Domino Michael addition-carbene rearrangement-cyclization reaction of 1-alkynyl(aryl)-λ^3-bromanes with 2-mercapto-1,3-benzazoles

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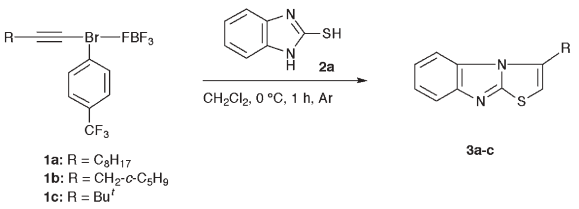
Exposure of 1-alkynyl[*p*-(trifluoromethyl)phenyl](tetrafluoroborato)-λ^3-bromanes to 2-mercaptobenzimidazole or benzothiazole in dichloromethane at 0 °C under argon resulted in a domino Michael addition–carbene rearrangement–cyclization reaction to produce directly tricyclic heterocycles in high yields, whereas the reaction with 2-mercaptobenzoxazole afforded 1-alkynyl sulfides.

Recently, we reported the synthesis of a new class of hypervalent bromanes, 1-alkynyl(aryl)-λ^3-bromanes **1**;[1] the method involves a BF_3-catalyzed ligand exchange of [*p*-(trifluoromethyl)phenyl]-(difluoro)-λ^3-bromane[2] with 1-alkynyl(trimethyl)stannanes in dichloromethane and affords 1-alkynyl[*p*-(trifluoromethyl)-phenyl](tetrafluoroborato)-λ^3-bromanes **1** in good yields. Interestingly, use of excess amounts of 1-alkynylstannanes (>2 equiv.) relative to the difluoro-λ^3-bromane dramatically changed the reaction course and resulted in homocoupling of 1-alkynylstannanes to yield symmetrical 1,3-butadiynes.[3] The 1,3-butadiyne synthesis probably involves a Michael addition of excess 1-alkynylstannane toward the initially formed 1-alkynyl(aryl)-λ^3-bromanes **1**, followed by 1,2-shift of the alkynyl group in the resulting alkylidene carbenes.

Because of the highly electron-withdrawing nature of aryl-λ^3-bromanyl groups with large Hammett substituent constants (for instance, σ_p = 1.63 for $PhBrBF_4$),[4] 1-alkynyl(aryl)-λ^3-bromanes **1** are highly electron-deficient species and hence would serve as efficient Michael acceptors toward the attack of nucleophiles, as observed in the reaction of 1-alkynyl(aryl)-λ^3-iodanes.[5] Thus, both sodium benzenesulfinate and trifluoromethanesulfinate undergo Michael addition to 1-alkynyl-λ^3-bromanes **1** in dichloromethane at 0 °C and produce 1-sulfonylcyclopentenes selectively through 1,5-carbon–hydrogen insertion of the reactive intermediate alkylidene carbenes.[6] We report herein a domino Michael addition–carbene rearrangement–cyclization of 1-alkynyl-λ^3-bromanes **1** by the reaction with 2-mercaptobenzimidazole (**2a**) or 2-mercaptobenzothiazole (**2b**) yielding directly the tricyclic heterocycles **3** or **6**, respectively. On the other hand, the reaction with 2-mercaptobenzoxazole (**2c**) affords 1-alkynyl sulfides **11** selectively.

Although the attempted Michael addition of thiophenol to 1-decynyl[*p*-(trifluoromethyl)phenyl](tetrafluoroborato)-λ^3-bromane (**1a**) afforded a complex mixture of products, the reaction with 2-mercaptobenzimidazole (**2a**) took place smoothly and gave an aromatic azapentalene **3a** directly (Scheme 1). Thus, exposure of 1-decynyl-λ^3-bromane **1a** to benzimidazole **2a** (one equiv.) in

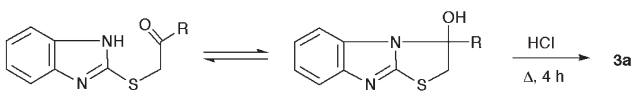


Scheme 1

dichloromethane at 0 °C for 1 h resulted in the formation of 3-octylthiazolo[3,2-*a*]benzimidazole (**3a**) in 83% yield, after purification by preparative TLC.† Similar results were obtained by the reactions of 3-(cyclopentyl)-1-propynyl-**1b** and 3,3-dimethyl-1-butynyl-λ^3-bromane **1c** under comparable conditions and 3-(cyclopentylmethyl)- (**3b**) and 3-*tert*-butylthiazolo[3,2-*a*]benzimidazole (**3c**) were produced in 86 and 92% yields, respectively.‡ ^{1}H NMR spectra of thiazolobenzimidazoles **3** showed a sharp singlet of C2–H at δ 6.33–6.41 ppm, which is not compatible with the alternative 2-alkyl-substituted thiazolo[3,2-*a*]benzimidazole structure.[7] The structure of **3a** was firmly established by the independent synthesis of an authentic sample (Scheme 2): intramolecular cyclodehydration of 1-(2-benzimidazolylthio)-2-decanone **4**,[8] which exists in equilibrium with the cyclized alcohol **5** in $CDCl_3$, by the reaction with concentrated HCl under refluxing for 4 h afforded the thiazolobenzimidazole **3a** in 95% yield.[9]

