Cation-Mediated, Substituent-Controlled, C^2-C^7 Cycloaromatization of an Enyne−Allene†

Rolf W. Saalfrank,*,‡ Martin Haubner,‡ Christian Deutscher,‡ Walter Bauer,‡ and Timothy Clark§

Institut für Organische Chemie der Universität Erlangen-Nürnberg, Henkestrasse 42, D-91054 Erlangen, Germany, and Computer-Chemie-Centrum, Universität Erlangen-Nürnberg, Nägelsbachstrasse 25, D-91052 Erlangen, Germany

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Reaction of (2-bromophenylethynyl)trimethylsilane **1** with trimethyl borate yielded the alkynearylboronic acid **2**, which was coupled in situ with the bromoallenes **3** to give enyne−allenes **4**. The intermediates **4** underwent a spontaneous cation-mediated C^2-C^7 cycloaromatization with a concomitant 1,2-shift of the trimethylsilyl group to give the naphthalene derivatives **5**. Besides **5**, yne−allenes **10** were isolated by chromatography of the crude reaction products. A key step in the formation of **10** is the hydrolysis of the aryl boronic acid **2**, which led to phenylethynyltrimethylsilane **8**. Under the reaction conditions used, the TMS group of **8** was subsequently removed to give phenylacetylene **9**, which further reacted with the bromoallenes **3** to furnish the yne−allenes **10**.

Introduction

The biological activity of the chromophore of the antitumor antibiotics calicheamicin,[1] dynemicin,[2] esperamicin,[3] and neocarzinostatin[4] is a result of their ability to cleave DNA.[5,6] Their mode of action is based on Bergman enediyne[7,8] or Myers−Saito enyne−allene[8−10] cycloaromatization reactions. Biomimetic studies of these natural products have led to the design, synthesis, and screening of a series of compounds with enyne−allene or enyne−cumulene groups.[7−13] One of the results of these studies is that, if the acetylene hydrogen in enyne−allenes is replaced by an aryl or sterically demanding group, the compound undergoes a C^2-C^6 diradical cyclization,[14−17] rather than a Myers−Saito C^2-C^7 cyclization.

As part of our work on the synthesis of substituted allenes, we have developed a method of making haloallenes via [2,3]-sigmatropic rearrangements from suitable halopropargyl derivatives.[18] Bromoallenes were also formed from bromoalkynyl vinyl ethers via [3,3]-sigmatropic rearrangements.[19]

Results and Discussion

We now report the use of bromoallenes for the synthesis of enyne−allenes. In this case, we reacted (2-bromophenylethynyl)trimethylsilane[20] **1** with trimethyl borate according to the literature procedure[16] to give the alkynearylboronic acid derivative **2**. **2** was then subjected to a Suzuki coupling[21,22] with the bromoallenes **3** in situ to give **4**. The enyne−allenes **4** undergo a spontaneous cation-mediated C^2-C^7 cycloaromatization with a concomitant 1,2-shift of the trimethylsilyl group to give the naphthalene derivatives **5**. The isomerization of **4** to **5** is probably induced by attack of a metal cation on C7 and completed by transfer of a methyl proton to position 7 (Scheme 1).

The substitution pattern of **5a** was determined by standard 1D/2D-NMR techniques (COSY, NOESY, HET-

* To whom correspondence should be addressed. Fax: Int. code + (49)9131-852-1165. E-mail: saalfrank@organik.uni-erlangen.de.

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‡ Institut für Organische Chemie der Universität Erlangen-Nürnberg.

§ Computer-Chemie-Centrum, Universität Erlangen-Nürnberg.

