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Synthesis and thermal cyclization of an enediyne-sulfonamide☆

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Abstract—The synthesis of an enediyne sulfonamide by alkylidene carbene rearrangement is reported. The compound cyclizes thermally to give the Bergman product, which was prepared independently for comparison. Like other σ-acceptor substituents at the enediyne alkyne termini, such as fluoride, oxonium or ammonium groups, the sulfonamide moiety enhances the reactivity for thermal Bergman cyclization as shown by the cyclization kinetic of the title compound.

1. Introduction

Apart from the ring strain, the Bergman cyclization is quite sensitive to substituent effects.[1] Substituents at the alkyne termini are generally more effective than at the vinyl positions,[2] but heteroarene anellation can have a large effect on the energetics, too.[3–5] Morokuma et al.[6] have predicted that electron acceptor substituents at the terminal alkyne carbons of an enediyne should facilitate its thermal cyclization. This prediction was narrowed to strong σ-acceptors and/or π-donors by Schreiner et al.[7] A doubly fluoro-substituted enediyne was expected to undergo an exothermic Bergman cyclization, which was recently confirmed experimentally by Sander et al.[8] Other structures predicted to show enhanced reactivity in thermal cyclizations are enediynes with protonated yne-ol (onium-ion) or protonated yne-amine (ammonium-ion) sub-structure.[9] These structures are not stable and have, to the best of our knowledge, not been reported in the literature so far. We describe here the synthesis of the first stabilized enediyne with yne-amine substructure and its properties in thermal cyclization.[10]

2. Results and discussion

Yne-amines are very sensitive to hydrolysis.[11,12] This prohibits the characterization and property investigation of yne-amine substituted enediynes. Therefore yne-sulfonamide structures were selected as target compounds. They are stable and crystalline due to the strong electron acceptor properties of the sulfone moiety.[13] The required σ-acceptor effect of the nitrogen atom on the enediyne system remains, while the π-donating character of the nitrogen atom is reduced similar to an ammonium ion.[14] For the synthesis of sulfonamide benzoenediynes two general routes can be envisaged: the coupling of an alkyne sulfonamide to a 1-bromo-2-ethynyl-benzene by the Sonogashira–Hagihara method (see Scheme 1, route 1), or the formation of the carbon–nitrogen bond by either copper-catalyzed N-alkynylation of a sulfonamide[15] (see Scheme 1, route 2) or the reaction of alkynyl-phenyl-iodonium triflate salts with sulfonamides[16] (see Scheme 1, route 3). A Sonogashira–Hagihara coupling of ethynyl sulfonamides has not been reported in the literature so far and all of our initial attempts to couple *N*-Ts,*N*-Bn-ethynylamine[17] or its tri-methyl-tin derivative to iodo- or bromoarenes in transition-metal mediated processes failed under various reaction conditions. The copper-catalyzed N-alkynylation of sulfonamides was recently described to be less efficient than the N-alkynylation of lactams.[15] Therefore, the target enediyne was prepared via the alkynyl-phenyl-iodonium triflate salt.

Starting material **1** was prepared following a modified literature procedure.[18] The TMS-alkyne was transformed with iodosobenzene into the phenyl iodonium triflate in 64% yield. The iodonium salt was then reacted in toluene with lithium *N*-Bn,*N*-Ts-amide to give sulfonated, benzylated alkyneamide **4** in 46%. The same reaction in THF was much less efficient. Mechanistically, this step consists most likely of an addition of the lithium amide to the alkyne in β position giving a alkyldiene-carbene iodonium ylide, which eliminates phenyl iodide. The so formed alkylidene carbene rearranges by movement of the bromoaryl moiety to **4**. To complete the enediyne system, an alkyne must be introduced at the position of the remaining bromine