As described later (Scheme 4), this azapentalene synthesis probably involves an intermediate formation of 1-alkynyl 2-benzimidazolyl sulfides **10** (X = NH). Although several methods are available for the synthesis of thiazolo[3,2-*a*]benzimidazoles because of their interesting biological activity, none of these methods utilizes the unique 1-alkynyl sulfides **10**.[10]

Direct formation of tricycles **6** was also observed in the reaction with 2-mercaptobenzothiazole (**2b**) (Scheme 3): treatment of 1-decynyl-λ^3-bromane **1a** with benzothiazole **2b** in dichloromethane at 0 °C for 1 h afforded directly a 71% yield of 3-octylthiazolo[2,3-*b*]benzothiazolium tetrafluoroborate (**6a**), in which carbocation was stabilized by three adjacent heteroatoms.[11] 1-Hexynyl-λ^3-bromane **1d** gave a comparable result with formation of **6d** (66%); however, a low yield of thiazolobenzothiazolium



Scheme 2

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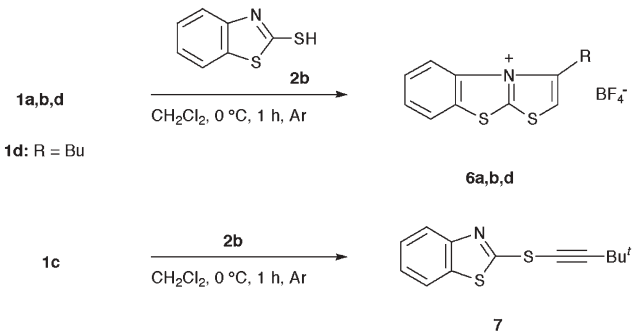
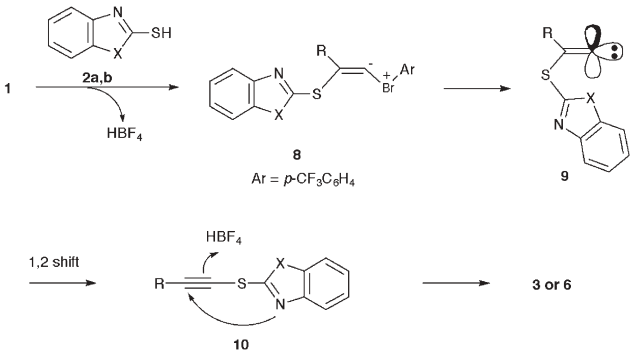
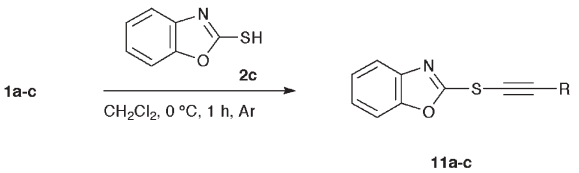


Scheme 3



Scheme 4



Scheme 5

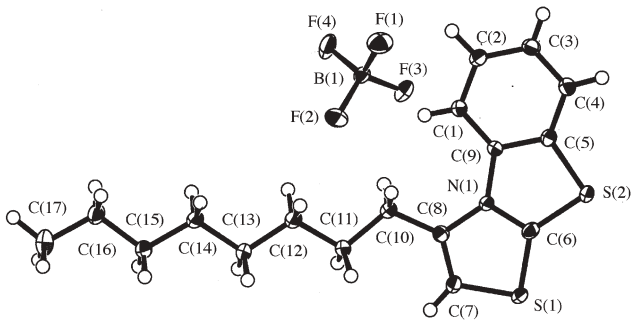


Fig. 1 ORTEP drawing of benzothiazolium tetrafluoroborate **6a**. Selected bond distances (Å): N1–C6 1.347(4), N1–C8 1.410(3), N1–C9 1.427(3).

salt **6b** (27%) was produced from the reaction using cyclopentylpropynyl-λ^3-bromane **1b**. Interestingly, use of the sterically demanding *tert*-butylethynyl-λ^3-bromane **1c** did not produce the thiazolo[2,3-*b*]benzothiazolium salt at all, but instead *tert*-butylethynyl sulfide **7** was obtained selectively in 89% yields.

