Benzo[*b*]fluorenes Formed in the Thermal Cyclization of 3-Ene-1,6-diynes

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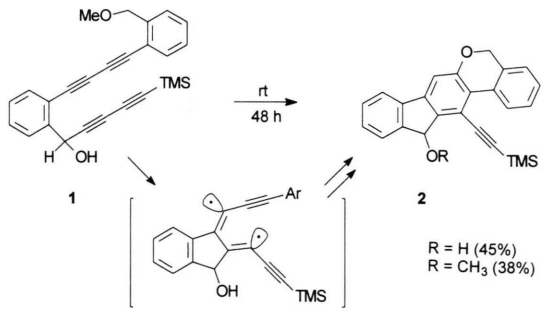
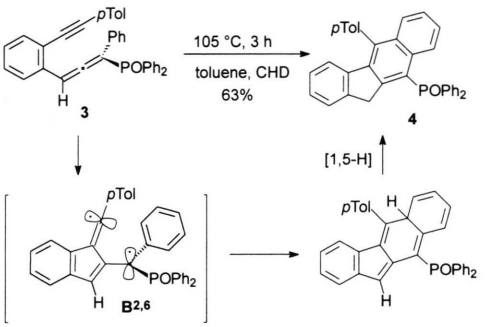
A three-step preparation of the benzofluorene core is presented. The last step involves thermal cyclization of 3-ene-1,6-diyne (**7**) leading to the formation of four benzofluorene derivatives, one of which has been investigated by X-ray analysis. The harsh thermal conditions indicate that the cyclization of **7** might not proceed *via* a biradical intermediate as would be anticipated by a mechanistic proposal from Ueda.

Recent work by Ueda *et al.* [1] has indicated that the thermal cyclization of bis-diyne **1** can be used for the construction of polycyclic ring systems, in particular fluorenes (Scheme 1). The mild conditions (room temperature, 48 h) and the simplicity of the procedure posed to us the question whether this synthetic strategy could equally be applied to other substrates.



Scheme 1. Biradical cyclization of **1** according to Ueda *et al.* [1].

As a key intermediate the authors have postulated a biradical formed in a bis-*exo-dig* cyclization between two alkynyl moieties. Such a motif is reminescent of the recently established C^2-C^6 biradical cyclization of enyne-allenes [2], where an alkynyl and an allenyl group are involved in a bis-*exo* biradical cyclization *via* $\mathbf{B}^{2,6}$ equally leading to five-membered ring systems.



Scheme 2. Biradical cyclization of **3** according to Schmittel *et al.* [2, 4].

Since the C^2-C^6 biradical cyclization was triggered when using radical stabilizing groups at the alkynyl terminus (in particular aryl groups) we wondered whether the bis-diyne **1** of Ueda could be simplified for more convenient preparative use. As a consequence we have studied the thermal reactions of the simple 3-ene-1,6-diynes **7** and **16**, which will be described in the following.

3-Ene-1,6-diyne **7** could be easily prepared in two steps. The Pd^0-catalyzed coupling of phenylacetylene with *o*-bromobenzaldehyde (**5**) afforded the alkynylated coupling product **6** in 92% yield. Reaction of **6** with sodium diethyl-bis(phenylacetylene)aluminate, prepared from the reaction of SDDA (sodium diethyldihydroaluminate) with phenylacetylene, resulted in the formation of 3-ene-1,6-diyne **7** (76%).

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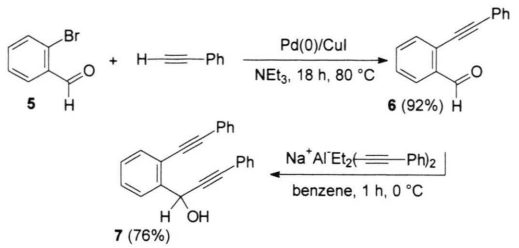
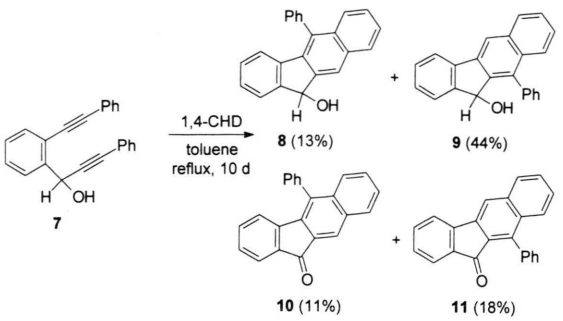


Scheme 3. Synthesis of propargyl alcohol **7**.



Scheme 4. Thermolysis of propargyl alcohol **7**.

