Regio- and Stereoselective Synthesis of Pterocarpan Derivatives on a Carbazole Scaffold by Cascade Sigmatropic Rearrangements

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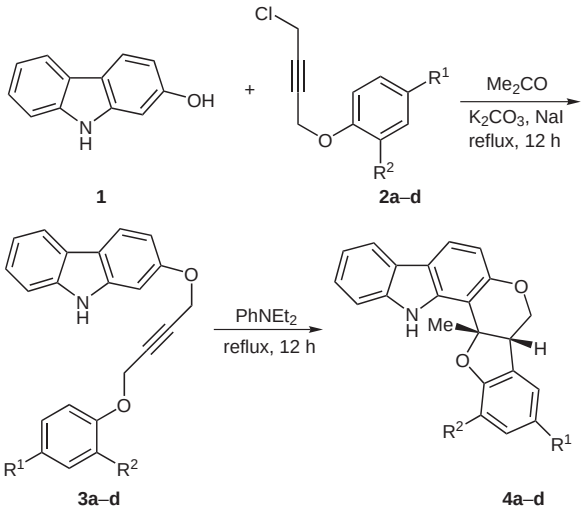
Abstract: Thermal rearrangement of 1-aryloxy-4-carbazolyloxybut-2-ynes, regio- and stereoselectively led to the formation of benzofuropyranocarbazoles in a single step in good yields. An investigation into the mechanism of the formation of these heteroannulated pterocarpan derivatives led to the serendipitous formation of isomeric benzofurofurocarbazole ring system.

Key words: sigmatropic rearrangements, heterocycles, regioselectivity, ring contractions

Thermal rearrangement of aryl propynyl ethers to benzofuran and/or benzopyran derivatives is well documented.[1] The operational simplicity and high efficacy of the process has rendered it an attractive and valuable methodology in heterocyclic synthesis over the last four decades.[2] Mechanistically, the process involves a series of consecutive sigmatropic rearrangements and a great deal of attention has been paid detailing these propositions.[3] In contemporaneous studies, Thyagrajan et al. reported a unique observation on the thermal behaviour of 1,4-diaryloxy-2-butynes in which pterocarpan-like structures were formed in a single step in high yields.[4] The reaction has found applications in heterocyclic synthesis and new observations have occasionally been made.[5,6] These interested us to study the thermal behaviour of 1-aryloxy-4-carbazolyloxy-but-2-ynes **3** (Scheme 1, Table 1) with an additional aim to synthesise polyoxacyclic carbazole derivatives in continuation of our interest in the synthesis of heteroannulated carbazoles.[7]

The starting materials **3a**–**d** were easily prepared by the reaction between commercially available 2-hydroxycarbazole (**1**) and easily obtainable 1-aryloxy-4-chlorobut-2-ynes **2a**–**d**.[8] When compound **3a** was refluxed in *N*,*N*-diethylaniline, a slow conversion to a new compound was observed. The product was characterised to be the benzofuropyranocarbazole derivative **4a** on the basis of spectral and analytical data. The stereochemistry of the ring junction, previously surmised from Drieding models in similar situations to be *cis*,[9] was established to be *cis* on the basis of NOE correlation between the methyl resonance at δ = 1.90 ppm and the benzylic proton at δ = 3.71 ppm. Similarly, compounds **3b**–**d** provided the products **4b**–**d** in good yields.



Scheme 1

Table 1 Synthesis of 1-Aryloxy-4-carbazolyloxybut-2-ynes **3** and benzofuropyranocarbazoles **4**

Compd	R^1	R^2	Yield of **3a**–**d** (%)	Yield of **4a**–**d** (%)
2a, **3a**, **4a**	H	H	**3a** (65)	**4a** (73)
2b, **3b**, **4b**	H	Me	**3b** (68)	**4b** (84)
2c, **3c**, **4c**	Me	H	**3c** (61)	**4c** (81)
2d, **3d**, **4d**	Cl	H	**3d** (59)	**4d** (82)

The formation of **4** from **3** could be mechanistically correlated by invoking preferential [3,3]-sigmatropic rearrangement of the carbazolyloxypropyne part followed by enolisation to provide the corresponding 2-allenyl phenol **5** (Scheme 2). The latter may undergo a [1,5]-prototropic shift to form the dienenone derivative **6**. Electrocyclic ring-closure of the latter then would lead to the pyranocarbazole derivative **7**. A second [3,3]-sigmatropic shift of the allyl vinyl ether part in **7** followed by enolisation would be expected to provide the phenol **8**. Ring-closure of the latter in a 5-*exo* fashion may explain the formation of the observed products. The regioselectivity of the first [3,3] shift to 1-position is similar to that observed during rearrangement of 2-allyloxycarbazole.[10]