The IR spectra of thiazolobenzothiazolium salts **6** showed a characteristic peak of the iminium group at around 1460 cm^{-1} as well as the strong broad absorptions of tetrafluoroborate ion at 1150–1000 cm^{-1}.[12] Single crystals of the benzothiazolium tetrafluoroborate **6a** for X-ray structural analysis were grown from a methanol–diethyl ether solution.[13] Fig. 1 clearly illustrates a planar tricyclic benzothiazolium structure with a short N1–C6 bond.

Direct formation of these tricycles **3** and **6** probably involves an initial Michael addition of a thiol nucleophile **2** to the highly electron-deficient 1-alkynyl(aryl)-λ^3-bromanes **1** (Scheme 4). The subsequent reductive elimination of the aryl-λ^3-bromanyl group in the resulting vinylbromonium ylides **8** (X = NH, S) generates the alkylidene carbenes **9**, which undergo spontaneous 1,2-rearrangement of the sulfenyl group yielding the 1-alkynyl sulfides **10**. Further intramolecular 5-*endo* digonal cyclization of the alkynyl sulfides **10** would provide thiazolo[3,2-*a*]benzimidazoles **3** or thiazolo[2,3-*b*]benzothiazolium salts **6**. In fact, 1,2-rearrangement of sulfenyl groups in alkylidene carbenes is known to be a facile, very rapid process, because of an excellent migratory aptitude of sulfenyl groups.[14] Isolation of the *tert*-butylethynyl sulfide **7** in the reaction of *tert*-butylethynylbromane **1c** with 2-mercaptobenzothiazole (**2b**) provides firm evidence suggesting the reaction process shown in Scheme 4: in the case of the sulfide **7**, the intramolecular cyclization does not seem to occur, because of the presence of a bulky *tert*-butyl group at the β-position.

1-Decynyl 2-benzoxazolyl sulfide (**11a**) was selectively produced by the reaction of λ^3-bromane **1a** with 2-mercaptobenzoxazole (**2c**) quantitatively under our conditions. Use of the λ^3-bromanes **1b** and **1c** afforded comparable results with formation of the alkynyl sulfides **11b** and **11c**, respectively. These results further support the reaction pathway shown in Scheme 4.

Intramolecular 5-*endo* digonal cyclization of the 1-alkynyl 2-benzoxazolyl sulfides **11** seems to be a difficult process compared to that of the 2-benzimidazolyl and 2-benzothiazolyl sulfides **10** (X = NH and S). The observed differences in the reactivity for the intramolecular cyclization probably reflect lower nucleophilicity as well as basicity of the nitrogen atom in the oxazole **11** than those in the imidazole and thiazole **10**. In fact, basicities of benzazoles in water decrease in the order benzimidazole (pK_a 5.56) > benzothiazole (1.2) > benzoxazole (−0.13).[15]

Notes and references

† *Representative procedure*: To a stirred solution of 1-decynyl-λ^3-bromane **1a** (31 mg, 0.068 mmol) in dichloromethane (2.6 mL) was added 2-mercaptobenzimidazole (**2a**) (10 mg, 0.068 mmol) at 0 °C under argon and the mixture was stirred for 1 h. The mixture was poured into water and extracted with dichloromethane. Drying of the extract with Na_2SO_4 and then concentration *in vacuo* afforded a crude oil, which was purified by preparative TLC (hexane–ethyl acetate 7 : 3) to give benzimidazole **3a** (16.2 mg, 83%, mp = 77–77.2 °C). ν_{max}(neat)/cm^{-1} 1614, 1470, 1454, 737; δ_H (400 MHz, $CDCl_3$) 7.80 (d, *J* 7.9 Hz, 1H), 7.73 (d, *J* 7.9 Hz, 1H), 7.37 (t, *J* 7.9 Hz, 1H), 7.26 (t, *J* 7.9 Hz, 1H), 6.34 (s, 1H), 3.05 (t, *J* 7.4 Hz, 2H), 1.85 (quint, *J* 7.4 Hz, 2H), 1.52 (quint, *J* 7.4 Hz, 2H), 1.44–1.22 (m, 8H), 0.89 (t, *J* 6.5 Hz, 3H); *m/z* (EI) 286 (M^+, 80%), 201 (30), 188 (100); HRMS calc. for $C_{17}H_{22}N_2S$ (M^+) 286.1504, found 286.1508. Anal. Calcd for $C_{17}H_{22}N_2S$: C, 71.28; H, 7.74; N, 9.78. Found: C, 71.00; H, 7.71; N, 9.78. ‡ *Selected data*: **3b**: mp 110.5–111.5 °C; δ_H ($CDCl_3$) 7.80 (d, *J* 7.9 Hz, 1H), 7.74 (d, *J* 7.9 Hz, 1H), 7.37 (t, *J* 7.9 Hz, 1H), 7.25 (t, *J* 7.9 Hz, 1H), 6.33 (s, 1H), 3.04 (d, *J* 7.4 Hz, 2H), 2.43 (sept, *J* 7.4 Hz, 1H), 1.98–1.86 (m, 2H), 1.79–1.53 (m, 4H), 1.43–1.29 (m, 2H). Anal. Calcd for $C_{15}H_{16}N_2S$: C, 70.27; H, 6.29; N, 10.93. Found: C, 70.41; H, 6.36; N, 10.67. **6a**: mp 138–140 °C; ν_{max}(neat)/cm^{-1} 1460, 1150–1000, 757; δ_H ($CDCl_3$) 8.31 (d, *J*