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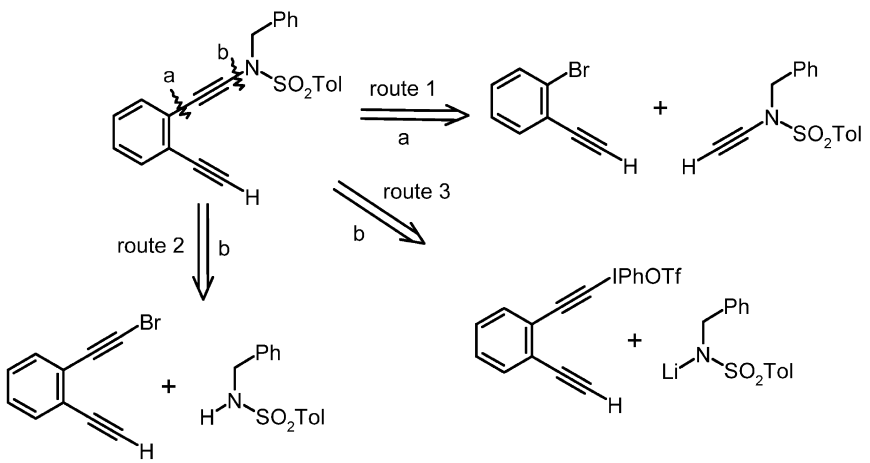
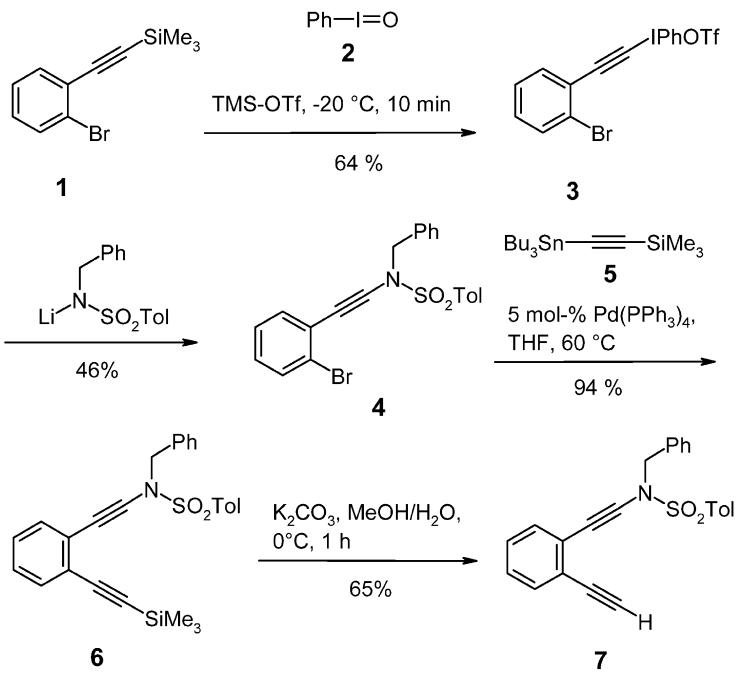
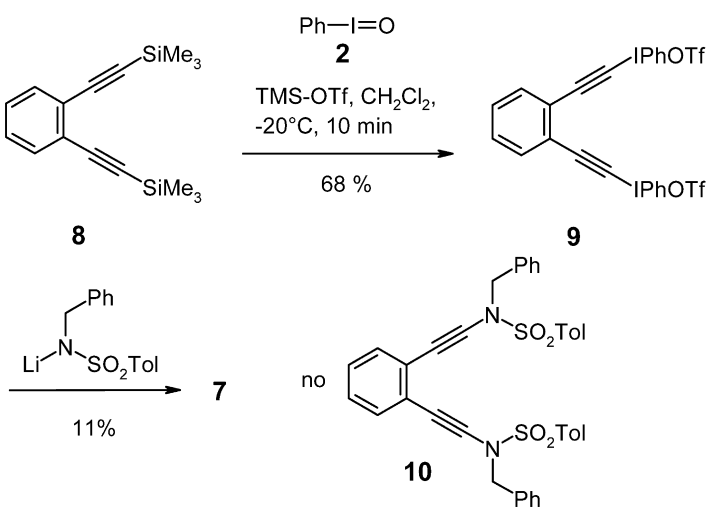


Scheme 1.



