One-Pot Synthesis and Functionalization of Polyynes via Alkylidene Carbenoids

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Abstract: A one-pot, two-step method for the synthesis of diynes and triynes is reported. The reaction of a dibromoolefinic precursor with BuLi effects a Fritsch–Buttenberg–Wiechell rearrangement and generates a lithium acetylide intermediate, which is then trapped with a variety of electrophiles to produce substituted diynes and triynes. Alternatively, transmetalation from the lithium acetylide to give a zinc acetylide provides a nucleophilic coupling partner for aryl iodides in the presence of palladium to form symmetrical or unsymmetrical diynes and triynes via the Negishi coupling.

Key words: carbenoid rearrangement, rearrangement deprotonation, polyyne, lithium acetylide, zinc acetylide



Scheme 1 General scheme for the transformation of dibromoolefins into diynes and triynes

Acetylene chemistry has played an important role in both organic synthesis and materials chemistry. Many alcohols bearing a polyyne framework have been isolated from species of plants, fungi, or sponges, and they often show important biological activity.² Moreover, conjugated polyynes are widely used as carbon-rich building blocks,³ and extended polyynes themselves show interesting optical properties.⁴ Over the years, a variety of methods have been developed to form divnes via a one-pot reaction; that is, transformations that accomplish both the generation and subsequent substitution of a metal acetylide all in a single step. Typical examples for the formation and trapping of diynes include (a) the elimination of 1-halobut-1en-3-ynes,^{5,6} (b) monodesilylation of 1,4-bis(trimethylsilvlbuta)-1,3-divne with MeLi/LiBr,7 and (c) the elimination of (Z)-1-methoxybut-1-en-3-ynes.⁸

We have recently developed a divergent approach that has been successful for the formation of functionalized diynes and triynes. In this process, a lithitated diyne or triyne is generated from a dibromoolefin with BuLi via a carbenoid rearrangement.⁹ This intermediate can then be trapped in

SYNTHESIS 2008, No. 7, pp 1158–1162 Advanced online publication: 10.01.2008 DOI: 10.1055/s-2007-1000937; Art ID: Z06807SS © Georg Thieme Verlag Stuttgart · New York situ with numerous electrophiles. Alternatively, aryl polyynes can result from the conversion of the intermediate lithium acetylide to a zinc acetylide, followed by palladium-catalyzed Negishi coupling.¹⁰ The current scope of this reaction is described herein.

The direct precursors, terminal enynes **1a–f**, are produced from the corresponding trimethylsilyl protected derivatives, which are either known or easily prepared.^{10,11} The general transformation to the desired products, diynes 2 and trivnes 3, is shown in Scheme 1. Precursor 1 is dissolved in toluene or a mixture of toluene and hexanes (1:5), depending on solubility, and cooled to -20 °C. BuLi (2.2 equiv) is added dropwise to this solution via a syringe and the temperature is raised to 0 °C giving the intermediate lithium acetylide 4. The solution is then recooled to -20 °C and an equal amount of anhydrous Et₂O (10 mL) added, followed by an electrophile dissolved in Et₂O. The reaction temperature is then slowly raised to room temperature and quenched. Aqueous workup and purification by column chromatography gives the desired products. Key to the success of this protocol is absolutely anhydrous reaction conditions, because both the carbenoid and acetylide intermediates are rapidly quenched by adventitious water, resulting in lower yields and more difficult chromatographic separations.

A slightly different procedure is employed to achieve the Negishi coupling. Terminal alkyne **1** is dissolved in toluene¹² and the temperature is lowered to -40 °C. BuLi (2.2 equiv) is added, and the reaction temperature is raised to -20 °C to ensure complete rearrangement of the alkylidene carbenoid to the lithiated polyyne. The reaction mixture is again cooled to -40 °C and ZnCl₂ (1.2 equiv) added to give the zinc acetylide **5**. Subsequently, the aryl

iodide coupling partner and $Pd(PPh_3)_4$ (5 mol%) are introduced¹³ and the reaction mixture heated to 70 °C for ca. 20 hours. Workup and purification gives the diynes and triynes in reasonable to excellent yield.

Dibromoenyne 1a has been used as a model system to explore the potential of this one-pot reaction. Under the conditions described above, lithium acetylide 4a reacted with methyl iodide to form diyne $2a^{14}$ in good yield, whereas

 Table 1
 Diynes 2a-j Formed from Dibromoolefin 1a

Electrophile	Product	Yield (%) ^a
MeI	Za Me	67
EtI	Zh	<5
CO ₂	2с	64
H TIPS	2d OH $TIPS$	75
H OTBDMS	2e OH OTBDMS	57
Å,,	HO (+)-2f	20
2	HO (-)-2g	30
OTBDMS		22 ^b
IMe	2h 2i 2i	90
	21	64

^a Isolated yield.