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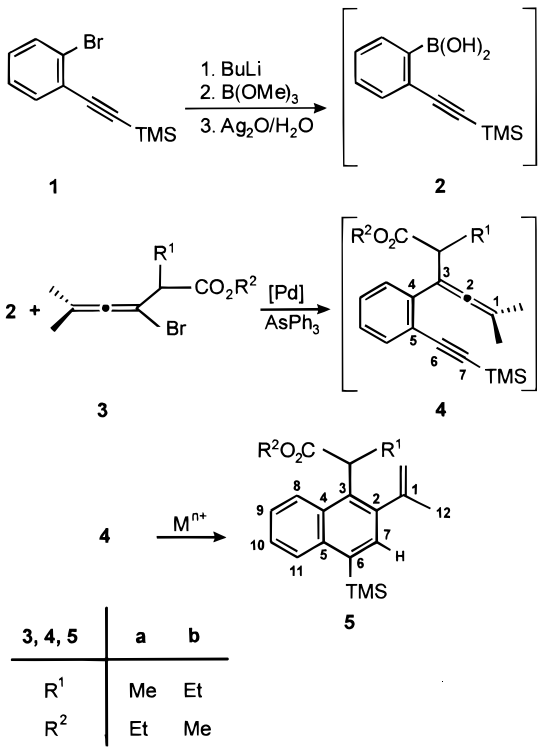
Scheme 1

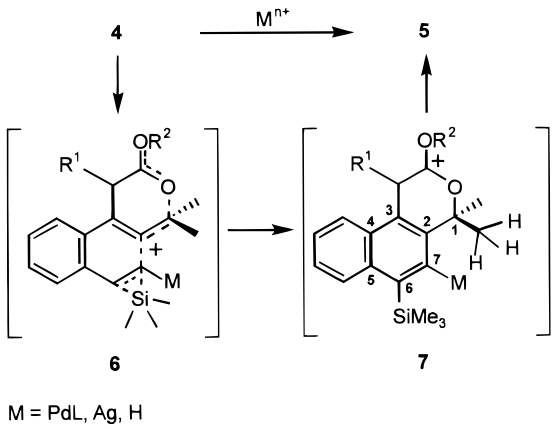


COR, and COLOC). The TMS group can be assigned definitively to position 6 by difference-NOE spectra. Irradiation at the frequency of the ^{1}H resonance of the $SiMe_3$ group gives roughly equal NOE effects for H7 and H11. Irradiation at the frequency of the H12 resonance gives an intensive NOE for H7 but none for the TMS group. Irradiation at the H7 frequency gives an intensive NOE for the TMS group and the methyl group in position 12.

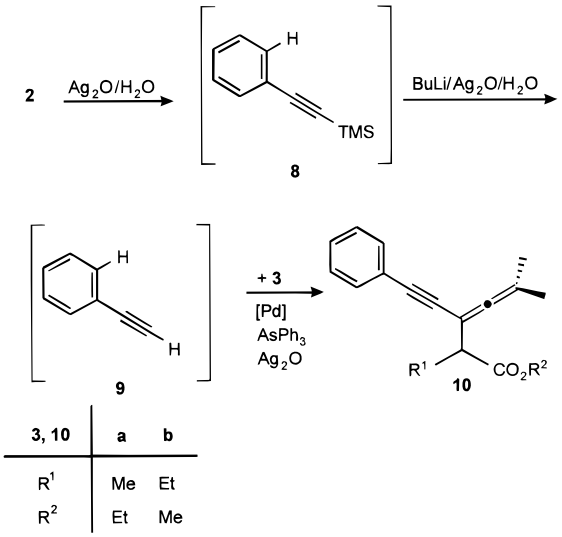
The mechanism of formation of **5** from **4**, however, remained unclear from the experimental results. The low temperature of the rearrangement and the regiochemistry of the products suggested that a mechanism other than the usual biradical one may be operating. We therefore used unrestricted Hartree−Fock (UHF) AM1 calculations with VAMP 7.0[24] to investigate a possible biradical mechanism. This technique allows us to include possible biradical effects. The results show that the activation energy for the cycloaromatization ($\Delta H^{\ddagger} = 37.8$ kcal mol^{-1}) and subsequent TMS shift ($\Delta H^{\ddagger} = 35.8$ kcal mol^{-1}) are too high for a radical reaction at room temperature. Therefore, a metal-mediated process (M = PdL, Ag) is more likely.