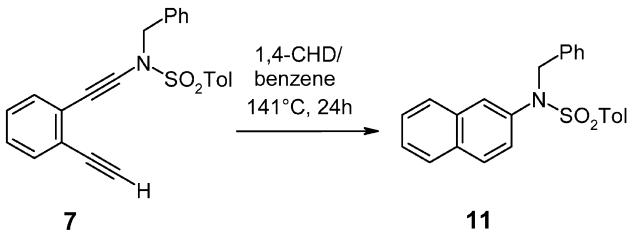
Scheme 2.



Scheme 3.

substituent. Standard Sonogashira–Hagihara coupling conditions with TMS-acetylene lead to decomposition of **4**, but a base-free Stille-type coupling protocol with **5** gave enediyne **6** in good yield. Finally, the TMS group was removed with K_2CO_3 in MeOH/water to give **7** in moderate yield.[19] Our attempts to prepare a twofold substituted enediyne-bis-sulfonamide[20] were not successful. The bis-iodoniumphenyl triflate **9** did not undergo a twofold rearrangement if treated with lithiated *N*-Bn,*N*-Ts-amine. Only compound **7** could be identified as reaction product, although in poor yield. A decreased ability of the substituted aryl moiety to undergo the rearrangement from the alkylidene carbene to the alkyne may explain the observation (Schemes 2 and 3).[21]

The thermal cyclization reaction of **7** was investigated by heating solutions of the compound (c=1.6×10^{-2} mol/l) in benzene/cyclohexadiene (ratio 2/1) to 141 °C. The conversion of the starting material and product formation was followed by HPLC analysis of the reaction mixture (Scheme 4).[22] The expected Bergman cyclization product **11** was synthesized independently from **12** for comparison using standard transformations (see Scheme 5 and Section 3 for details).



7 **11**

Scheme 4.

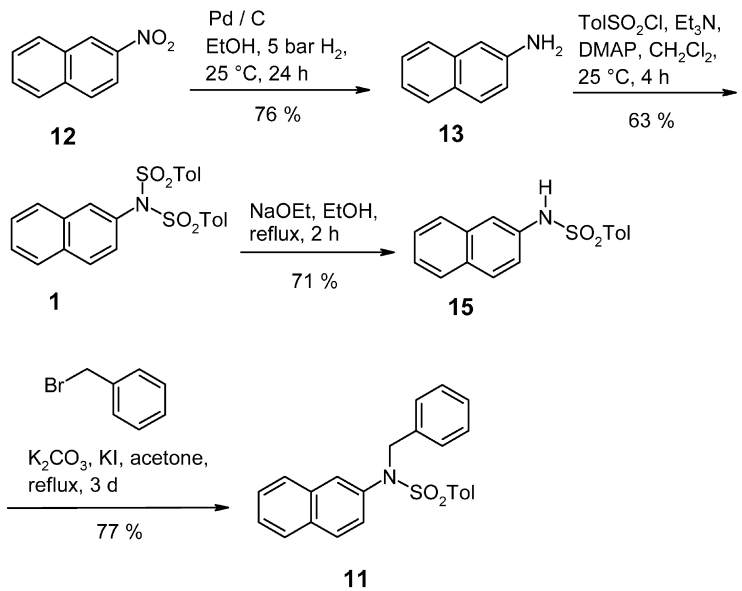
The HPLC analysis confirmed the formation of **11** from **7**, by identical retention times, UV- and mass spectra to the independently prepared material. A kinetic analysis of the reaction following the consumption of the starting material under pseudo first order conditions revealed a rate constant of k=2.66×10^{-4} s^{-1} which corresponds to a half life time of τ=44 min of the compound at this reaction temperature.[23] For the parent enediyne system benzo-1,2-diyne an activation energy for thermal cyclization of E_a=105.1 kJ/mol has been reported. This corresponds to a rate constant of k=9.77×10^{-5} s^{-1} and a half life of τ=118 min at 141 °C. Although the steric hindrance for a cyclization is significantly increased in **7** due to the large *N*-benzyl and *N*-tosyl substituents,[24] the reactivity of **7** is comparable or even higher than that of benzo-1,2-diyne. This supports the theoretical prediction[7] that σ-acceptor substituents at the terminal alkyne carbon atoms of an enediyne increase the thermal reactivity of the system. The alkyne sulfonamide substituent described here adds another option to electronically modify thermal enediyne reactivity.

