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Synthesis of the benzo[*b*]fluorene core of the kinamycins by cycloaromatization of non-conjugated benzotriynes †

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Abstract

Non-conjugated benzotriynes **2** undergo a novel radical cycloaromatization to provide the benzo[*b*]fluorene core of the kinamycins. The overall process involves a thermal intramolecular cyclization to the non-benzenoid biradicals **4** followed by radical cyclization and hydrogen abstraction.

Keywords: benzo[*b*]fluorene; enediynes; enetriynes; kinamycin; radical cycloaromatization.

Current research on the thermal biradical cyclizations of conjugated polyenyne systems such as enediynes (Bergman cyclization) and enyne-allenes (the Myers–Saito and Schmittel cyclizations) focuses on the synthesis of models of the natural enediyne antibiotics[1] and on their utilization in the construction of polycyclic ring systems.[2] Interesting examples of the latter have been reported by Echavarren and Schmittel, who describe the synthesis of the tetracyclic core of kinamycins by means of thermal cyclizations of enyne-allenes[3] and the 3-ene-1,6-diyne non-conjugated benzodiyne.[4]

Research on the cycloaromatization of polyenynes is being pursued in this laboratory[5] with efforts currently centered on non-conjugated benzotriynes and their applications in natural product synthesis. Ueda has shown that one class of these systems, benzotetraynes, undergo thermal cyclization under very mild conditions to give polycyclic aromatic structures.[6] We report here the thermal cyclization of the non-conjugated benzotriynes **2**, which provides the tetracyclic nucleus of the benzo[*b*]fluorene antibiotics, metabolites structurally related to the kinamycins, and which display a variety of interesting biological activities.[7]

Benzaldehyde **1a** (R^1=H), chosen as the immediate synthetic precursor of unsubstituted benzotriyne **2** (Scheme 1), was prepared in 90% yield by Sonogashira coupling of *o*-bromobenzaldehyde and phenylacetylene.[8] Treatment of aldehyde **1a** with 4-trimethylsilyl-1,3-butadiyn-1-yl lithium[9] afforded

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† This paper is dedicated to the memory of the late Prof. Joaquín de Pascual Teresa.

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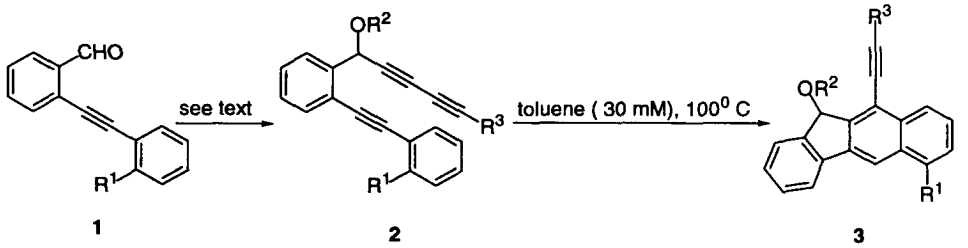
benzotriyne **2a** in 90% yield.[10] When the lithium alkoxide salt was quenched with TBDMSCl or Ac_2O, the corresponding protected alcohols **2b** and **2c** were obtained in 92% and 99% yield, respectively.[11]

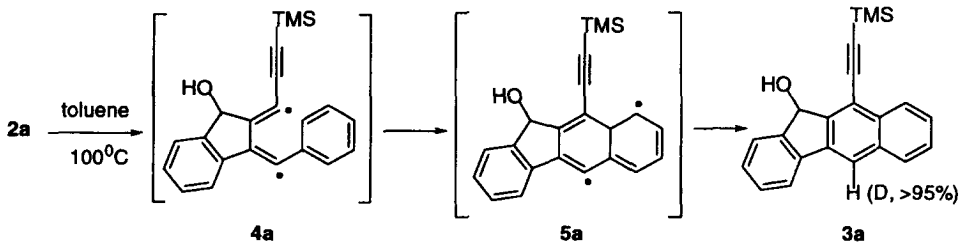


Benzotriyne	R^1	R^2	R^3	Reaction time	Product	Yield
2a	H	H	TMS	10 h	**3a**	56%
2b	H	TBDMS	TMS	10 h	**3b**	46%
2c	H	Ac	TMS	6 h	**3c**	80%
2d	H	H	H	10 h	**3d**	60%
2e	OMe	H	H	10 h	**3e**	21%

Scheme 1.

When **2a** was subjected to the thermal conditions described by Ueda (C_6H_6, rt, several days),[6] the starting material was totally unaffected. However, stirring in toluene at 100°C for 10 h resulted in a novel cycloaromatization, giving benzo[*b*]fluorene **3a** in 56% yield (Scheme 1).[12] The desilylated compound **2d** behaved similarly giving **3d** in 60% yield.[13] To evaluate the role of the unprotected hydroxyl group, silyl ether **2b** and acetate **2c** were subjected to the same thermal conditions as **2a** and **2d**; again, cycloaromatization took place, giving benzo[*b*]fluorenes **3b** and **3c** in 46% and 80% yield, respectively. The fact that the reaction of **2c** had a higher yield and was faster than the others (6 h vs 10 h) suggests that electron-withdrawing groups favor the cyclization. Conversely, when an electron-rich aromatic ring was present, as in **2e**, the yield of the reaction dropped to 21%.[14]