^b HMPA (2.6 equiv) added.

the analogous reaction with ethyl iodide to produce **2b** was unsuccessful. The formation of diyne carboxylic acid **2c**¹⁵ was achieved in good yield by trapping the intermediate lithium acetylide with carbon dioxide, and the desired product was purified by an acid-base extraction. Secondary alcohols **2d** and **2e** were produced when either an alkynyl or alkyl aldehyde was used as the electrophile, although the yield was lower in the case of **2e** due presumably to the acidic α -protons of the alkyl aldehyde.

Epoxides were used as electrophiles in reactions with **4a**, giving optically active homopropargylic alcohols **2f** and **2g**, albeit the yields were consistently low. The product from the reaction of (*R*)-propylene oxide, (+)-**2f** $([\alpha]_D^{20}$

+6, c 0.55, MeOH), shows analogous spectral data and optical rotation as pilosol A, a diyne isolated from *Bidens pilosa*.¹⁶ Thus, both the structure and *R*-stereochemistry for this natural product were confirmed. The use of HMPA used as an additive did not improve the yield of the epoxide addition reactions (e.g., compound **2h**).

Formation of the zinc acetylide **5a** provided a nucleophilic coupling partner necessary for the Negishi reaction, via reaction with aryl iodides. Diyne **2i** was produced in excellent yield, and using a double Negishi coupling, **5a** was reacted with 1,3-diiodobenzene to form compound **2j** in 64% yield (80% yield per coupling event).

Table 2Triynes 3a-k Formed from Dibromoolefins 1b-f



^a Isolated yield.

^b Oxirane was dissolved in NH₃.

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Because of the inherent challenges that have faced trivne syntheses in the past, both the ability to form the polyyne skeleton and functionalize one terminus in a single step was quite desirable. Gratifyingly, the protocol optimized for the synthesis of 2a-j has been equally applicable for trivnes (Table 2), and the scope of the reaction has been demonstrated over a broader range of dibromoolefinic substrates 1b-f. For example, reaction of the methyl-terminated lithium acetylide 4d with paraformaldehyde gave the propargylic alcohol **3a** in reasonable yield, a natural product identified from the fungi Kuehneromyces mutabilis, Psilocybe merdaria, and Ramaria flava.¹⁷ The corresponding homopropargylic alcohol 3b was derived from the reaction of 4d with oxirane in a reaction mixture diluted with NH₃. The product, 3,5,7-nonatriyn-1-ol, was isolated as a white solid that turned pink when exposed to light. This compound has been isolated from a number of natural sources including Collybia peronata,18 Lentinus edodes (shiitake mushroom),19 and Tridax trilobata.20 Using the phenyl-substituted dibromoolefin 1b, rearrangement and reaction with MeI and CO₂ gave the known natural products $3c^{21}$ and $3d^{22}$ in respectable yields, while using benzaldehyde as the electrophile gave secondary alcohol 3e. Generation of the butyl derivative 4e from 1e and reaction with a diynone produced compound 3f in excellent yield as a stable brown oil.

The synthesis of aryl triynes through Negishi coupling was explored via the generation of intermediate triyne acetylides **4b**,**c**,**e**,**f** and subsequent transmetalation to give the zinc acetylide intermediates **5b**,**c**,**e**,**f**. The palladiumcatalyzed cross-coupling of butyl acetylide **5e** with 4-(*N*,*N*-dimethyl)iodoaniline gave triyne **3g** in low yield, which is not unexpected for an electron-rich coupling partner. Coupling with *p*-iodoanisole was more successful and gave **3h** in good yield (80%). *p*-Iodotoluene reacted with *tert*-butyl derivative **5c** and TIPS derivative **5f** to give **3i** and **3j**, respectively. Completing the series, zinc acetylide **5f** was coupled with the electron-deficient 4-cy-anoiodobenzene to produce **3k** as a stable, light yellow crystalline solid in 78% yield.