3. Experimental

3.1. General

All ^{1}H NMR spectra were recorded at 400 MHz, all ^{13}C NMR spectra at 100 MHz in $CDCl_3$ unless otherwise stated. The multiplicity of the ^{13}C signals was determined with the DEPT technique and quoted as: (+) for CH_3 or CH, (−) for CH_2 and (C_{quat}) for quaternary carbons. CC means column chromatography on silica gel. PE means petrol ether with a boiling range of 60–70 °C. EA means ethyl acetate. All reactions were carried out under nitrogen atmosphere.

3.1.1. (2-Bromophenylethynyl)trimethylsilane (1). After stirring a mixture of $PdCl_2(PPh_3)_2$ (351 mg, 0.50 mmol), CuI (191 mg, 1 mmol) and 1,2-dibromobenzene (1.21 ml, 2.36 g, 10 mmol), dissolved in 5 ml of THF and 5 ml of triethylamine at room temperature for 10 min, ethynyltrimethylsilane (1.55 ml, 1.08 g, 10 mmol) was added. The reaction mixture was stirred at 60 °C for 16 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2, and washed with aqueous NH_4Cl. The combined organic phases were dried over Na_2SO_4, the solvent was removed and CC with hexanes gave **1** as a yellow oil (1.47 g, 58%).



12 **13** **1** **15** **11**

Scheme 5.

R_f=0.34 (hexanes). All spectroscopic data are identical to the ones reported in the literature.[18]

3.1.2. (2-Bromophenylethynyl)phenyliodonium triflate (3). To a stirred suspension of iodosobenzene (1.57 g, 7.14 mmol) in 50 ml of CH_2Cl_2, TMS-OTf (1.39 ml, 1.59 g, 7.14 mmol) and then **1** (1.80 g, 7.14 mmol) were added via syringe at −20 °C over 10 min. After warming to room temperature, the reaction mixture was concentrated and 15 ml of cold ether was added. The precipitated solid was filtered off and washed with cold ether. The residue was dried under reduced pressure to give a colorless solid (2.43 g, 64%). Mp: 94–95 °C. IR (KBr): $\tilde{\nu}$=2929 cm^{-1}, 2859, 2374, 2342, 2165, 1688, 1634, 1465, 1436, 1263, 1178, 1037, 990, 755, 735, 678, 649, 580, 522. UV/Vis (CH_3CN): λ_{max} (log ε)=209 nm (3.873), 249 (3.520). ^1H NMR (250 MHz, $CDCl_3$): δ=7.26–7.37 (m, 3H), 7.50–7.69 (m, 5H), 8.16–8.21 (m, 2H). ^{13}C NMR (60 MHz, $CDCl_3$): δ=36.4 (C_{quat}), 105.7 (C_{quat}), 117.3 (C_{quat}), 122.1 (C_{quat}), 126.6 (C_{quat}), 127.4 (+), 130.3 (C_{quat}), 132.4 (+), 132.5 (+), 132.7 (+), 132.8 (+), 134.2 (+), 135.1 (+), 137.5 (+). MS (ESI) *m/z* (%): 385 (97) [$M^+-CF_3SO_3$], 383 (100) [$M^+-CF_3SO_3$], 258 (18) [$M^+-CF_3SO_3-I$], 256 (19) [$M^+-CF_3SO_3-I$]. $C_{15}H_{10}BrF_3IO_3S$ (534.11): calcd C 33.80 H 1.70; found C 33.61 H 1.71.

