ORGANIC LETTERS

2001
Vol. 3, No. 18
2883−2886

Synthesis of Diynes and Tetraynes from in Situ Desilylation/Dimerization of Acetylenes

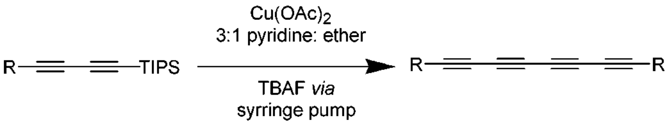
Matthew A. Heuft, Shawn K. Collins, Glenn P. A. Yap,[†] and Alex G. Fallis*

Department of Chemistry, University of Ottawa, 10 Marie Curie,
Ottawa, Ontario, Canada K1N 6N5

afallis@science.ottawa.ca

Received July 10, 2001

ABSTRACT



An efficient method for the in situ desilylation/oxidative dimerization of (trialkylsilyl)acetylenes is described. This protocol avoids the complications encountered with sensitive diynes by eliminating the deprotection and isolation steps. Various aromatic and alkyl diynes and tetraynes can be synthesized in a straightforward manner in good yields (82–99%) from TIPS-protected acetylenes. This method facilitates the efficient synthesis of novel tetrayne-bridged acetylenic cyclophanes 6 and 7 in a direct manner.

The unique properties of polyynes and acetylenic arrays continue to garner attention and increased research interest.[1] In addition to their unusual electrical and optical properties, they are encountered in numerous natural products and display a wide range of potential applications in both biology and material sciences. Consequently, research into the synthesis of well-defined polyynes continues to expand. The electronic properties and spectra of polyynes and polyyne polymers[2] have been studied for their interesting bathochromic shifts.[3] These shifts are proportional to the number of acetylene linkages.[4] α,ω-Diarylpolyynes display efficient charge transfer through their conjugated polyyne bridges in applications as dyes and pigments.[5] The efficiency of the energy and electron transfer processes have been examined, as potential molecular wires and chemosensors, particularly in polyyne-bridged porphyrin systems[6] and bis(benzocrown ethers).[7]

Polyyne segments in both natural[8a] and unnatural[8b,c] products exhibit a wide range of biological activity. These include potential as potent antiinflammatory,[9a] antibiotic[9b] (caryoynencins), antitumor[9c] (panaxydol), and antibacterial[9d] agents (falcarrindiol). Polyynes are also crucial components for the construction of carbon-rich materials such as novel dehydrobenzoannulenes[10] and innovative acetylenic cyclophanes with potential to act as precursors to fullerenes.[11]

The most common synthetic method for the assembly of polyynes involves bond formation between two acetylenes

---

[†] Contact this author for enquiries regarding x-ray analysis.

(1) (a) Ginsburg, E. J.; Gorman, C. B.; Grubbs, R. H. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995. (b) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632. (c) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier, Amsterdam. 1988.

(2) (a) Shirakawa, H.; Louis, E. J.; MacDiarmid, A. G.; Chiang, C. K.; Heeger, A. J. *J. Chem. Soc., Chem. Commun.* **1977**, 578. (b) Chiang, C. K.; Fincher, C. R. Jr.; Park, Y. W.; Heeger, A. J.; Shirakawa, H.; Louis, E. J.; Gau, S. C.; MacDiarmid, A. G. *Phys. Rev. Lett.* **1977**, *39*, 1098.

(3) Akiyama, S.; Nakasuji, K.; Akashi, K.; Nakagawa, M. *Tetrahedron Lett.* **1968**, *24*, 1121.

(4) Prabhakara, R.; Mathur, S. C.; Dube, D. C.; Tewari, D. P.; Banerjee, M. *Can. J. Chem.* **1997**, *75*, 1041.

(5) Akiyama, S.; Nakashima, K.; Nakatsuji, S.; Nakagawa, M. *Dyes Pigm.* **1990**, *13*, 117.

(6) Maruyama, K.; Kawabata, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 170.

(7) Lee, L.-H.; Lynch, V.; Lagow, R. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2805.

(8) (a) Svirskaya, P. I.; Leznoff, C. C.; Roelofs, W. L. *Synth. Commun.* **1980**, *10*, 391.(b) Rodbotten, S.; Benneche, T.; Undhiem, K. *Acta Chem. Scand.* **1997**, *51*, 873. (c) Hopf, H.; Krause, N. *Tetrahedron Lett.* **1985**, *26*, 3323.