The heat evolvement at 160 °C in a DSC experiment indicated that **7** cyclizes at much higher temperature than Ueda's system **1**, but on the same time at much lower temperatures than phenyl substituted 3-ene-1,5-diynes [3]. Heating **7** in toluene (10^{-2} M) to reflux for 10 d in presence of an excess of 1,4-cyclohexadiene (1,4-CHD) afforded the four benzo[*b*]fluorenes **8–11** in an overall yield of 86% (after isolation by chromatography).

As we were able to obtain a X-ray analysis of the benzo[*b*]fluorenone **10** the assignment of the various structures can be taken as conclusive. The phenyl group at C-9 in **10** is placed nearly perpendicular to the benzo[*b*]fluorene skeleton as demonstrated by a dihedral angel of 100.46° (C23-C18-C9-C10).

For this reason the proton at C-6 resides in the shielding region of the adjacent phenyl ring and appears upfield (δ = 6.34 in **10** and δ = 6.45 in **8** respectively). Analogously, a shift of 6.34 ppm has been reported for compound **4** [4]. With this knowledge we were able to assign unambiguously the position of the phenyl group in the benzo[*b*]fluorenes **8–11** by their characteristic ^{1}H NMR and ^{13}C NMR data.

Two mechanistic pathways can be envisaged to account for the course of the cyclization, one of which involves a concerted [4+2] cycloaddition generating the 1,2,4-cyclohexatriene moiety in **12** and **13**. Alternatively, **7** could undergo a cycliza-

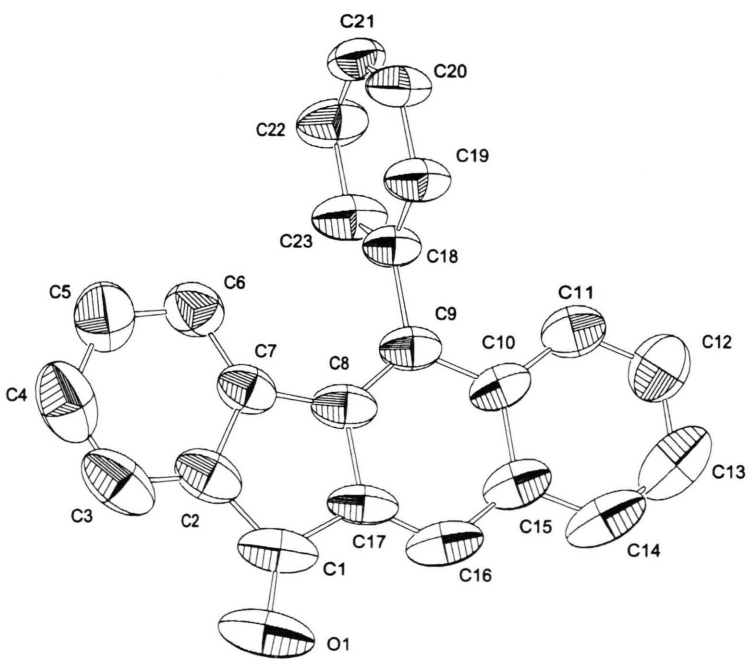
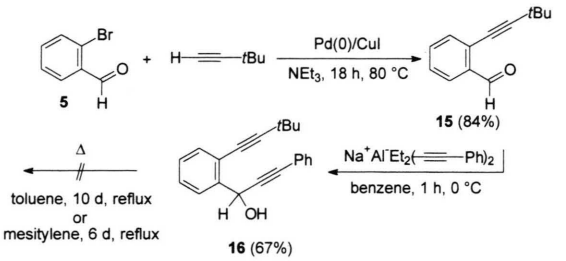


Fig. 1. ORTEP representation of the crystal structure of **10**.

Table I. Characteristic spectroscopic data of benzo[*b*]-fluorenes **8–11.**

	8	**9**	**10**	**11**
1-H [ppm]	5.80	5.80	*	*
6-H [ppm]	6.45	*	6.34	*
9-H [ppm]	–	8.07	–	7.93
16-H [ppm]	8.16	–	8.24	–
C1 [ppm]	74.0	73.8	187.1	192.8
(C=O) [cm^{-1}]	–	–	1714	1719
(O-H) [cm^{-1}]	3354	3594	–	–

* Signal cannot be unambiguously identified as it is located among the resonances of various other aromatic protons.



