ORGANIC
LETTERS

2009
Vol. 11, No. 3
519−522

Mechanistic Aspects of Alkyne Migration in Alkylidene Carbenoid Rearrangements

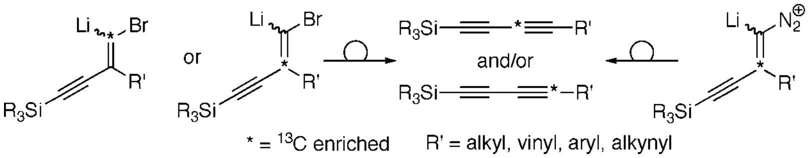
**Paul Bichler, Wesley A. Chalifoux, Sara Eisler,† Annabelle L. K. Shi Shun,
Erin T. Chernick, and Rik R. Tykwinski***

Department of Chemistry, University of Alberta, Edmonton, Alberta, T6G 2G2 Canada

rik.tykwinski@ualberta.ca

Received October 13, 2008

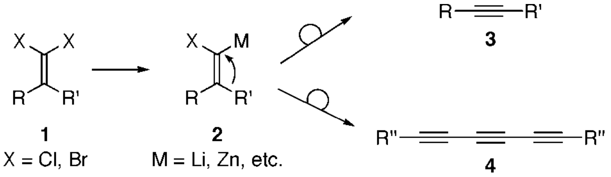
ABSTRACT



The mechanism of the Fritsch−Buttenberg−Wiechell rearrangement of ^{13}C labeled precursors has been examined to determine the propensity of the alkynyl (R−C≡C−) group to migrate in an alkylidene carbenoid species. Reaction of dibromoolefins with *n*-BuLi and ketones with $Me_3SiC(Li)N_2$ both demonstrate that the alkynyl moiety readily undergoes 1,2-migration from carbenoid intermediates.

The transformation of a carbenoid intermediate into an alkyne is a versatile synthetic procedure that has become known as the Fritsch−Buttenberg−Wiechell (FBW) rearrangement.[1,2] This reaction typically proceeds via metal halogen exchange of 1,1-dihaloolefins **1** leading to the formation of a carbenoid intermediate **2** (Scheme 1). α-Elimination of MX and concurrent migration of a pendant group from the adjacent carbon then provides the acetylenic product **3**.[3] This general protocol has proven useful for the formation of acetylenes when R and R′ are aryl[4] and heteroaryl,[5] as well as, to a lesser extent, alkenyl[6] and alkyl groups.[7,8] Alkynes also efficiently undergo 1,2-migration in both alkylidene carbenoids[9] and free carbenes[10] to provide, for example, triynes such as **4** (Scheme 1, R = R′ = C≡C−R″).[11]

Scheme 1. Fritsch−Buttenberg−Wiechell Rearrangement



[†] Current address: Department of Chemistry, University of New Brunswick, Fredericton, New Brunswick, E3B 5A3, Canada.

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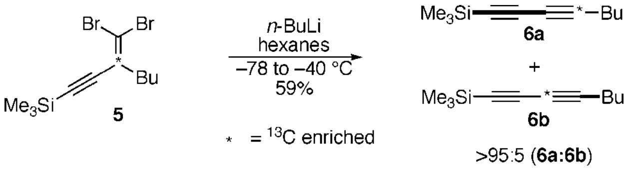
10.1021/ol8023665 CCC: $40.75

Mechanistic studies of the FBW rearrangement by Bothner-By,[12] Curtin,[13] and Köbrich[14] have explored the stereoselectivity of this rearrangement for carbenoid intermediates **2** in which R and R′ are aryl or alkyl groups. In most cases, the group *trans* to the halide (i.e., R′ in the carbenoid species **2**) migrates preferentially. It has been suggested, however, that *cis*-migration of an aryl group (e.g., **2**, R = Ar) can be favored over *trans*-migration when the group *trans* to the leaving group has a substantially reduced migratory aptitude. This is the case, for example, when the substituent R′ for intermediate **2** is an alkyl group.[3,15−18] Conspicuously absent from these earlier analyses is an evaluation of the propensity of the alkynyl moiety to migrate in a carbenoid species. We report herein an examination of alkyne migration in the FBW rearrangement in comparison to other common hydrocarbon groups.