(9) (a) Zeni, G.; Panatieri, R. B.; Lissner, E.; Menezes, P. H.; Braga, A. L.; Stefani, H. A. *Org. Lett.* **2001**, *3*, 819. (b) Yamaguchi, M.; Park, H.-J.; Hirama, M.; Torisu, K.; Nakamura, T.; Minami, H.; Nishihara, H.; Hriraoka, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1717. (c) Lu, W.; Haji, G. Z.; Cai, J. *Tetrahedron Lett.* **1998**, *39*, 9521. (d) Zheng, G.; Lu, W.; Cai, J. *J. Nat. Prod.* **1999**, *62*, 626.

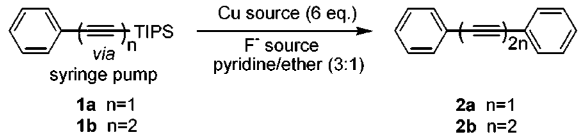
10.1021/ol016414u CCC: $20.00

via oxidative coupling. Frequently, the classic protocols developed by Hay,[12] Glaser,[13] and Eglinton[14] are the methods of choice, although newer combinations and modifications have also been developed.[15] Diederich and co-workers have introduced a solution spray flash vacuum pyrolysis of suitable precursors for the formation of even- *and* odd-numbered polyynes.[16]

The instability of simple and higher polyynes is a major challenge in their preparation. They are highly sensitive to polymerization and prone to rapid decomposition.[17] Terminal phenylbutadiynes are particularly sensitive.[10] Recently, different protocols have been developed for the in situ one-pot desilylation/dimerization of acetylenes. Mori and Hiyama and co-workers[18] employed CuCl in DMF under air or oxygen with (trimethylsilyl)acetylene in the absence of fluoride ion to afford high yields (80−100%) of the homocoupled product. This procedure has also been applied to the synthesis of unsymmetrically substituted diacetylenes when alkynyltrimethylsilanes are mixed with 1-chloroalkynes.[19] Haley et al. reported a different in situ one-pot desilylation/dimerization strategy for the synthesis of tetrayne-linked dehydrobenzoannulenes. This method combines standard Eglinton coupling conditions with an excess of potassium carbonate to effect the protodesilylation of trimethylsilyl (TMS) protected acetylenes in good yields.[20]

We have previously investigated the synthesis of a novel family of acetylenic cyclophanes[21] and wished to extend these studies to tetrayne-bridged systems. Our synthesis of acetylenic precursors involved the use of triisopropylsilyl (TIPS) protected phenylbutadiyne units. Deprotection and isolation of the terminal acetylenes was not possible as the products rapidly decomposed before oxidative coupling could occur. Consequently, we chose to develop an alternative desilylation/dimerization protocol using a fluoride source to effect desilylation of TIPS-protected acetylenes.

Table 1. Optimization of Copper and Fluoride Ion Mediated Dimerization of (Triisopropylsilyl)acetylenes



entry	[**1**] (mM)	copper source	fluorine⁻ source	time (h)	yield (%)
1	**1a**, 2.0	Cu(OAc)$_2$	TBAF 1 equiv	4	**2a**, 68[a]
2	**1a**, 4.0	Cu(OAc)$_2$	TBAF 1 equiv	4	**2a**, 45[a]
3	**1a**, 4.0	Cu(OAc)$_2$	TBAF 1 equiv	3	**2a**, 42
4	**1a**, 4.0	Cu(OAc)$_2$	TBAF 2 equiv	2	**2a**, 45
5	**1a**, 4.0	CuF$_2$	-	2	NR[b]
6	**1b**, 2.0	Cu(OAc)$_2$	TBAF 1 equiv	2	**2b**, 15−40
7	**1b**, 2.0	Cu(OAc)$_2$	CsF 1 equiv	3	**2b**, 6
8	**1b**, 2.0	Cu(OAc)$_2$	TBAF 1 equiv	**3**	**2b**, 100[c]
9	**1b**, 2.0	CuCl, TMEDA	TBAF 1 equiv	2	**2b**, <5[d]

[a] Substrate not added by syringe pump. [b] NR = no reaction. [c] TBAF added via syringe pump instead of substrate. [d] Benzene used as solvent.