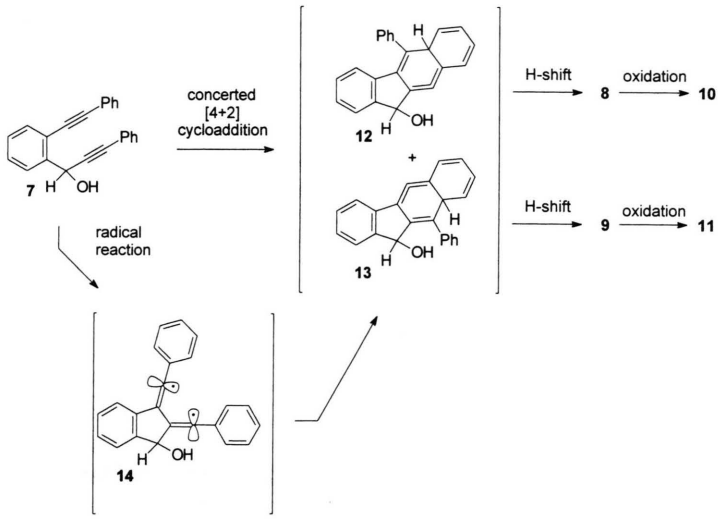
Scheme 6. Preparation of 3-ene-1,6-diyne **16**.

tion to form the biradical **14**, which then ring closes to **12** and **13**. A subsequent hydrogen shift should then lead to the corresponding alcohols **8** and **9** that under the thermolysis conditions were partly oxidized to the benzo[*b*]fluorenones **10** and **11**.

3-Ene-1,6-diyne **16** was prepared analogously to **7**. Pd^0-catalyzed coupling of *tert*-butylacetylene with *o*-bromobenzaldehyde (**5**) afforded **15** in 84% yield, which upon reaction with sodium diethylbis(phenylacetylene)aluminate furnished **16** (67%). However, thermolysis of **16** under various conditions (toluene, 10 d, reflux; mesitylene, 6 d, reflux) didn't provide any cyclization product but only unreacted **16**.

At present we are unable to distinguish between the two alternative pathways, *i.e.* a concerted [4+2]-cycloaddition and that *via* biradical intermediate **14**. However, if both cyclizations, *i.e.* of **1** and **7**, would involve biradical intermediates one would definitively expect that the transformation of **7** should take place at milder conditions because of the roughly similar radical stabilizing effect of the phenyl and the alkynyl group [5]. Additional steric effects should not be present in **7** *vs.* **1**. But as mentioned before, the thermolysis of **7** (toluene, 10 d, reflux) needed much more drastic reaction conditions than that of **1** (rt, 48 h). Hence, further mechanistic studies are certainly warranted to ascertain biradicals as intermediates in this reaction.

As a prerequisite for the thermal cyclization, two aryl groups seem to be helpful at the two alkynyl termini, a limitation which should still allow for many variations. Although the cyclization of **7** afforded two constitutionally different benzofluorenols (and benzofluorenones as oxidation products) the simple, two-step preparation of **7** is expected to make this thermal, high yield pathway



Scheme 5. Formation of the benzo[*b*]-fluorenes.

attractive for the combinatorial [6] preparation of substituted benzofluorenones, since such compounds quite often exhibit interesting biological activity [7–10] (*cf.* Kinafluorenone [11, 12] and Kinobscurinone [13, 14]).

Experimental Section

Compound **7**: Phenylacetylene (1.55 g, 15.2 mmol) was added dropwise to a solution of 2 M SDDA (sodium diethyldihydroaluminate) (3.80 ml, 7.60 mmol) in benzene (8 ml). The mixture was stirred for 3 h until gas evolution ceased. The mixture was then cooled to 0 °C and a solution of *o*-(phenylethinyl)benzaldehyde [4] (1.55 g, 7.50 mmol) in benzene (5 ml) was added. After being stirred for 1 h at 0 °C the mixture was quenched with saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3x50 ml). The combined organic layers were dried ($MgSO_4$) and filtered. Concentration furnished **7** (1.78 g, 5.81 mmol, 76%) as colorless crystalls. M.p. 71 °C; IR (neat) $\tilde{\nu}$ = 3549, 3385 (OH), 3060, 2878, 2221 (C≡C), 1599, 1493, 1380, 1267, 1184, 1096, 1030, 960, 916, 810, 757, 691 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 3.17 (s, 1H, OH), 6.25 (s, 1H), 7.26–7.46 (m, 8H), 7.49–7.54 (m, 2H), 7.56–7.67 (m, 3H), 7.86 (d, ^3J (H, H) = 7.6 Hz, 1H); ^{13}C-NMR (63 MHz, $CDCl_3$): δ = 63.8, 86.6, 86.8, 88.6, 95.2, 121.6, 122.7, 123.0, 126.9, 128.4, 128.5, 128.6, 128.8, 129.9, 131.7, 131.8, 131.9, 132.6, 142.4.