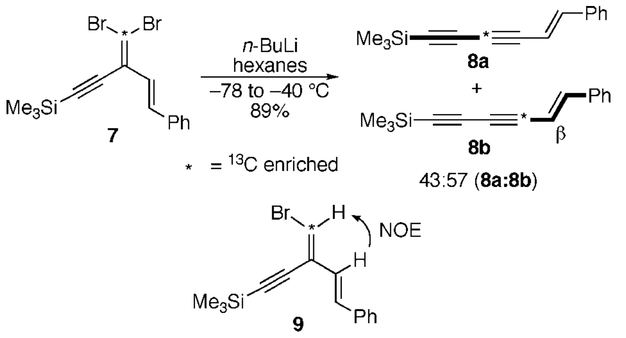
Enyne **5** was synthesized with a ^{13}C labeled dibromoolefin to evaluate the migratory potential of an alkynyl group versus that of an alkyl group (Scheme 2).[19] Rearrangement was accomplished by slow addition of *n*-BuLi to a solution of **5** in dry hexanes at −78 °C, followed by warming to −40 °C, at which point the reaction was quenched.[20] Workup and purification by column chromatography gave diyne **6** in moderate yield. ^{13}C NMR spectroscopy of the isolated product shows only one enhanced carbon signal, found at 80.2 ppm. Analysis of the alkyl region of the spectrum shows the signal of the propargylic carbon as a doublet at 18.9 ppm, and the large $^1J_{CC}$ = 66 Hz indicates that the isotopomer formed by alkyne migration (**6a**)[21] is the exclusive product. It is worth noting that no evidence of cyclopentene formation via 1,5-C−H bond insertion of the intermediate carbene/carbenoid species was observed in this reaction, based on ^{1}H NMR spectroscopic analysis.

Scheme 2. Alkyl versus Alkynyl Migration



The migration of an alkynyl moiety relative to a styryl group was explored by the rearrangement of dibromoolefin **7** (Scheme 3). It is interesting to note that product ratio of **8a**:**8b** was seemingly dependent on the progress of the reaction. Thus, when the reaction temperature was maintained at −78 °C for ca. 30 min, the conversion of **7** was incomplete and gave an 83:17 ratio of **8a**:**8b** in 22% yield.[22] In addition to recovered starting material (**7**), this reaction also gave a substantial quantity (16%) of *Z*-vinyl bromide **9**,[23] resulting from quenching of the carbenoid intermediate upon workup. When the reaction temperature was raised to −40 °C prior to quenching (over a period of ca. 30 min), the ratio **8a**:**8b** approached 1:1 (53:47, 54% combined yield) and the amount of byproduct **9** isolated was reduced to 11%. Finally, a

Scheme 3. Vinyl versus Alkynyl Migration



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(9) See, for example: (a) Luu, T.; Morisaki, Y.; Cunningham, N.; Tykwinski, R. R. *J. Org. Chem.* **2007**, *72*, 9622–9629. (b) Luu, T.; Elliott, E.; Slepkov, A. D.; Eisler, S.; McDonald, R.; Hegmann, F. A.; Tykwinski, R. R. *Org. Lett.* **2005**, *7*, 51–54. (c) Eisler, S.; Slepkov, A. D.; Elliott, E.; Luu, T.; McDonald, R.; Hegmann, F. A.; Tykwinski, R. R. *J. Am. Chem. Soc.* **2005**, *127*, 2666–2676. (d) Eisler, S.; Chahal, N.; McDonald, R.; Tykwinski, R. R. *Chem.−Eur. J.* **2003**, *9*, 2542–2550. (e) Luu, T.; Shi, W.; Lowary, T. L.; Tykwinski, R. R. *Synthesis* **2005**, 3167–3178.

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(15) Köbrich, G.; Ansari, F. *Chem. Ber.* **1967**, *100*, 2011–2020.

(16) A lack of *trans*-stereoselectivity has been noted, see: Rezaei, H.; Yamanoi, S.; Chemla, F.; Normant, J. F. *Org. Lett.* **2000**, *2*, 419–421.

(17) See also: Bertha, F.; Fetter, J.; Lempert, K.; Kajtér-Peredy, M.; Czira, G.; Koltai, E. *Tetrahedron* **2001**, *57*, 8889−8895. von der Schulenburg, W. G.; Hopf, H.; Walsh, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 1128−1130.

(18) For a recent mechanistic study regarding the FBW rearrangement in ynol ether formation, see: Darses, B.; Milet, A.; Philouze, C.; Greene, A. E.; Poisson, J.-F. *Org. Lett.* **2008**, *10*, 4445–4447.

(19) Dibromoolefins were formed from the corresponding ketone using the procedure of Ramirez: Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745−1747. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769−3772.