In conclusion, a one-pot protocol has been developed for synthesis of diynes and triynes in reasonable to excellent yield. Overall, this method shows several advantages, but also some limitations. Advantages of this method include: (a) it is divergent and assembles and functionalizes the polyyne framework in a single step, (b) it does not require kinetically unstable polyyne precursors that can be difficult to obtain neat, and (c) it readily provides unsymmetrical substituted diynes and triynes, including both polyyne natural products and carbon-rich scaffolds. Unfortunately, this method is not suitable for use in all cases, including (a) situations where a polar ethereal solvent such as THF or Et₂O is needed to solubilize the precursor dibromoolefin 1; even small amounts of such solvents effectively prevent the carbenoid rearrangement step, (b) cases where an acidic or electrophilic substrate would be desired as a substituent on the dibromoolefin; that is, groups that will not tolerate BuLi, and (c) in some cases,

the stability of a dibromoolefinic precursors limits the success of the one-pot procedure, providing lower overall yields of the desired product.

Reagents were purchased reagent grade from commercial suppliers and used without further purification. Et₂O, toluene, and THF were distilled from sodium/benzophenone ketyl, and hexanes and CH₂Cl₂ were distilled from CaH₂, immediately prior to use. Evaporation and concentration in vacuo was done at water-aspirator pressure. All reactions were performed in standard, dry glassware under an inert atmosphere of Ar or N2. Column chromatography: silica gel-60 (230-400 mesh) from General Intermediates of Canada. TLC: aluminum sheets covered with silica gel-60 F_{254} from Macherey-Nagel; visualization by UV light or KMnO₄ stain. Melting points: Gallenkamp apparatus. IR spectra (cm⁻¹): Nic-Plan IR Microscope. ¹H NMR and ¹³C NMR spectra: Varian Inova 300, 400 or 500 instruments, at r.t. in CDCl₃; solvent peaks (7.24 ppm for ¹H and 77.0 ppm for ¹³C) were used as reference. EI MS (m/z): Kratos MS50 instrument. Elemental analyses were conducted by Spectral Services at the University of Alberta. Spectral data for compounds not provided below or referenced in the text can be found in reference 10b.

Enynes 1; General Procedure

To a solution of the appropriate trimethylsilyl-protected precursor of **1** (1 mmol)¹¹ in THF (10 mL) and MeOH (10 mL) was added pulverized K_2CO_3 (0.1 g, 0.75 mmol) at r.t. TLC analysis was used to monitor the reaction until desilylation was complete (typically ca. 1 h; the R_f of the product is always slightly less than that of the starting material). Sat. aq NH₄Cl (10 mL) and Et₂O (10 mL) were then added, the organic layer was separated, washed with H₂O (2 × 50 mL), and dried (MgSO₄). After filtration, the solvent was reduced to ca. 1–2 mL, and this solution was passed through a short silica gel column to afford the terminal alkyne **1**. The product was dried under vacuum. Care must be taken to ensure that the desilylated product is absolutely anhydrous to prevent quenching of the carbenoid intermediate during the subsequent step. In some cases, products **1** slow-ly discolor over time (e.g., **1b,d,e**), and are therefore either best used immediately or stored in solution under refrigeration.

1,3-Bis(3-phenylbuta-1,3-diynyl)benzene (2j); Typical Procedure 1

To a stirred solution of dibromoolefin **1a** (215 mg, 0.752 mmol) in toluene (10 mL) at -40 °C under argon was added BuLi (2.5 M in hexanes, 0.66 mL, 1.7 mmol) by a syringe over a period of ca. 5 min. The mixture was allowed to warm slowly to -20 °C and then recooled to -40 °C. ZnCl₂ (0.5 M in THF, 1.8 mL, 0.9 mmol) was added by a syringe over a period of ca. 5 min. The mixture was then allowed to warm slowly to 0 °C over ca. 10 min. 1,3-Diiodobenzene (110 mg, 0.333 mmol) and Pd(PPh₃)₄ (60 mg, 0.052 mmol) were added, and this mixture was heated to reflux under a positive pressure of argon. After 20 h, the mixture was cooled and filtered through a pad of Celite. The resulting solution was concentrated under reduced pressure and the residue purified by column chromatography (silica gel, hexanes-CH₂Cl₂, 6:1), giving **2j** as a yellow solid; yield: 71.1 mg (64%); mp 115–117 °C; $R_f = 0.3$ (hexanes-CH₂Cl₂, 6:1).

IR (μ scope, neat solid): 3062 (w), 2220 (m), 1589 cm⁻¹ (m).

¹H NMR (500 MHz, CDCl₃): δ = 7.66–7.64 (m, 1 H), 7.54–7.48 (m, 6 H), 7.39–7.29 (m, 7 H).

 ^{13}C NMR (125 MHz, CDCl₃): δ = 136.1, 133.0, 132.6, 129.4, 128.7, 128.5, 122.5, 121.6, 82.1, 80.2, 74.8, 73.7.