To support this hypothesis, model AM1 calculations were carried out for proton catalysis (M = H). In contrast to the biradical mechanism, the proton-catalyzed reaction requires an activation energy of only 20.7 kcal mol^{-1} and can thus proceed at room temperature. The heats of formation calculated with the AM1 Hamiltonian[23] suggest the following reaction path for the proton-catalyzed rearrangement of **4** to **5**. Protonation of **4** in position 7 is more favorable than in position 6 by 14.6 kcal mol^{-1}.

Scheme 2



Scheme 3



Rearrangement of the vinyl cation thus formed ($\Delta H° = 124.2$ kcal mol^{-1}) via transition state **6** ($\Delta H° = 144.9$ kcal mol^{-1}) with a concomitant 1,2-TMS shift and cyclization gives cation **7** ($\Delta H° = 65.8$ kcal mol^{-1}). This step is favored strongly by the stabilization of the positive charge by the ester group. As far as intermediate **7**, the transformation of **4** to **5** follows the same route, independently of whether the reaction is proton- or metal-catalyzed. Proton elimination from the methyl group of the model system **7** (M = H) leads to **5**, whereas **5** is generated in the cation-mediated process from **7** (M = PdL or Ag) by transfer of a methyl proton to position 7. This can occur either directly or by hydride transfer to palladium (Scheme 2).

However, the naphthalene derivatives **5** are not the only reaction products. After chromatography of the crude material we also obtained the yne−allenes **10**. A key intermediate in the formation of **10** is phenylacetylene **9,** which is generated by hydrolysis of the aryl boronic acid **2** and concomitant spontaneous desilylation of the phenylethynyltrimethylsilane **8**. Further metal-catalyzed [Pd(0)/Ag(I)] reaction of phenylacetylene **9** with the bromoallenes **3** yielded the yne−allenes **10**.

The proposed mechanism is supported by control experiments as the [Pd(0)/Ag(I)] catalyzed cross-coupling of **9** with **3** also yields the yne−allenes **10**, while the coupling of **8** and **3** was unsuccessful (Scheme 3).

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Experimental Section

General Methods. Unless otherwise noted, all reactions were carried out under Ar in flame-dried glassware using standard syringe, cannula, and septa techniques. Tetrahydrofuran was freshly distilled from sodium/benzophenone and stored under nitrogen. (2-Bromo-phenylethynyl)-trimethylsilane **1** was prepared by literature methods.[20] Bromoallenes **3** were prepared by literature methods.[18,19] Column chromatography was performed with 230−400 mesh silica gel.

Tetramethylsilane and $CDCl_3$ were used as internal standards in the ^1H and ^{13}C NMR spectra, respectively. IR spectra were obtained on an FT-IR spectrophotometer.

General Procedure for the Preparation of Naphthalenes (5a,b) and Yne−Allenes (10a,b). To a stirred solution of (2-bromophenylethynyl)trimethyl-silane **1** (4 mmol) in dry THF (20 mL) was added *n*-BuLi (3.25 mL, 1.6 M in hexane, 5.2 mmol) at −95 °C. After the mixture was stirred for 10 min, trimethylborate (0.54 g, 5.2 mmol) was added. The solution was allowed to warm to −5 °C, and silver(I) oxide (3.71 g in 16 mL water, 16 mmol), 5 mol % tetrakis(triphenylphosphine)-palladium (0.23 g, 0.2 mmol), 40 mol % triphenylarsine (0.49 g, 1.6 mmol), and the corresponding bromoallene **3** (4 mmol) were successively added. The reaction was stirred at 25 °C for 24 h. Silver(I) oxide was removed by filtration, and the crude product was diluted in diethyl ether (40 mL). The organic layer was washed with distilled water (50 mL), saturated sodium hydrogen carbonate (50 mL), and brine (50 mL) and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the residue was purified by column chromatography with hexane/diethyl ether (10:1).