(20) Typical reaction conditions for FBW rearrangement. A solution of the dibromoolefin in rigorously dry hexanes was cooled to −78 °C under an inert atmosphere of N_2. *n*-BuLi (ca. 1.2 equiv) was added over a period of about 2 min. The cold bath was removed, and the reaction mixture was allowed to warm to −40 °C and stir for a period of ca. 1 h. The reaction was then quenched by the addition of satd. aq. NH_4Cl (10 mL). Work up and column chromatography gave the desired product. Full synthetic and spectroscopic details for all new compounds are provided as Supporting Information.

(21) In Schemes 2−7, the group that has migrated is shown in bold in the di- or triyne product.

(22) Product ratios were obtained based on integration of the two alkyne carbons in the ^{13}C NMR spectra. These values are reported as observed, acknowledging that there is likely a small error due to differences in T1 relaxation times for these nuclei. In cases where only one product is observed by NMR spectroscopic analysis, the ratio is reported as >95:5. Observed coupling patterns in the ^{13}C spectra allowed for unambiguous assignment of the products. See Supporting Information for details.

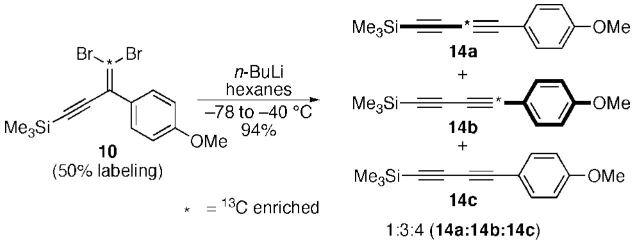
(23) The stereochemistry for **9** was set based on a GOESY experiment. Irradiation of the β-styryl at 6.66 ppm afforded enhancement of the signal of the vinylidene proton. See Supporting Information for spectra.

43:57 mixture of enediynes **8a**:**8b** was produced in 89% yield when the reaction was allowed to warm and react at −40 °C over a period of 1 h. Thus, the evolving ratio of **8a**:**8b** as a function of reaction progress, coupled with the presence of **9** (via quenching of the *Z*-carbenoid that would give rise to **8b** via styryl migration) for incomplete reactions, empirically suggests that migration of the alkynyl moiety occurs more rapidly than that of the styryl moiety.[24] A definitive answer to this premise, however, awaits a more in-depth analysis.

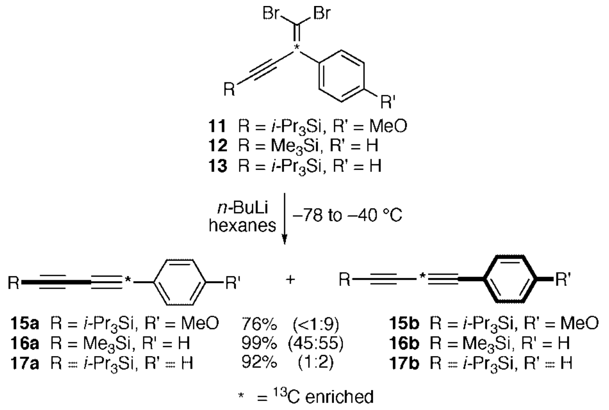
Establishing the identity of the two isotopomers was also straightforward in this case. The ^{13}C NMR spectrum of the product showed enhanced signals at 76.5 (major) and 76.3 (minor) ppm from the labeled acetylene carbons of the two products **8a**/**8b**.[25] The major isotopomer showed a doublet at 106.3 ppm for the β-styryl carbon, with strong one-bond coupling ($^{1}J_{CC}$ = 93 Hz) to the ^{13}C labeled carbon of **8b**. Thus, the larger resonance at 76.5 ppm could be assigned to **8b**, and the smaller resonance at 76.3 ppm then belonged to **8a**.