MS (EI, 70 eV): m/z (%) = 326.1 (100, [M]⁺).

HRMS (EI): *m*/*z* [M]⁺ calcd for C₂₆H₁₄: 326.1096; found: 326.1099.

Nona-3,5,7-triyn-1-ol (3b); Typical Procedure 2

Dibromoolefin **1d** (451 mg, 1.82 mmol) was dissolved in toluene (10 mL) and cooled to -20 °C under argon. To this solution, BuLi (2.5 M in hexanes, 1.6 mL, 4.0 mmol) was added via a syringe over a period of ca. 1 min. The mixture was allowed to warm slowly to 0 °C, recooled to -20 °C, and Et₂O (10 mL) was added. To this solution was added, via a cannula, a mixture of oxirane (2 mL, 40 mmol) in NH₃ (5 mL) cooled to -20 °C. The solution was allowed to warm to r.t., stirred overnight, and quenched with sat. aq NH₄Cl (10 mL) and Et₂O (10 mL). The organic phase was separated, washed with brine (2 × 10 mL), and dried (MgSO₄). Solvent removal and purification by column chromatography (silica gel, CH₂Cl₂) gave compound **3b** as a white crystalline solid that turned pink when exposed to light; yield: 140 mg (58%); mp 54–56 °C; $R_f = 0.3$ (CH₂Cl₂).

IR (µscope, neat solid): 3262 (vs), 2946 (s), 2876 (s), 2219 (s), 2036 (w), 1054 cm^{-1} (m).

¹H NMR (500 MHz, CDCl₃): δ = 3.74 (t, *J* = 6.0 Hz, 2 H), 2.55 (t, *J* = 6.0 Hz, 2 H), 1.94 (s, 3 H), 1.64 (br s, 1 H).

¹³C NMR (125 MHz, CDCl₃): δ = 75.4, 75.3, 67.5, 64.8, 61.2, 60.6, 59.3, 23.8, 4.5.

MS (EI, 70 eV): m/z (%) = 132.1 (72, [M]⁺), 102.0 (100, [M – CH₂O]⁺).

HRMS (EI): *m*/*z* [M]⁺ calcd for C₉H₈O: 132.0575; found: 132.0577.

Anal. Calcd for C_9H_8O (132.16): C, 81.79; H, 6.10. Found: C, 81.58; H, 6.26.

Spectral data were consistent with those reported.^{17a}

3-(3-Triisopropylsilylethynyl)-1-triisopropylsilyl-1,4,6,8-tridecatetrayn-3-ol (3f); Typical Procedure 3

Dibromoolefin **1e** (273 mg, 0.947 mmol) was dissolved in toluene (2 mL) and this solution was diluted with hexanes (10 mL). To this stirred mixture at -20 °C was added BuLi (2.5 M in hexanes, 0.83 mL, 2.1 mmol) and the reaction was warmed to 0 °C. 1,5-Bis(triiso-propylsilyl)penta-1,4-diyn-3-one (321 mg, 0.822 mmol) dissolved in Et₂O (10 mL) was added, and the reaction was allowed overnight to warm to r.t. Workup and purification as described above for **3b** gave compound **3f** as a brown oil; yield: 370 mg (82%); $R_f = 0.44$ (hexanes–CH₂Cl₂, 6:1).

IR (CHCl₃, cast): 3435 (w), 2943 (vs), 2866 (vs), 2219 (m), 2155 (w), 1463 cm⁻¹ (m).

¹H NMR (500 MHz, CDCl₃): δ = 2.75 (br s, 1 H), 2.30 (t, *J* = 7.0 Hz, 2 H), 1.54–1.48 (m, 2 H), 1.44–1.36 (m, 2 H), 1.06 (s, 42 H), 0.89 (t, *J* = 7.0 Hz, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 102.7, 85.9, 82.3, 72.6, 67.8, 66.1, 65.3, 58.6, 54.8, 29.9, 21.9, 19.1, 18.5, 13.4, 11.1.

MS (EI, 70 eV): m/z (%) = 477.3 (17, $[M - i-Pr]^+$).

HRMS (EI): $m/z [M - i-Pr]^+$ calcd for $C_{30}H_{45}OSi_2$: 477.3009; found: 477.3019.