3.1.3. *N*-Benzyl-*N*-(2-bromophenylethynyl)-4-methylbenzenesulfonamide (4). To a solution of *N*-benzyl-4-methylbenzene-sulfonamide (0.94 g, 3.58 mmol) in 50 ml of toluene, *n*-buli (2.70 ml, 4.30 mmol, 1.6 M in hexane) was added via syringe at 0 °C. After stirring for 30 min at this temperature **3** (2.29 g, 4.30 mmol) was added in small portions. The reaction mixture was stirred overnight, the solvent was removed and the residue was dissolved in Et_2O. The organic phase was washed with H_2O, brine and was dried over Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel with 7:3 hexanes/Et_2O to give **4** as a colorless solid (0.72 g, 46%). R_f=0.34 (7:3 hexanes/Et_2O). Mp: 87–88 °C. IR (KBr): $\tilde{\nu}$=2923 cm^{-1}, 2852, 2231, 1596, 1429, 1368, 1173, 762. UV/Vis (CH_3CN): λ_{max} (log ε)=207 nm (4.996), 258 (4.144). ^1H NMR: δ=2.44 (s, 3H, CH_3), 4.63 (s, 2H, CH_2), 7.05–7.51 (m, 11H), 7.82–7.85 (m, 2H). ^{13}C NMR: δ=21.7 (+), 55.8 (−), 70.6 (C_{quat}), 87.2 (C_{quat}), 124.4 (C_{quat}), 125.2 (C_{quat}), 126.9 (+), 127.8 (+), 128.4 (+), 128.5 (+), 128.6 (+) 129.0 (+), 129.8 (+), 132.2 (+), 132.5 (+), 134.3 (C_{quat}), 134.7 (C_{quat}), 144.7 (C_{quart}). MS (CI) *m/z* (%): 459 (100)/457 (94) [$M+NH_4^+$], 442 (39)/440 (37) [$M+H^+$], 288 (37) [$M-C_7H_7SO_2+H^+$]/286 (38) [$M-C_7H_7SO_2+H^+$]. $C_{22}H_{18}BrNO_2S$ (439.02): calcd C 60.01 H 4.12 N 3.18; found C 59.51 H 4.08 N 3.00.

3.1.4. *N*-Benzyl-4-methyl-*N*-(2-trimethylsilanyl-ethynyl-phenyl-ethynylbenzenesulfonamide (6). To a solution of **4** (388 mg, 0.88 mmol), $Pd(PPh_3)_4$ (53 mg, 0.12 mmol) and CuI (7 mg, 0.01 mmol) in 5 ml of THF, trimethylstannyl ethynylsilane (116 mg, 0.30 mmol) was added, and the reaction mixture was stirred at 60 °C for 2 d. The solvent was removed and CC with 7:3 hexanes/Et_2O gave **6**, as a light yellow oil (376 mg, 94%). R_f=0.45 (7:3 hexanes/Et_2O). IR (film): $\tilde{\nu}$=3055 cm^{-1}, 2987, 2306, 2234, 1741, 1265, 739. UV/Vis (CH_3CN): λ_{max} (log ε)=230 nm (4.633), 246 (4.588), 288 (4.164). ^1H NMR (250 MHz, $CDCl_3$): δ=0.19 (s, 9H, $Si(CH_3)_3$), 2.42 (s, 3H, CH_3), 4.62 (s, 2H, CH_2), 7.12–7.46 (m, 11H), 7.76–7.84 (m, 2H). ^{13}C NMR (100 MHz, C_6D_6): δ=21.7 (+), 56.2 (−), 70.5 (C_{quat}), 87.1 (C_{quat}), 98.1 (C_{quat}), 103.6 (C_{quat}), 124.2 (C_{quat}), 125.7 (C_{quat}), 126.9 (+), 127.8 (+), 128.1 (+), 128.4 (+), 128.6 (+), 128.9 (+), 129.7 (+), 131.0 (+), 132.7 (+)), 134.6 (C_{quat}), 135.0 (C_{quat}), 144.6 (C_{quat}). MS (EI) *m/z* (%): 457 (24) [M^+], 302 (13) [$M-C_7H_7SO_2^+$], 91 (100). $C_{27}H_{27}NO_2SSi$ (457.15): calcd C 70.86 H 5.95 N 3.06; found C 70.02 H 6.17 N 2.98.