The competition between aryl groups and an alkyne was then explored with dibromoolefins **10**−**13**. Rearrangement of anisyl derivative **10** (50% ^{13}C labeling) gave a 1:3 mixture of isotopomers **14a** and **14b** resulting from alkynyl and aryl migration, respectively (Scheme 4).[26] Altering the identity of the alkynyl protective group from trimethylsilyl (**10**) to the bulkier triisopropylsilyl (**11**, Scheme 5) had a substantial impact on the observed product mixture. In the case of **11**, the ratio of isotopomeric products **15a** and **15b** was more heavily skewed toward **15b**, the product of aryl migration.[27] To some extent, the results observed for substrates that bear a pendent phenyl group (**12** and **13**) followed the same trend. Rearrangement of **12** gave a nearly equal ratio of products **16a**/**16b**,[28] while the reaction of **13** gave a 2-fold higher proportion of the diyne **17b**versus **17a**.[29] In all cases for diynes **14**−**17**, the strong one-bond coupling ($^{1}J_{CC}$ = 92−95 Hz) between the labeled acetylenic carbon of **14b** or **15a**−**17a** to the *ipso*-carbon of the aryl ring (δ 113 for **14** and **15**, δ 121 for **16** and **17**) allowed for structural identification.

Scheme 4. Anisyl versus Alkynyl Migration

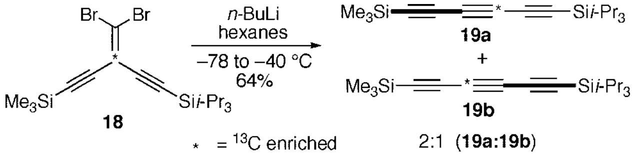


Scheme 5. Aryl versus Alkynyl Migration



Finally, it was intriguing to see if a difference in the silyl protecting group of an enediyne precursor would affect the outcome of the rearrangement. Thus, labeled dibromoolefin **18** was synthesized (Scheme 6). FBW rearrangement under typical conditions gave a preference for the product resulting from migration of the trimethylsilyl-terminated alkyne, with the triyne products **19a** and **19b** formed in a 2:1 ratio.[30]

Scheme 6. Alkynyl Migration



The first attempt toward forming a free alkylidene carbene intermediate utilized the Seyferth−Gilbert reagent, $(CH_3O)_2POCHN_2$.[31] Unfortunately, all attempts to induce the rearrangement of ketones such as **23** were unsuccessful; i.e.,

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(24) No evidence for isomerization of the intermediate carbenoid has been found to date. Specifically, reverse addition of dibromoolefin **7** to a solution of *n*-BuLi provided a ratio of **8a**:**8b** of 57:43 (61%) after reaction for 1 h at −40 °C, and a ratio of **8a**:**8b** of 44:56 (84%) was formed after reaction for 2 h at −40 °C. Thus, the results of the reverse addition reactions are analogous to those of the normal protocol (see Supporting Information for details and NMR spectra). For a discussion of carbenoid isomerization under analogous conditions, see ref 3, page 3827. We thank a reviewer for suggesting this experiment.

(25) The analogous unlabeled diyne product has been previously formed by the same route. See: Shi Shun, A. L. K.; Chernick, E. T.; Eisler, S.; Tykwinski, R. R. *J. Org. Chem.* **2003**, *68*, 1339–1347.

(26) The analogous unlabeled diyne has been reported. See ref 25 and: Wan, W. B.; Haley, M. M. *J. Org. Chem.* **2001**, *66*, 3893–3901.

(27) In the case of diynes **15a**:**15b**, the ^{13}C NMR spectrum shows a ca. 1:9 ratio of **15a**:**15b**, although the ^{1}H NMR shows no indication of **15a** based on the expected ^{13}C coupling to the *ortho*-aryl protons of $^{3}J_{CH}$ = 5.2 Hz. Thus, the ratio of **15a**:**15b** could be less than 1:9.

(28) The analogous unlabeled diyne has been reported: Klusener, P. A. A.; Hanekamp, J. C.; Brandsma, L. *J. Org. Chem.* **1990**, *55*, 1311–1321.

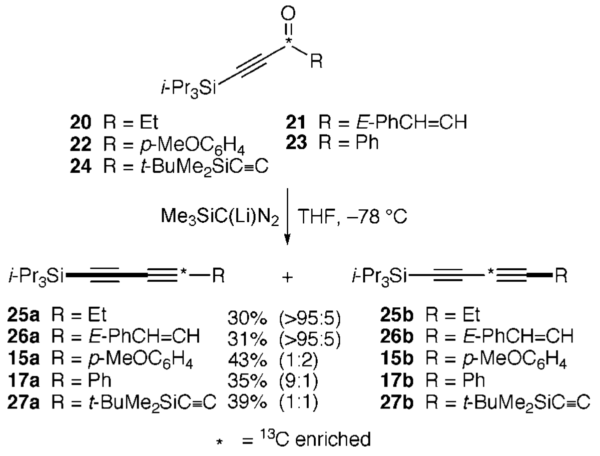
(29) The analogous unlabeled diyne has been reported: Heuft, M. A.; Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2001**, *3*, 2883–2886.