Initially, the dimerization of model compounds **1a** and **1b** (Table 1) was investigated. Compound **1a** was stirred with a fluoride source (TBAF)[22] and Cu(OAc)$_2$ in pyridine/ether (3:1) for 4 h to give a 68% yield of the diyne product. Doubling the concentration of **1a** did not increase the yield (entry 2). It appeared that the deprotected phenylbutadiyne was polymerizing rapidly and thus competing with the desired dimerization. Thus, controlled addition of substrate **1a** via syringe pump was attempted (entry 3). Unfortunately, under identical concentrations, yields comparable to those without controlled addition were obtained. An increase in the number of equivalents of fluoride ion also had no effect (entry 4). Exposure of **1a** to CuF$_2$ as a combined source of fluoride ion for desilylation and copper ion for oxidative coupling also proved futile. Copper(II) fluoride is insoluble in common organic solvents, and under heterogeneous reaction conditions only the starting material was recovered. Despite the modest yields, the dimerization of **1b** was investigated, but results were irreproducible and the yields varied from 15 to 40%. Substitution of TBAF with CsF[23] as the fluoride source decreased the yield to 6% for the corresponding tetrayne (entry 7), while altering the Cu source using Hay's conditions (entry 9) gave a 5% isolated yield. These disappointing results appeared to be a consequence

---

(10) Haley, M. M.; Bell, M. L.; English, J. J.; Johnson, C. A.; Weakley, T. J. R. *J. Am. Chem. Soc.* **1997**, *119*, 2956.

(11) (a) Haley, M. M.; Langsdorf, B. L. *Chem. Commun.* **1997**, 1122. (b) Rubin, Y.; Parker, T. C.; Khan, S. I.; Holliman, C. L.; McElvany, S. W. *J. Am. Chem. Soc.* **1996**, *118*, 5308. (c) Tobe, Y.; Nakagawa, N.; Naemura, K.; Wakabayashi, T.; Shida, T.; Achiba, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4544. (d) Rubin, Y.; Parker, T. C.; Pastor, S. J.; Jalisatgi, S.; Boulle, C.; Wilkins, C. L. *Angew Chem., Int. Ed.* **1998**, *110*, 1353. (e) Fallis, A. G. *Can. J. Chem.* **1999**, *77*, 159.

(12) (a) Hay, A. S. *J. Org. Chem.* **1960**, *25*, 1275. (b) Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320.

(13) (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422. (b) Glaser, C. *Ann. Chem. Pharm.* **1870**, *154*, 137.

(14) Eglinton, G.; Galbraith, A. R. *Chem. Ind. (London)* **1956**, 737.

(15) (a) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632. For additional palladium-based alkyne coupling methods, see: (b) Liu, Q.; Burton, D. J. *Tetrahedron Lett.* **1997**, *38*, 4371. (c) Godt, A. *J. Org. Chem.* **1997**, *62*, 7471.

(16) Rubin, Y.; Lin, S. S.; Knobler, C. B.; Anthony, J.; Boldi, A. M.; Diederich, F. *J. Am. Chem. Soc.* **1991**, *113*, 6943.

(17) Patel, G. N.; Chance, R. R.; Turi, E. A.; Khanna, Y. P. *J. Am. Chem. Soc.* **1978**, *100*, 6644.

(18) Ikegashira, K.; Nishihara, Y.; Hirabayashi, K.; Mori, A.; Hiyama, T. *Chem. Commun.* **1997**, 1039.

(19) Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1998**, *39*, 4075.

(20) Haley, M. M.; Bell, M. L.; Brand, S. C.; Kimball, D. B.; Pak, J. J.; Wan, W. B. *Tetrahedron Lett.* **1997**, *38*, 7483.

(21) Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Angew Chem., Int. Ed.* **2000**, *39*, 385.(b) Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2000**, *2*, 3189.

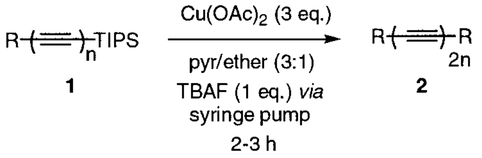
(22) (a) Oda, H.; Sato, M.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3257. (b) Johnson, T. R.; Walton, D. R. M. *Tetrahedron* **1972**, *28*, 5221.

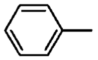
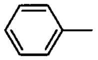
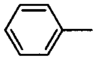
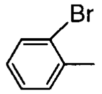
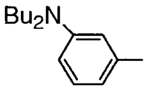
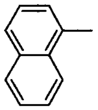
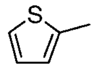
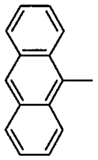
(23) (a) Chan, T. H.; Massuda, D. *Tetrahedron Lett.* **1975**, 3383. (b) Chan, T. H.; Ong, B. S. *J. Org. Chem.* **1978**, *43*, 2994.

of the large relative concentration of fluoride ion present in solution, which hindered the dimerization. Consequently, a THF solution of TBAF was added directly via syringe pump (entry 8). The tetrayne was isolated in quantitative yield!

The generality of this method was established by investigation of the dimerization of compounds listed in Table 2.