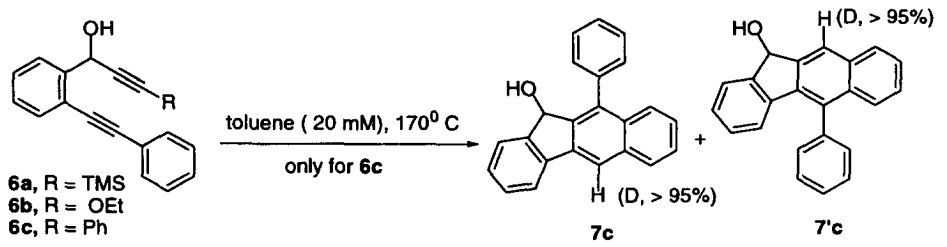
A plausible mechanism is outlined in Scheme 2 for **2a** as a typical example. In successive steps, thermal intramolecular cyclization (Ueda's cyclization) gives the non-benzenoid biradical **4a**,[15] radical cyclization **5a**, and hydrogen abstraction the benzo[*b*]fluorene **3a**. This radical mechanism was confirmed by the finding that **3a** obtained by cycloaromatization of **2a** in MeOH-d_4 was more than 95% deuterated at position 5 (Scheme 2).[11,16]



Scheme 2.

Interestingly, all observed products corresponded to cycloaromatization with the phenyl substituent via the *trans*-stilbene-like biradicals **4**; cyclization with the alkyne via the *cis*-stilbene-like biradical did not occur.[17]

To understand and modulate the cyclization 'triggering device', we applied conditions similar to these described above to the non-conjugated benzodiynes **6**, which were prepared in good yields by addition of the corresponding lithium acetylides to benzaldehyde **1a**.[11] When **6a** was heated, even under forced conditions (toluene, sealed tube, 170°C, 20 h), all the starting material was recovered. When the ethynylethylether derivative **6b** was heated in benzene at 55°C for 2 days, all the starting material disappeared, but no single compound could be isolated or identified. Finally, when the phenylethynyl derivative **6c** was heated in toluene for 11 h at 170°C in a sealed tube (conditions considerably more severe than those employed by Schmittel), an almost quantitative combined yield of the 10-phenyl and 5-phenylbenzo[*b*]fluoren-11-ols **7c** and **7'c** was obtained (70% **7c**, 26% **7'c**); see Scheme 3.[4] Again, a radical mechanism was confirmed by cycloaromatization of **6c** in a 4:1 mixture of toluene-d_8 and MeOH-d_4, which afforded benzo[*b*]fluorenols **7c** (from the corresponding *trans*-stilbene-like biradical) and **7'c** (from the *cis*-stilbene-like biradical) that were more than 95% deuterated at positions 5 and 10, respectively.[11] We therefore believe that the presence of a substituent R capable of stabilizing the corresponding radical intermediate **4** is crucial for the success of this cyclization process.



Scheme 3.

In conclusion, we have found that non-conjugated benzotriynes and phenyl-substituted benzodiynes undergo a thermal radical cycloaromatization to yield the benzo[*b*]fluorene core of the kynamicins. Application of this methodology to the synthesis of benzo[*b*]fluorene antibiotics is in progress.

Acknowledgements

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10. Benzotriyne **2a**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 7.71–7.63 (m, 4H), 7.51–7.35 (m, 5H), 6.06 (s, 1H), 3.24 (br s, 1H), 0.30 (s, 9H). ^{13}C NMR+DEPT ($CDCl_3$, 62.8 MHz) δ: 141.6 (C), 133.0 (CH), 132.1 (2×CH), 129.5 (CH), 129.2 (CH), 129.0 (2×CH), 128.9 (CH), 127.2 (CH), 123.2 (C), 121.8 (C), 95.8 (C), 88.9 (C), 87.9 (C), 86.8 (C), 77.2 (C), 71.7 (C), 64.0 (CH), 0.0 (3×CH_3). MS *m/z* (rel. intensity%): 328 (M^+, 27), 327 (45), 313 (50), 239 (93), 73 (100).
11. All new compounds gave satisfactory analytical and spectroscopic data.
12. Benzo[*b*]fluorene **3a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.31 (d, *J*=7.5 Hz, 1H), 8.01 (s, 1H), 7.89 (d, *J*=7.3 Hz, 1H), 7.78 (d, *J*=7 Hz, 1H), 7.72 (dd, *J*=7, 0.9 Hz, 1H), 7.60–7.36 (m, 4H), 6.01 (s, 1H), 3.30 (br s, 1H), 0.41 (s, 9H). ^{13}C NMR+DEPT ($CDCl_3$, 75.47 MHz) δ: 147.9 (C), 145.1 (C), 139.6 (C), 138.3 (C), 134.3 (C), 132.1 (C), 129.7 (CH), 129.2 (CH), 129.1 (CH), 127.2 (CH), 127.1 (CH), 126.4 (CH), 126.1 (CH), 121.0 (CH), 119.6 (CH), 117.2 (C), 105.8 (C), 100.7 (C), 74.8 (CH), 0.5 (3×CH_3). MS *m/z* (rel. intensity%): 328 (M^+, 77), 327 (42), 239 (100), 73 (55).
13. Benzotriyne **2d** was obtained in 99% yield by treatment of **2a** with K_2CO_3 in MeOH at rt for 1 h.
14. Benzotriyne **2e** was prepared by Sonogashira coupling between *o*-ethynylbenzaldehyde[5] and *o*-iodoanisole in 82% yield.
15. A similar 1,4-biradical has been assumed to be involved in the cycloaromatization of 1,6,11-dodecatriyne, see: Kociolek, M. G.; Johnson, R. P. *Tetrahedron Lett.* **1999**, *40*, 4141–4144.
16. The ^{1}H NMR of deuterated **3a** does not show the singlet at 8.01 ppm due to H5.
17. When a benzotetrayne was used as starting material, the intermediate biradical species cycloaromatized with the alkyne to give an *o*-aryl biradical: see Ref. 6.