$C_{23}H_{16}O$ (308.1)
Calcd C 89.58 H 5.23%,
Found C 90.00 H 5.14%.

Compound **15**: A solution of *o*-bromobenzaldehyde (10.7 g, 57.6 mmol) and 3,3-dimethylbutyne [15] (5.50 g, 66.9 mmol) in NEt_3 (200 ml) was treated with dichloro-bis(triphenylphosphine)palladium(II) (586 mg, 835 μmol) and copper(I)iodide (268 mg, 1.40 mmol). After the reaction mixture had been stirred at 40 °C for 24 h, saturated aqueous NH_4Cl was added. The organic layer was then separated and the aqueous layer extracted with *n*-pentane (3 x 100 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The resulting crude product was purified by column chromatography (trichloromethane, R_f = 0.74) to afford **15** (9.00 g, 84%) as a brown oil. IR (neat): $\tilde{\nu}$ = 2970, 2903, 2896, 2743 (CHO), 2234 (C≡C), 1698 (C=O), 1651, 1595, 1472, 1450, 1387,1283, 1264, 1203, 1158, 826, 761, 669, 635 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.33 (s, 9H, CH_3), 7.31 (m, 1H), 7.46 (m, 2H), 7.84 (d, ^3J (H,H) = 6.7 Hz, 1H), 10.51 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 28.9, 31.2, 74.8, 106.0, 126.7, 127.7, 127.8, 133.0, 133.5, 136.2, 192.0; HRMS calcd for $C_{13}H_{14}O$ [M^+]: 186.1045, found 186.1041.

Compound **16**: As described above for the synthesis of **7**, phenylacetylene (860 μl, 7.89 mmol), **SDDA** (1.92 ml, 3.84 mmol) and **15** (625 mg. 3.50 mmol) were brought to reaction. Purification of the crude product by column chromatography (trichloromethane, R_f = 0.68) afforded **16** (627 mg, 67%) as a colorless oil. IR (neat): $\tilde{\nu}$ = 3384 (OH), 3060, 2968, 2896, 2232 (C≡C), 2218 (C≡C), 1598, 1484, 1448, 1365, 1291, 1203, 1096, 1031, 961, 821, 757, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.29 (s, 9H, CH_3), 2.90 (brs, 1H, OH), 5.95 (s, 1H), 7.19 (m, 1H), 7.22–7.30 (m, 4H), 7.35–7.42 (m, 3H), 7.63 (dd, ^3J (H, H) = 7.5 Hz, ^4J (H, H) = 1.4 Hz, 1H); ^{13}C-NMR (63 MHz, $CDCl_3$): δ = 28.3, 30.9, 64.0, 76.5, 86.3, 88.3, 104.7, 122.0, 122.6, 126.6, 128.1, 128.1, 128.2, 128.4, 131.8, 132.4, 142.1; HRMS calcd for $C_{21}H_{20}O$ [M^+]: 288.1514, found 288.1505.

Thermoylsis of **7**: A mixture of **7** (308 mg, 1.00 mmol) and 1,4-cyclohexadiene (1.60 g, 20.0 mmol) in toluene was heated to reflux for 10 d. After evaporation of the solvent, the crude residue was purified by column chromatography (cyclohexane/ethyl acetate 1:1) to afford four benzo[*b*]fluorenes **8–11**: **8** (39.4 mg, 128 μmol, 13%, R_f = 0.46); IR (neat): $\tilde{\nu}$ = 3354 (OH), 3063, 3032, 2922, 1598, 1496, 1453, 1361, 1206, 1018,914, 824, 749 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.26 (s, 1H), 5.79 (s, 1H), 6.45 (d, ^3J (H, H) = 7.8 Hz, 1H). 7.13 (dd, ^3J (H, H) = 7.5 Hz, ^3J (H, H) = 7.5 Hz, 1H), 7.32–7.52 (m, 4H), 7.56–7.65 (m, 5H), 7.70 (d, ^3J (H, H) = 7.5 Hz, 1H), 7.91 (d, ^3J (H, H) = 7.0 Hz, 1H), 8.16 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 74.0, 123.9, 125.6, 126.9, 127.3, 127.5, 127.8, 128.3, 128.4, 128.8, 128.9, 129.0, 129.4, 129.5, 129.9, 134.4, 135.8, 138.3, 140.4, 143.3, 146.2; HRMS calcd for $C_{23}H_{13}O$ [M^+-3H]: 305.0966, found 305.0970. **9** (135 mg, 439 μmol, 44%, R_f = 0.48); IR (CCl_4): $\tilde{\nu}$ = 3594 (OH), 3061, 3031, 2928, 2852, 1628, 1586, 1494, 1471, 1443, 1365, 1316, 1254, 1206, 1174, 1100, 1037 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.89 (s, 1H), 5.80 (s, 1H), 7.35 (ddd, ^3J (H, H) = 7.3 Hz, ^3J (H, H) = 7.3 Hz, ^4J (H, H) = 1.2 Hz, 1H), 7.36–7.50 (m, 4H), 7.54–7.63 (m, 6H), 7.83 (d, ^3J (H, H) = 7.0 Hz, 1H), 7.94 (d, ^3J (H, H) = 7.6 Hz, 1H), 8.07 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 73.8, 117.9, 120.4, 125.4, 125.8, 126.1, 126.2, 127.7, 128.3, 128.4, 128.9, 129.0, 129.1, 130.6, 131.7, 132.6, 134.4, 137.4, 139.5, 141.1, 145.3.