Table 2. Examples of TBAF/Cu(OAc)$_2$-Mediated Desilylation/Oxidative Dimerization of Aromatic Acetylene and Butadiynes



entry	R	n	[substrate] mM	yield (%)
1		2	**1b**, 1.7 **1b**, 3.3	**2b**, 73 **2b**, 100
2		1	**1a**, 3.3	**2a**, 100
3		2	**1c**[a], 3.3	**2c**, 93
4		2	**1d**, 3.3	**2d**, 98
5		2	**1e**, 3.3	**2e**, 82
6		2	**1f**, 3.3	**2f**, 96
7		2	**1g**, 3.3	**2g**, 92
8		2	**1h**, 3.3	**2h**, 82
9		3	**1i**, 3.3	-

[a] TMS group in place of a TIPS group.

Model compound **1b** at various concentrations was exposed to TBAF. A concentration of 1.7 mM afforded the isolated tetrayne product (**2b**) in 73−77% yield. However, doubling the concentration of **1b** gave quantitative yields. The use of a TMS silyl protected diyne (**1c**, entry 3) also gave, as expected, the diaryl tetrayne in 93% yield. Substituent effects were also investigated. Compound **1d**, which has an electron-withdrawing *o*-bromo phenyl, was dimerized in 98% yield. X-ray crystallographic analysis established the structure of the tetrayne (**2d**).[24] This material displayed crystal packing similar to that of the system reported by Tykwinski and coworkers[25] for cross-conjugated polyenynes (Figure 1). The electron-rich *m*-*N*,*N*-dibutylaminophenyl diyne **1e** formed the corresponding tetrayne in 82%. Desilylation/dimerization of **1f** afforded the known tetrayne 1,8-(1-naphthyl)octa-1,3,5,7-tetrayne (**2f**, 96%), investigated previously for its interesting spectral properties.[3] Alkyl substituents were also compatible with this synthetic protocol as **1g** dimerized in 98% yield. Heteroaromatic substituted polyynes may also be easily prepared by this procedure. For example, **1h** produced the thiophene−tetrayne (**2h**) in 82% yield. An attempt to form a hexayne product via this procedure failed. The anthracenyl triyne **1i**[26] (entry 9) gave two red solid products upon treatment with the TBAF/Cu(OAc)$_2$ system that were sparingly soluble in organic solvents. At present, these cannot be properly identified and characterized.

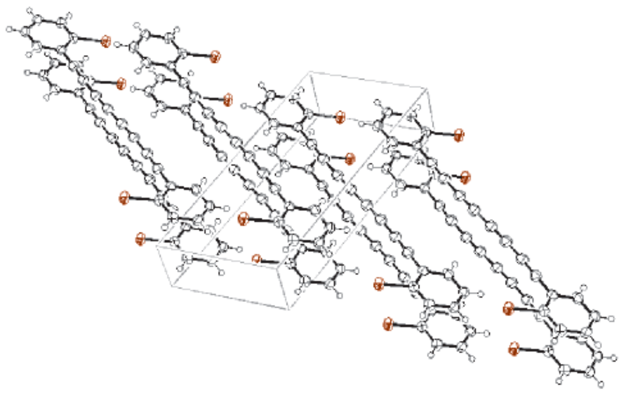


Figure 1. View of the unit cell crystal packing for the 1,8-di(2-bromophenyl)-1,3,5,7-octatetrayne (**2d**).

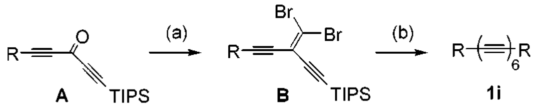
It was of interest to apply this desilylation/dimerization sequence to the synthesis of a novel acetylenic cyclophane bearing tetrayne linkages (Scheme 1). In principle, it should be possible to generate the target cyclophane **6** from the dimerization of **5**. Dibutyl amino groups were installed on the "corner" phenyl rings in order to aid solubility, as done previously with similar large macrocycles.[27] Treatment of compound **3** with *n*BuLi caused elimination of the chloride ion to produce the diynyl anion which was transmetalated

---

[24] X-ray data for compound **2** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 163717. Copies of the data may be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: (+44) 1223-336-033. E-mail: deposit@ccdc.cam.ac.uk).