8.3 Hz, 1H), 8.13 (d, *J* 8.3 Hz, 1H), 7.84 (s, 1H), 7.82–7.72 (m, 2H), 3.38 (t, *J* 7.5 Hz, 2H), 1.94 (quint, *J* 7.5 Hz, 2H), 1.57 (quint, *J* 7.5 Hz, 2H), 1.45–1.23 (m, 8H), 0.88 (t, *J* 6.4 Hz, 3H). Anal. Calcd for $C_{17}H_{22}BF_4NS_2$: C, 52.18; H, 5.67; N, 3.58. Found: C, 52.02; H, 5.63; N, 3.58. **6d**: ν_{max}(Nujol)/cm^{-1} 1459, 1150–1000, 761; δ_H ($CDCl_3$) 8.31 (d, *J* 7.9 Hz, 1H), 8.11 (d, *J* 7.9 Hz, 1H), 7.84–7.74 (m, 3H), 3.40 (t, *J* 7.5 Hz, 2H), 1.95 (quint, *J* 7.5 Hz, 2H), 1.64 (quint, *J* 7.5 Hz, 2H), 1.07 (t, *J* 7.5 Hz, 3H); HRMS (FAB) calc. for $C_{13}H_{14}NS_2$ [$(M - BF_4)^+$] 248.0568, found 248.0555. **11a**: ν_{max}(neat)/cm^{-1} 2202, 1504, 1451, 742; δ_H ($CDCl_3$) 7.66 (br d, *J* 7.4 Hz, 1H), 7.50 (br d, *J* 7.4 Hz, 1H), 7.31 (m, 2H), 2.49 (t, *J* 7.2 Hz, 2H), 1.63 (quint, *J* 7.2 Hz, 2H), 1.50–1.38 (m, 2H), 1.38–1.20 (m, 8H), 0.88 (t, *J* 6.4 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 160.5, 152.3, 142.0, 124.6, 124.5, 119.2, 110.2, 102.7, 57.7, 31.8, 29.2, 29.1, 28.9, 28.2, 22.7, 20.4, 14.1; *m/z* (EI) 287 (M^+, 100%), 202 (43), 189 (97), 151 (47); HRMS calc. for $C_{17}H_{21}NOS$ (M^+) 287.1344, found 287.1330. **11c**: ν_{max}(neat)/cm^{-1} 2171, 1466, 1427, 755; δ_H ($CDCl_3$) 7.65 (br d, *J* 7.4 Hz, 1H), 7.50 (br d, *J* 7.4 Hz, 1H), 7.31 (m, 2H), 1.34 (s, 9H); *m/z* (EI) 231 (M^+, 69), 216 (100), 83 (30); HRMS calc. for $C_{13}H_{13}NOS$ (M^+) 231.0718, found 231.0724.

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13 Crystal data for **6a**: $C_{17}H_{22}BF_4NS_2$, $M = 391.29$, triclinic, space group *P*-1(no. 2), $a = 9.556(3)$, $b = 9.578(3)$, $c = 11.187(4)$ Å, $\alpha = 88.22(3)^\circ$, $\beta = 110.16(3)^\circ$, $\gamma = 109.98(3)^\circ$, $V = 899.0(5)$ Å^3, $T = 93$ K, $Z = 2$, Mo-Kα radiation ($\lambda = 0.71075$ Å), 8746 reflections measured, [$I > 2.00\sigma(I)$, $R_{int} = 0.0540$], $\mu = 3.35$ cm^{-1}, $R = 0.089$, $R_w = 0.170$. CCDC 275861. See http://dx.doi.org/10.1039/b509269h for crystallographic data in CIF or other electronic format.

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