While the spectroscopic data fit well with the structure of **4**, alternative formation of the isomeric compound **10** (Scheme 3) from the rearrangement of **3**, involving the

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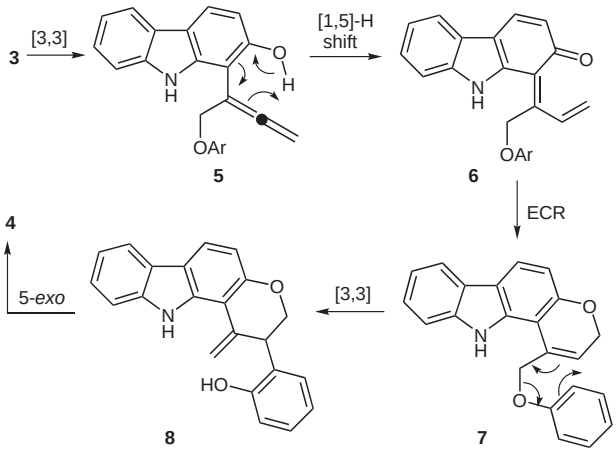
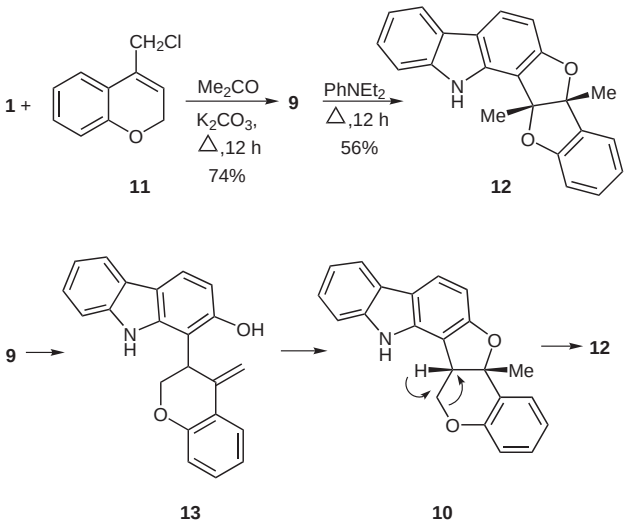
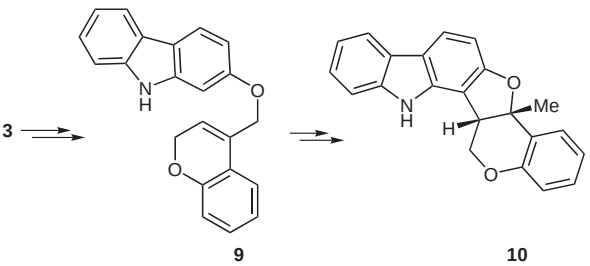


Scheme 2



Scheme 4

first [3,3]-sigmatropic shift in the aryloxypropynyl part, through the structure **9** could not be ruled out. Since, the available spectroscopic data did not allow distinction between the structures **4** and **10**, we undertook an alternative synthetic route for this distinction. We reasoned that rearrangement of preformed **9** under analogous conditions should provide **10** if the mechanistic route detailed in Scheme 2 is followed. Thus, treatment of **1** with the known 4-chloromethyl-Δ^3-chromene[11] (**11**, Scheme 4) in refluxing acetone in the presence of anhydrous potassium carbonate led to the formation of the desired **9**. However, thermal rearrangement of **9** in refluxing *N*,*N*-diethylaniline quite unexpectedly gave rise to an entirely different product. Examination of the ^{1}H NMR and ^{13}C NMR spectra quickly revealed the presence of two methyl groups as only signals in the entire aliphatic region. The compound was characterised to be the benzofurofurocarbazole derivative **12** on the basis of spectroscopic and analytical data. The stereochemistry of the ring junction has been tentatively assigned *cis* based on the belief that a 5,5-*cis*-fused structure will be more strain free. Mechanistically, compound **9** may undergo Claisen rearrangement to **13**, which then would form **10** through a 5-*exo* cyclisation. The latter may then undergo ring contraction to **12** via a [1,2]-H shift. This type of ring contraction has been observed previously.[12] However, its utility in heterocyclic synthesis is not well documented to the best of our knowledge.