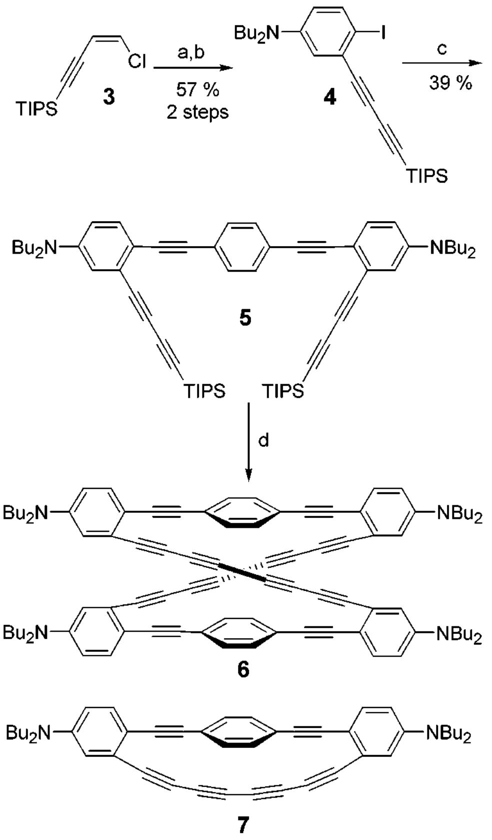
[25] Zhao, Y.; McDonald, R.; Tykwinski, R. R. *Chem. Commun.* **2000**, 77.

[26] Compound **1i** was prepared from a Fritsch−Buttenberg−Wiechell (FBW) rearrangement of the dibromide **B** derived from ketone **A** (recent applications: Eisler, S.; Tykwinski, R. R. *J. Am. Chem. Soc.* **2000**, *122*, 10736).



R = Anthracenyl, (a) CBr$_4$, PPh$_3$, CH$_2$Cl$_2$, 21 °C, 15 h, 64%
(b) *n*BuLi, hexane, -40 °C to 21 °C, 1 h, 41%

Scheme 1. Synthesis of a Novel Acetylenic Cyclophane Using an in Situ Desilylation/Dimerization Sequence[a]



[a] (a) (i) *n*BuLi, THF, −78 °C, 5 min, (ii) $ZnBr_2$, THF, 0 °C, 15 min, (iii) *N*,*N*-dibutyl-3-iodoaniline,[24] $Pd(PPh_3)_4$, reflux, 15 h; (b) $BnNMe_3ICl_2$, $CaCO_3$, THF/MeOH (5:1), 4 h; (c) 1,4-diethynylbenzene, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, THF, reflux, 15 h; (d) $Cu(OAc)_2$ (6 equiv), TBAF (1 equiv), pyridine/Et_2O (3:1), 3 h.

with $ZnBr_2$ and subjected to palladium(0)-based coupling to give the corresponding phenylbutadiyne product.[28] Iodination with $BnNMe_3ICl_2$[29] gave **4** in 57% yield over two steps. Sonogashira coupling of **4** with 1,4-diethynylbenzene produced the cyclophane precursor **5** in 39% yield. Compound **5** was subjected to the desilylation/dimerization protocol at two separate concentrations. At the lower concentration, the tetrayne-linked monomer product, **7**, was the sole macrocycle isolated in 46%. However, when the concentration of **5** was increased, dimer **6** was formed in 5% yield, although formation of **7** still dominated (26%).

In conclusion, we have developed an efficient method for the in situ desilylation and oxidative dimerization of TIPS-protected monoynes and diynes, based upon the addition of a fluoride source to a solution of the substrate and a copper salt. The optimized synthetic method [$Cu(OAc)_2$ (3 equiv); alkyne (3.3 mM) in a mixture of pyridine/ether (3:1); TBAF (1 equiv) via syringe pump] afforded yields of diynes and tetraynes in the range of 82−99% for various substituted aromatic and alkyl systems. The method also provides an expedient route to novel acetylenic cyclophanes. This method should prove to be a valuable synthetic tool for the construction of new polyyne-containing compounds.

Acknowledgment. We are grateful to the National Sciences and Engineering Research Council of Canada for financial support of this research. S. K. Collins and M. A. Heuft thank NSERC and the University of Ottawa for Graduate Scholarships.

Supporting Information Available: ^1H NMR, ^{13}C NMR, and MS data for compounds **1a**,**b**, **2a**−**e**, and their corresponding dimers and full characterization for **4**, **5**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016414U

---

(27) Pak, J. J.; Weakley, T. J. R.; Haley, M. M. *J. Am. Chem. Soc.* **1999**, *121*, 8182.

(28) (a) Sengupta, S.; Snieckus, V. *J. Org. Chem.* **1990**, *55*, 5680. (b) Knochel, P.; Seebach, D. *Tetrahedron Lett.* **1982**, *32*, 3897.

(29) Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 600.