3.1.5. *N*-Benzyl-*N*-(2-ethynyl-phenylethynyl)-4-methylbenzenesulfonamide (7). Compound **6** (156 mg, 0.34 mmol) was dissolved in 20 ml of methanol and K_2CO_3 (140 mg, 1.01 mmol) was added. After stirring for 1 h at room temperature, the reaction mixture was diluted with EtOAc and washed three times with H_2O. The organic phase was dried over Na_2SO_4 and the solvent was removed. The residue was purified by CC with 9:1 hexanes/Et_2O to yield **7** as a light yellow oil (85 mg, 65%). R_f=0.18 (9:1 hexanes/Et_2O). IR (film): $\tilde{\nu}$=3283 cm^{-1}, 3065, 3033, 2925, 2233, 2108, 1923, 1597, 1366, 1170, 1088, 1021, 799, 759, 653, 598. UV/Vis (CH_3CN): λ_{max} (log ε)=227 nm (4.715), 254 (4.281), 261 (4.240). ^1H NMR (300 MHz, $CDCl_3$): δ=2.43 (s, 3H, CH_3), 3.12 (s, 1H, CH), 4.63 (s, 2H, CH_2), 7.14–7.45 (m, 11H), 7.81–7.85 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.6 (+), 55.9 (−), 70.2 (C_{quat}), 80.7 (C_{quat}), 82.2 (+), 86.9 (C_{quat}), 123.3 (C_{quat}), 126.2 (C_{quat}), 127.0 (+), 127.8 (+), 128.3 (+), 128.4 (+), 128.5 (+), 128.9 (+), 129.7 (+), 130.9 (+), 132.4 (+), 134.5 (C_{quat}), 134.8 (C_{quat}), 144.6 (C_{quat}). MS (EI, 70 eV) *m/z* (%): 91 (100) [$C_7H_7^+$], 155 (15) [$CH_3C_6H_4SO_2^+$], 230 (6) [$M^+-CH_3C_6H_4SO_2$], 385 (3) [M^+]. HRMS $C_{24}H_{19}NO_2S$: calcd 385.1137; found 385.1138±0.8 ppm.

3.1.6. 2-Naphthyl-amine (13). 2-Nitronaphthalene (**12**, 2.00 g, 11.56 mmol) was dissolved in 50 ml of ethanol and Pd/C (50 mg, 10% Pd) was added. The reaction mixture was stirred at room temperature at a H_2 pressure of 5 atm for 24 h. After filtration and removal of the solvent, the residue was recrystallized from hexanes to give **13** as a yellow solid (1.25 g, 76%). All spectroscopic data are identical to the ones reported in the literature.[25] *Caution*: Compound **13** is a cancer inducing substance!

3.1.7. 4-Methyl-(4-benzenesulfonyl)-*N*-naphthalen-2-ylbenzenesulfonamide (14). A mixture of **13** (1.25 g, 8.74 mmol), 4-methyl-benzene-sulfonyl chloride (5.03 g, 26.4 mmol), triethylamine (9.00 ml, 6.48 g, 64 mmol) and *N*,*N*-dimethyl-amino-pyridine (53 mg, 0.44 mmol) in 50 ml of CH_2Cl_2 were stirred at room temperature for 4 h. The reaction mixture was extracted with 1 N HCl, H_2O and brine. The combined organic phases were dried over Na_2SO_4, the solvent was removed and the residue was recrystallized from ethanol to give **14** as a colorless solid (2.48 g, 63%). Mp: 165–166 °C. IR (KBr): $\tilde{\nu}$=3061 cm^{-1}, 2923, 2231, 1919, 1596, 1493, 1370, 1169, 1085, 928, 661, 550, 482. UV/Vis (CH_3CN): λ_{max} (log ε)=197 nm (5.097), 224 (5.074). ^1H NMR (300 MHz, $CDCl_3$): δ=2.48 (s, 6H, CH3), 7.08 (dd, *J*=8.7 Hz, *J*=2.2 Hz, 1H), 7.31–7.38 (m, 4H), 7.48–7.60 (m, 3H), 7.74–7.89 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.8 (+), 126.9 (+), 127.7 (+), 127.8 (+), 128.3 (+), 128.5 (+), 128.7 (+), 128.9 (C_{quat}), 129.0