Scheme 3

In short, we have demonstrated the utility of cascade sigmatropic rearrangements for the synthesis of hitherto unknown benzofuropyranocarbazole and isomeric benzofurofurocarbazole derivatives, which are otherwise difficult to prepare. The process is general, regio- and stereoselective, atom economic, efficacious and operationally simple. The compounds prepared[13] may prove to be useful in view of the known importance of naturally occurring furo- and pyranocarbazoles and synthetic analogues thereof.[14]

Acknowledgment

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(13) All new compounds reported here gave satisfactory spectroscopic and/or analytical data. **General Procedure for the Rearrangement of 3 to 4.**
A solution of compound **3** (0.6 mmol) in *N*,*N*-diethylaniline (6 mL) was heated to reflux for 12 h under nitrogen atmosphere. It was then allowed to come to r.t. and then poured into ice-cold 2 N HCl (50 mL) while stirring with a glass rod. The aqueous solution was extracted with EtOAc (3 × 25 mL) and the combined organic extract was washed sequentially with sat. aq $NaHCO_3$ (2 × 20 mL), H_2O (20 mL), brine (25 mL) and then dried (Na_2SO_4). It was then filtered, and the filtrate was concentrated in vacuo to leave a solid mass, which was chromatographed over silica gel using mixture of EtOAc and PE as eluent.
Analytical Data.
Compound **4a**: mp 184–185 °C. IR (KBr): 3392, 1595, 1493, 1211, 1177 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.65 (s, 1 H), 7.98 (d, 1 H, *J* = 7.6 Hz), 7.86 (d, 1 H, *J* = 8.4 Hz), 7.52 (d, 1 H, *J* = 8.0 Hz), 7.38 (t, 1 H, *J* = 8.0 Hz), 7.30–7.17 (m, 3 H), 6.93–6.80 (m, 3 H), 4.49 (dd, 1 H, *J* = 10.8, 5.0 Hz), 3.83 (t, 1 H, *J* = 10.4 Hz), 3.71 (dd, 1 H, *J* = 10.0, 4.9 Hz), 1.90 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.1 (s), 153.7 (s), 139.8 (s), 138.5 (s), 129.2 (d), 125.8 (s), 124.9 (d), 124.7 (d), 123.5 (s), 120.9 (d), 120.7 (d), 119.7 (d), 119.5 (d), 118.5 (s), 110.8 (d), 110.4 (d), 109.9 (d), 109.0 (s), 83.8 (s), 67.6 (t), 49.5 (d), 26.2 (q). Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.94; H, 5.37; N, 4.40. MS (TOFMS ES$^+$): *m/z* = 350 [M^+ + Na].
Compound **4b**: mp 160–161 °C. IR (KBr): 3457, 1610, 1463, 1427, 1302, 1219 cm^{-1}.^1H NMR (300 MHz, $CDCl_3$): δ = 8.54 (s, 1 H), 7.91 (d, 1 H, *J* = 7.5 Hz), 7.78 (d, 1 H, *J* = 8.4 Hz), 7.45 (d, 1 H, *J* = 8.1 Hz), 7.34 (dt, 1 H, *J* = 7.2, 1.0 Hz), 7.15 (d, 1 H, *J* = 7.2 Hz), 7.04 (d, 1 H, *J* = 7.5 Hz), 6.93 (d, 1 H, *J* = 7.5 Hz), 6.79–6.72 (m, 2 H), 4.41 (dd, 1 H, *J* = 11.1, 5.1 Hz), 3.81 (t, 1 H, *J* = 9.6 Hz), 3.64 (dd, 1 H, *J* = 9.6, 5.1 Hz), 2.17 (s, 3 H), 1.84 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.0 (s), 154.1 (s), 140.2 (s), 139.1 (s), 130.8 (d), 125.5 (s), 125.1 (d), 124.0 (s), 122.6 (d), 121.3 (d), 121.1 (d), 120.8 (s), 120.1 (d), 119.9 (d), 118.9 (s), 111.2 (d), 110.4 (d), 109.7 (s), 83.8 (s), 67.9 (t), 50.1 (d), 26.8 (q), 15.8 (q). Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 81.23; H, 5.77; N, 4.28. MS (TOFMS ES$^+$): *m/z* = 342 [M^+ + H].