Naphthalene (5a). Starting with (2-bromophenylethynyl)-trimethylsilane **1** (1.01 g, 4 mmol) and **3a** (0.99 g, 4 mmol), 0.39 g of **5a** (29%) and 0.44 g of **10a** (41%) were isolated as pale yellow oils: R_f 0.57; IR 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.35 (s, 9H), 1.16 (t, J = 7.1 Hz, 3H), 1.49 (d, J = 7.2 Hz, 3H), 1.98 (s, 3H), 3.90 (q, J = 7.2 Hz, 1H), 4.02−4.18 (m, 2H), 4.90 (s, 1H), 5.36 (s, 1H), 6.33 (s, 1H), 7.14−7.64 (m, 4H); ^{13}C NMR (100.5 MHz) δ −0.12 ($Si(CH_3)_3$), 14.09, 15.76, 25.19 (3 CH_3), 38.32 (CH), 60.78 (OCH_2), 117.87 (=CH_2), 120.06, 122.99, 124.59, 127.72, 133.51 (5 ArCH), 135.87, 137.53, 139.43, 142.35 (4 ArC), 143.37 (=C), 153.59 (1 ArCSi), 173.99 (C=O); HRMS calcd for $C_{21}H_{28}O_2Si$ 340.185859, found 340.184846.

Yne−Allene (10a): R_f 0.41; IR 2208, 1966, 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 3H), 1.34 (d, J = 7.1 Hz, 3H), 1.79 (s, 6H), 3.24 (q, J = 7.1 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 7.26−7.43 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 14.25, 15.93, 20.23 (4 CH_3), 44.30 (CH), 60.73 (OCH_2), 84.43, 88.66, 90.49, 100.05 (2 =C, 2 ≡C), 123.60 (ArC), 127.93, 128.18, 131.45 (5 ArCH), 173.62 (C=O), 206.56 (=C=); HRMS calcd for $C_{18}H_{20}O_2$ 268.146330, found 268.146095.

Naphthalene (5b). Starting with (2-bromophenylethynyl)-trimethylsilane **1** (1.01 g, 4 mmol) and **3b** (0.988 g, 4 mmol), 0.48 g of **5b** (35%) and 0.53 g of **10b** (49%) were isolated as yellow oils: R_f 0.66; IR 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.33 (s, 9H), 0.87 (t, J = 7.3 Hz, 3H), 1.87−1.92 (m, 2H), 1.96 (s, 3H), 3.61 (s, 3H), 3.68 (dd, J = 6.6 Hz 1H), 4.90 (s, 1H), 5.38 (s, 1H), 6.31 (s, 1H), 7.10−7.62 (m, 4H); ^{13}C NMR (100.5 MHz) δ −0.12 ($Si(CH_3)_3$), 12.47, 25.30 (2 CH_3), 29.70 (CH_2), 45.87 (CH), 51.93 (OCH_3), 118.16 (=CH_2), 120.40, 122.93, 124.59, 127.75, 133.62 (5 ArCH), 135.68, 135.85, 139.36, 142.48 (4 ArC), 144.75 (=C), 153.48 (1 ArCSi), 173.96 (C=O); HRMS calcd for $C_{21}H_{28}O_2Si$ 340.185859, found 340.187210.

Yne−Allene (10b): R_f 0.44; IR 2206, 1965, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 7.3 Hz, 3H), 1.79 (s, 6H), 1.82−1.88 (m, 2H), 3.03 (t, J = 7.6 Hz, 1H), 3.72 (s, 3H), 7.26−7.43 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 11.95, 20.12, 20.23 (3 CH_3), 23.77 (CH_2), 51.81, 51.91 (CH, OCH_3), 84.33, 87.00, 90.38, 99.59 (2 =C, 2 ≡C), 123.58 (ArC), 127.94, 128.18, 131.49 (5 ArCH), 173.53 (C=O), 207.22 (=C=); HRMS calcd for $C_{18}H_{20}O_2$ 268.146330, found 268.146217.

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