$C_{23}H_{16}O$ (308.1)
Calcd C 89.58 H 5.23%,
Found C 88.95 H 5.22%.

10 (33.4 mg, 109 μmol, 11%, R_f = 0.73); IR (CCl_4): $\tilde{\nu}$ = 3062, 2962, 2928, 1714 (C=O), 1626, 1601, 1514, 1495, 1470, 1444, 1362, 1314, 1262, 1110, 1046, 946, 909 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 6.34 (m, 1H), 7.18–7.23 (m, 2H), 7.38–7.48 (m, 5H), 7.47 (m, 1H), 7.52–7.62 (m, 2H). 7.73 (m, 1H), 7.93 (m, 1H), 8.24 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 123.8, 124.2, 125.2, 126.8, 127.1, 128.3, 128.6, 128.7, 128.9, 129.3, 129.7, 130.7, 133.3, 134.7, 136.5, 136.9, 137.4, 153.7, 187.1. In accordance with the literature [16]; **11** (55.3 mg, 181 μmol, 18%, R_f = 0.76); IR (CCl_4): $\tilde{\nu}$ = 3060, 2961, 2855, 1719 (C=O), 1625, 1605, 1584, 1471, 1336, 1278, 1261, 1185, 1036, 954, 908 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.29 (ddd, ^3J (H, H) = 7.3 Hz, ^3J (H, H) = 7.3 Hz, ^4J (H, H) = 0.9 Hz, 1H), 7.36–7.41 (m, 3H), 7.54–7.58 (m, 5H), 7.62 (m, 2H), 7.76 (d, ^3J (H, H) = 7.6 Hz, 1H), 7.86 (d, ^3J (H, H) = 8.2 Hz, 1H), 7.93 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 118.6, 120.7, 124.1, 126.8, 128.0, 128.1, 128.8, 128.8, 129.0, 129.2, 129.5, 129.5, 133.8, 134.6, 135.5, 136.2, 136.6, 138.4, 141.2, 144.0, 192.8.

$C_{23}H_{14}O$ (306.3)
Calcd C 90.17 H 4.61%,
Found C 89.84 H 4.59%.

In accordance with the literature [17].

Crystal data of **10**: The structure of **10** was established by an X-ray structural analysis. Crystal data and the details of the procedure are compiled in Table II. The structure was solved by direct methods (SHELXS 96 program) [18] and refined by the block-matrix least-squares method (SHELXL 96 program) [18].

Table II. Crystal data and experimental details of **10** (recrystallized from chloroform).

Formula (M_F)	$C_{23}H_{14}O$ (306.34)
Space group	P-1
Lattice constants [Å]	a = 9.269(3)
	b = 9.344(3)
	c = 10.381(3)
	α = 70.04(2)°
	β = 68.78(2)°
	γ = 75.39(2)°
Z	2
F(000)	320
Cell volume [Å^3]	779.3(4)
Temperature	293(2) K
Density [g·cm^{-1}] calc.	1.306
Diffractometer	Enraf-Nonius-CAD4
Radiation	MoKα, Graphite monochromator, λ = 0.70930 Å
Index range	$0 \leq h \leq 11$
	$-11 \leq k \leq 11$
	$-12 \leq l \leq 12$
Θ-Range	2° – 26°
Total reflections	3249
Symmetry independent Reflections (N)	3049
Parameters (P)	274
N/P	11.13
R-value	0.0661
R_ω-value	0.1379

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary material.

Acknowledgements

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