Compound **4c**: mp 261–262 °C. IR (KBr): 3369, 1610, 1481, 1464, 1302, 1208, 1083 cm^{-1}.^1H NMR (300 MHz, $CDCl_3$): δ = 8.65 (s, 1 H), 7.97 (d, 1 H, *J* = 7.8 Hz), 7.85 (d, 1 H, *J* = 8.4 Hz), 7.51 (d, 1 H, *J* = 8.1 Hz), 7.37 (dt, 1 H, *J* = 7.1, 1.0 Hz), 7.22 (t, 1 H, *J* = 7.2 Hz), 7.09 (s, 1 H), 6.98 (d, 1 H, *J* = 7.2 Hz), 6.81 (d, 1 H, *J* = 7.2 Hz), 6.75 (d, 1 H, *J* = 8.1 Hz), 4.46 (dd, 1 H, *J* = 11.1, 5.3 Hz), 3.82 (dd, 1 H, *J* = 11.0, 10.1 Hz), 3.66 (dd, 1 H, *J* = 10.0, 5.2 Hz), 2.30 (s, 3 H), 1.88 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.0 (s), 153.6 (s), 139.8 (s), 138.6 (s), 130.3 (s), 129.6 (d), 125.7 (s), 125.5 (d), 124.7 (d), 123.5 (s), 120.7 (d), 119.7 (d), 119.5 (d), 118.5 (s), 110.8 (d), 110.9 (d), 109.8 (d), 109.1 (s), 83.7 (s), 67.6 (t), 49.5 (d), 26.1 (q), 20.8 (q). Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 81.06; H, 5.79; N, 4.31. MS (TOFMS ES$^+$): *m/z* = 342 [M + H].
Compound **4d**: mp 238–240 °C. IR (KBr): 3382, 1609, 1465, 1427, 1300, 1224 cm^{-1}.^1H NMR (300 MHz, $CDCl_3$): δ = 8.58 (s, 1 H), 7.98 (d, 1 H, *J* = 7.7 Hz), 7.87 (d, 1 H, *J* = 8.5 Hz), 7.52 (d, 1 H, *J* = 8.0 Hz), 7.38 (dt, 1 H, *J* = 7.2, 1.0 Hz), 7.23–7.20 (m, 2 H), 7.14 (dd, 1 H, *J* = 8.5, 2.1 Hz), 6.80 (t, 2 H, *J* = 8.4 Hz), 4.46 (dd, 1 H, *J* = 11.1, 5.1 Hz), 3.86 (t, 1 H, *J* = 9.8 Hz), 3.69 (dd, 1 H, *J* = 9.5, 5.3 Hz), 1.91 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.8 (s), 153.5 (s), 139.7 (s), 138.4 (s), 129.1 (d), 127.7 (s), 125.6 (s), 125.1 (d), 124.8 (d), 123.5 (s), 121.0 (d), 119.8 (d), 119.5 (d), 118.6 (s), 111.4 (d), 110.8 (d), 109.9 (d), 108.5 (s), 84.8 (s), 67.0 (t), 49.3 (d), 26.0 (q). Anal. Calcd for $C_{22}H_{16}ClNO_2$: C, 73.03; H, 4.46; N, 3.87. Found: C, 73.27; H, 4.63; N, 4.11. MS (TOFMS ES$^+$): *m/z* = 362, 364 [M^+ + H].
Compound **12**: mp 288–290 °C. IR (KBr): 3348, 1639, 1460, 1226 cm^{-1}.^1H NMR (300 MHz, $CDCl_3$): δ = 8.20 (s, 1 H), 7.94–7.86 (m, 2 H), 7.48–7.43 (m, 2 H), 7.34 (t, 1 H, *J* = 7.4 Hz), 7.23–7.18 (m, 2 H), 6.96 (t, 1 H, *J* = 7.4 Hz), 6.78 (d, 1 H, *J* = 8.0 Hz), 6.70 (d, 1 H, *J* = 8.4 Hz), 2.01 (s, 3 H), 1.85 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.0 (s), 157.5 (s), 139.6 (s), 136.2 (s), 130.7 (d), 129.3 (s), 124.7 (d, two signals), 123.8 (s), 122.5 (d), 121.3 (d), 120.0 (d), 119.3 (d), 118.6 (s), 110.7 (d, two signals), 110.1 (s), 103.5 (d), 96.1 (s), 96.0 (s), 20.8 (q), 20.0 (q). Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.99; H, 5.31; N, 4.45. MS (TOFMS ES$^+$): *m/z* = 328 [M^+ + H].
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