(30) All six carbons resonances of **19a**/**19b** were assigned by analogy to bis(trimethylsilyl)hexatriyne and bis(triisopropylsilyl)hexatriyne. See ref 9c. See also: Rubin, Y.; Lin, S. S.; Knobler, C. B.; Anthony, J.; Boldi, A. M.; Diederich, F. *J. Am. Chem. Soc.* **1991**, *113*, 6943–6949.

(31) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379−1386. Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837−1845. Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G.; Hoye, T. R. *J. Org. Chem.* **1996**, *61*, 2540−2541.

the formation of the desired polyyne was not observed. Attention was then turned to using lithiotrimethylsilyldiazomethane (Colvin's reagent).[32,33] It was quickly realized, however, that the reactions of ynones bearing trimethylsilyl protected acetylenes with Colvin's reagent were problematic: the ynones were not tolerant of the reaction conditions, and significant baseline material was observed upon TLC analysis of the reaction mixtures. This is likely a result of siloxide (Me_3SiO^-) formation during the reaction which leads to desilylation of the trimethylsilylethynyl groups from either the ynone precursor or the polyyne product. In either case, the formation of the terminal acetylene would account for the observed decomposition products. Moving to triisopropylsilyl protected acetylenes **20**−**24** did, however, provide for formation of diynes **25**, **26**, **15**, **17**, and triyne **27**, respectively (Scheme 7). The yields for these reactions were, however, consistently lower than those obtained from the dibromoolefin route.

Scheme 7. Rearrangement via Colvin's Reagent



Under the assumption that Colvin's reagent would afford an intermediate capable of cyclopentene formation via 1,5-H−C insertion,[3,34] labeled ketone **20** was chosen as a substrate since the terminal ethyl group is sufficiently short to prevent this competing reaction. Upon subjecting ketone **20** to $Me_3SiC(Li)N_2$, diyne **25a** was formed exclusively from migration of the alkynyl moiety. As was the case with **6a**, large one-bond coupling between the ^{13}C label and the propargylic carbon at 12.9 ppm provided for a doublet with $^1J_{CC} = 67$ Hz and confirmed the constitution of the product. The reaction of styryl derivative **21** also led only to the product resulting from alkyne migration **26a**, as confirmed by the doublet at 106.6 ppm ($^1J_{CC} = 93$ Hz) for the β-styryl carbon. Reaction of anisyl ynone **22** led to a 1:2 mixture of isotopomers **15a**:**15b**, with migration of the anisyl group dominating over that of the alkyne. Conversely, ynone **23** gave a 9-fold preference for diyne **17a** via alkyne migration. Finally, rearrangement of diynone **24** gave a nearly equal mixture of **27a** and **27b**. In the case of polyyne formation via Colvin's reagent, the alkynyl group migrates preferentially in comparison to all other substituents, except for anisyl.

In conclusion, alkynyl moieties migrate efficiently in alkylidene carbenoids derived from lithium halogen exchange affected on 1,1-dibromoolefins and from the reaction of ynones with Colvin's reagent. It is clear that the migration of alkyl groups is disfavored under both reaction scenarios, while that of the anisyl group is favored in all cases. Unfortunately, no other general trend emerges based on expectations derived from known migratory aptitudes. Further studies, including those toward establishing the stereochemical implications of the migration process, are ongoing.

Acknowledgment. This work has been generously supported by the University of Alberta and the Natural Sciences and Engineering Research Council of Canada (NSERC) through the Discovery Grant program. We thank NSERC for scholarships to P.B., W.E.C, and E.L.C. W.E.C. thanks the Alberta Ingenuity Fund for scholarship support.

Supporting Information Available: ^1H and ^{13}C NMR spectra, synthetic, and characterization details for all new diynes and triynes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 869−874. Shioiri, T.; Aoyama, T. *J. Synth. Org. Chem. Jpn.* **1996**, *54*, 918−928.

(33) To our knowledge, there is only one other reported example of polyyne formation via Colvin's reagent. See: Kendall, J.; McDonald, R.; Ferguson, M. J.; Tykwinski, R. R. *Org. Lett.* **2008**, *10*, 2163–2166.

(34) Taber, D. F.; Yu, H. *J. Org. Chem.* **1997**, *62*, 1687−1690. Taber, D. F.; Plepys, R. A. *Tetrahedron Lett.* **2005**, *46*, 6045−6047.