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References

- Current address: Department of Polymer Chemistry, Graduate School of Engineering, Kyoto University, Japan.
- (2) Shi Shun, A. L. K.; Tykwinski, R. R. Angew. Chem. Int. Ed. 2006, 45, 1034.
- (3) Acetylene Chemistry: Chemistry, Biology, and Material Science; Diederich, F.; Stang, P. J.; Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, 2005.
- (4) (a) Luu, T.; Elliott, E.; Slepkov, A. D.; Eisler, S.; McDonald, R.; Hegmann, F. A.; Tykwinski, R. R. Org. Lett. 2005, 7, 51. (b) Eisler, S.; Slepkov, A. D.; Elliott, E.; Luu, T.; McDonald, R.; Hegmann, F. A.; Tykwinski, R. R. J. Am. Chem. Soc. 2005, 127, 2666.
- (5) (a) Himbert, G.; Umbach, H.; Barz, M. Z. Naturforsch., B 1984, 39, 661. (b) Negishi, E.; Okukado, N.; Lovich, S. F.; Luo, F.-T. J. Org. Chem. 1984, 49, 2629. (c) Kende, A. S.; Smith, C. A. J. Org. Chem. 1988, 53, 2655. (d) Alami, M.; Crousse, B.; Linstrumelle, G. Tetrahedron Lett. 1995, 36, 3687.
- (6) This general approach has very recently been extended to triand tetra- and pentaynes, see: Métay, E.; Hu, Q.; Negishi, E. Org. Lett. 2006, 8, 5773.
- (7) (a) Holmes, A. B.; Jennings-White, C. L. D.; Schulthess, A. H.; Akinde, B.; Walton, D. R. M. J. Chem. Soc., Chem. Commun. 1979, 840. (b) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. Tetrahedron 2006, 62, 5126.
- (8) (a) Stracker, E. C.; Zweifel, G. *Tetrahedron Lett.* **1990**, *31*, 6815. (b) Kwon, J. H.; Lee, S. T.; Shim, S. C. J. Org. Chem. **1994**, *59*, 1108.
- (9) For a review, see: Chalifoux, W. A.; Tykwinski, R. R. Chem. Rec. 2006, 6, 169.
- (10) For a more thorough description of this process, see:
 (a) Morisaki, Y.; Luu, T.; Tykwinksi, R. R. Org. Lett. 2006, 8, 689. (b) Luu, T.; Morisaki, Y.; Cunningham, N.; Tykwinksi, R. R. J. Org. Chem. 2007, 72, 9622.
- (11) (a) Shi Shun, A. L. K.; Chernick, E. T.; Eisler, S.; Tykwinski, R. R. J. Org. Chem. 2003, 68, 1339. (b) Eisler, S.; Tykwinski, R. R. J. Am. Chem. Soc. 2000, 122, 10736.
 (c) Eisler, S.; Chahal, N.; McDonald, R.; Tykwinski, R. R. Chem. Eur. J. 2003, 9, 2542.
- (12) Toluene was used instead of hexanes to achieve a higher temperature for reflux in the Negishi cross-coupling.
- (13) Negishi, E. In Handbook of Organopalladium Chemistry for Organic Synthesis; Negishi, E., Ed.; Wiley-VCH: New York, 2002, 229.
- (14) Reisch, J.; Walker, H. Arch. Pharm. (Weinheim, Ger.) 1964, 297, 628.
- (15) Fleming, I.; Ramarao, C. Org. Biomol. Chem. 2004, 2, 1504.
- (16) Chang, M.-H.; Wang, G.-J.; Kuo, Y.-H.; Lee, C.-K. J. Chin. *Chem. Soc.* **2000**, *47*, 1131.
- (17) (a) Luu, T.; Tykwinski, R. R. J. Org. Chem. 2006, 71, 8982.
 (b) Luu, T.; Wei, S.; Lowary, T. L.; Tykwinski, R. R. Synthesis 2005, 3167.
- (18) Higham, C. A.; Jones, E. R. H.; Keeping, J. W.; Thaller, V. J. Chem. Soc., Perkin Trans. 1 1974, 1991.
- (19) Tokimoto, K.; Fujita, T.; Takeda, Y.; Takaishi, Y. *Proc. Jpn. Acad., B* **1987**, *63*, 277.
- (20) Bohlmann, F.; Zdero, C.; Weickgenannt, G. *Liebigs Ann. Chem.* **1970**, *739*, 135.
- (21) Alvarez, L.; Marquina, S.; Villarreal, M. L.; Alonso, D.; Aranda, E.; Delgado, G. *Planta Med.* **1996**, *62*, 355.
- (22) Bohlmann, F.; Sucrow, W.; Queck, I. Chem. Ber. 1964, 97, 2586.