(C_{quat}), 129.2 (+), 129.4 (C_{quat}) 129.7 (+), 130.0 (+), 131.5 (+), 131.8 (C_{quat}), 133.2 (+), 133.7 (+), 136.3 (C_{quat}), 136.7 (+), 144.8 (C_{quat}), 145.2 (+), 145.6 (C_{quat}). MS (EI, 70 eV) *m/z* (%): 451 (81) [M+], 296 (100) [$M-C_7H_7SO_2^+$], 155 (10) [$C_7H_7SO_2^+$], 139 (59) [$C_7H_7SO^+$], 91 (63) [$C_7H_7^+$]. $C_{24}H_{21}NO_4S_2$ (451.56): calcd C 63.84 H 4.69 N 3.10; found C 63.79 H 4.71 N 3.11.

3.1.8. 4-Methyl-*N*-naphthalen-2-ylbenzenesulfonamide (15). Sodium (1.20 g, 52.17 mmol) was added to 30 ml of ethanol. After completion of the reaction, **14** (0.45 g, 1.00 mmol) was added and the reaction mixture was refluxed for 2 h, then diluted with H_2O and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, the solvent was removed and the residue was recrystallized from ethanol to give **14** as a colorless solid (0.21 g, 71%). All spectroscopic data are identical to the ones reported in the literature.[26]

3.1.9. *N*-Benzyl-4-methyl-*N*-naphthalen-2-ylbenzenesulfonamide (11). To a mixture of **15** (0.1 g, 0.34 mmol) and benzyl bromide (0.12 ml, 0.17 g, 1.01 mmol) in 5 ml of acetone, K_2CO_3 (0.14 g, 1.01 mmol) and KI (0.06 g, 0.34 mmol) were added and the reaction mixture was refluxed for 3 d. After cooling to room temperature the resulting precipitate was filtered off and washed with acetone. The filtrate was evaporated and the residue was recrystallized from ethanol to give **11** as a colorless solid (0.10 g, 77%). All spectroscopic data are identical to the ones reported in the literature.[27]

Acknowledgements

The authors thank the Fonds der chemi-schen Industrie for support and Professor B. Witulski for advice in yne-amine chemistry.

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9. Amino-enediynes show a little lower reactivity than the parent system in calculations. Because ammonium has no π-donor and only σ-acceptor properties, the ammonium-enediyne has a relatively low barrier for cyclization and an almost thermoneutral reaction energy as predicted from calculations. Doubly substituted bis-ammonium-enediynes are far less reactive, because of the repulsion of the positively charged groups of the *ortho*-ammonium substituents in the cyclization product. See Ref. 7 for a systematic computational study.
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20. Theory predicts a significantly reduced thermal reactivity for a bis-ammonium enediyne, because of strong repulsion of the *ortho* ammonium moieties in the cyclization product. In the case of a bis-sulfonamide at least the contribution from charge to repulsion is omitted.
21. Compound **7** may have been obtained from **9** by one addition of a lithium amide and rearrangement to the alkyne amide. The second iodoniumphenyl moiety was hydrolyzed upon work up.
22. The analytical method follows previously described procedures: (a) Choy, N.; Kim, C.-S.; Ballestero, C.; Artigas, L.; Diez, C.; Lichtenberger, F.; Shapiro, J.; Russell, K. C. *Tetrahedron Lett.* **2000**, *41*, 6955–6958. (b) Wisniewski Grissom, J.; Calkins, T. L.; McMillen, H. A.; Jiang, Y. *J. Org. Chem.* **1994**, *59*, 5833–5835. (c) Kim, C.-S.; Russell, K. C. *J. Org. Chem.* **1998**, *63*, 8229–8234.

23. The derived rate constant describes the thermal conversion of **7**. HPLC analyses showed that the Bergman cyclisation product is the main product of the thermolysis. HPLC-MS shows side products in minor amounts.
24. For a recent study on the effect of the steric influence of functional groups at the termini of acylic enediynes on the Bergman cyclization temperature, see: Rawat, D. S.; Zaleski, J. M. *Chem. Commun.* **2000**, 2493–2494.
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