S.; Goldberg, I. H. *J. Am. Chem. Soc.* **1993**, *115*, 11030-11031. (e) Myers, A. G.; Cohen, S. B.; Kwon, B.-M. *J. Am. Chem. Soc.* **1994**, *116*, 1670-1682.
3. (a) Wang, K. K.; Liu, B.; Lu, Y.-d. *J. Org. Chem.* in press. (b) For a similar synthetic method, see Chow, H.-F.; Cao, X.-P.; Leung, M.-k. *J. Chem. Soc., Chem. Commun.* **1994**, 2121-2122.
4. (a) Arnold, Z.; Holy, A. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3059-3073. (b) Robertson, I. R.; Sharp, J. T. *Tetrahedron* **1984**, *40*, 3095-3112.
5. (a) Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier, New York, 1981; pp 52-54. (b) Rajagopalan, S.; Zweifel, G. *Synthesis* **1984**, 111-112. (c) Bennetau, B; Pillot, J.-P.; Dunogues, J.; Calas, R. *J. Chem. Soc., Chem. Commun.* **1981**, 1094-1095. (d) Nativi, C.; Taddei, M.; Mann, A. *Tetrahedron* **1989**, *45*, 1131-1144.
6. Flood, T.; Peterson, P. E. *J. Org. Chem.* **1980**, *45*, 5006-5007.
7. See ref 5a, pp 144-146.
8. The ^{1}H and/or ^{13}C NMR spectra (C_6D_6) of **6a**, **6d**, **6f**, **8a**, and **8f**. **6a**: ^{1}H δ 5.71 (1 H, s), 2.62 (2 H, tt, J = 7.6 and 1 Hz), 2.38 (2 H, tm, J = 7 and 1 Hz), 1.93 (s, OH), 1.60 (2 H, quintet, J = 7.5 Hz), 1.08 (3 H, s), 1.07 (3 H, s), 0.14 (9H, s), 0.03 (9 H, s); ^{13}C δ 152.06, 120.03, 101.35, 100.07, 92.86, 79.92, 60.47, 37.10, 31.53, 24.01, 22.49, 17.34, 0.06, -4.44.; **6d** (1:1 mixture of two diastereomers): ^{1}H δ 6.03 (1 H, m), 5.76 and 5.75 (1 H, s), 2.69 (2 H, t, J = 7.5 Hz), 2.45 (2 H, t, J = 7.5 Hz), 2.07 (3 H, m), 1.80 (2 H, m), 1.67 (2 H, m), 1.58 (1 H, m), 1.4-1.2 (8 H, m), 0.87 (3 H, t), 0.06 (9 H, s); ^{13}C δ 149.41, 149.37, 134.63, 121.36, 120.55, 120.50, 97.42, 87.60, 87.58, 82.87, 81.03, 81.02, 60.78, 60.75, 37.37, 32.29, 31.62, 29.59, 29.15, 25.85, 22.68, 22.56, 21.74, 20.23, 14.21, -3.10.; **6f** (1:1 mixture of two diastereomers): ^{1}H ($CDCl_3$) δ 7.45-7.1 (10 H, m), 5.62 (1 H, s) 3.17 and 3.16 (1 H,s), 2.70 (2 H, t), 2.62 (2 H, m), 2.22 (s, OH), 1.95 (2 H, m), 0.04 (9 H, s); ^{13}C ($CDCl_3$) δ 149.38, 149.37, 138.94, 138.92, 131.43, 128.23, 128.12, 126.90, 125.10, 123.19, 120.52, 120.51, 95.04, 86.13, 86.10, 84.59, 84.57, 81.60, 81.58, 60.44, 60.41, 36.91, 31.42, 29.44, 29.41, 22.35, -3.27.; **8a**: ^{1}H δ 6.84 (1 H, s), 3.05 (1 H, s), 2.50 (2 H, t), 2.46 (2 H, t), 1.70 (3 H, s), 1.65 (3 H, s), 1.53 (2 H, quintet, J = 7.5 Hz).; **8f** (1:1 mixture of the *E* and the *Z* isomers): ^{1}H δ 7.5-6.9 (11 H, m), 6.38 and 6.30 (1 H, d, J = 7.5 Hz), 2.58 (4 H, m), 1.6 (2 H, m).
9. The presence of THF causes a significant upfield shift of the ^{1}H NMR signal of the vinylic hydrogen.

(*Received in USA* 26 *January* 1995; *revised* 28 *March* 1995; *accepted* 31 *March* 1995)