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Thermal Ring Contraction of Dibenz[*b*,*f*]azepin-5-yl Radicals: New Routes to Pyrrolo[3,2,1-*jk*]carbazoles

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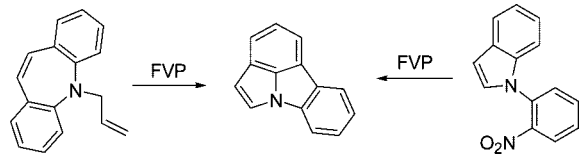


Flash vacuum pyrolysis (FVP) of *N*-allyl- or *N*-benzyldibenz[*b*,*f*]azepine at temperatures from 750 to 950 °C gives pyrrolo[3,2,1-*jk*]carbazole as the major product. The mechanism of the ring contraction involves dibenzazepin-1-yl radical formation, followed by transannular attack and formation of a 2-(indol-1-yl)phenyl radical which cyclizes. The mechanism is supported by independent generation of 2-(indol-1-yl)phenyl radicals by two different methods, and the use of 1-(2-nitrophenyl)indole as a radical generator gives an optimized synthetic route to pyrrolo[3,2,1-*jk*]carbazole (54% overall yield in two steps from indole). The first substituted pyrrolo[3,2,1-*jk*]carbazoles have been synthesized by FVP methods and also by reactions of the parent compound with electrophiles, leading to a range of 4-substituted pyrrolocarbazoles.

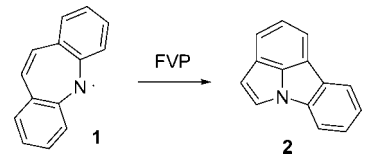
Introduction

Very little is known of the chemical properties of 5- or 7-membered heterocyclic species in which the heteroatom bears a radical center. In previous work, we have shown that 1,2,4-triazol-4-yl species, generated by flash vacuum pyrolysis (FVP) of a 4-amino compound, can cyclize with high regioselectivity onto a 3-*S*-allyl group to provide thiazolo[3,2-*b*]triazoles.[1] Here, we extend this work to the 7-membered ring series and demonstrate that, under FVP conditions, dibenzazepin-5-yl radicals **1** undergo ring contraction leading to pyrrolo[3,2,1-*jk*]carbazole **2** (Scheme 1) via cyclization of an intermediate 2-(indol-1-yl)phenyl radical. By further exploiting this phenyl radical cyclization, we have optimized the synthetic route to pyrrolo[3,2,1-*jk*]carbazole **2** and present the first studies of its chemical properties.

Results and Discussion

Cleavage of *N*-benzyl or *N*-allyl groups at ca. 700 °C under FVP conditions is a good route to phenylaminyl and related radical species.[2] In the dibenz[*b*,*f*]azepine series, the corresponding FVP precursors **4** and **5** were easily obtained in moderate yield by alkylation of the parent compound **3** ("iminostilbene") under conditions used for the *N*-alkylation of pyrroles and indoles[3] (Scheme 2).

SCHEME 1



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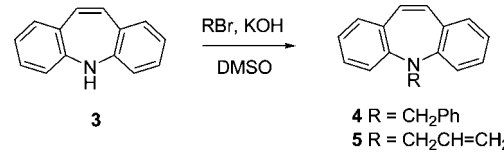

When the *N*-benzyl compound **4** was subjected to FVP at 750 °C, four products were identified from the reaction mixture (Scheme 3).

The formation of bibenzyl **6** (ca. 20%) provided confirmation that radical generation had been successful. Recovered 5*H*-dibenz[*b*,*f*]azepine **3** (20%) suggested that hydrogen capture (a well-known reaction of aminyl and phenoxyl radicals under FVP

(1) Cartwright, D. D. J.; Clark, B. A. J.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 424–428.
(2) Cadogan, J. I. G.; Hickson, C. L.; McNab, H. *Tetrahedron* **1986**, *42*, 2135–2165.
(3) Heaney, H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1973**, 499–500.

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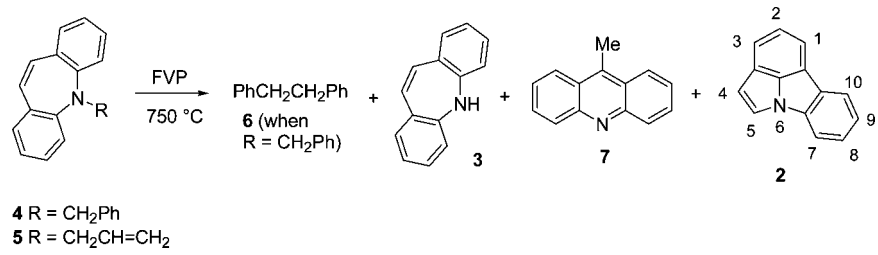
SCHEME 3



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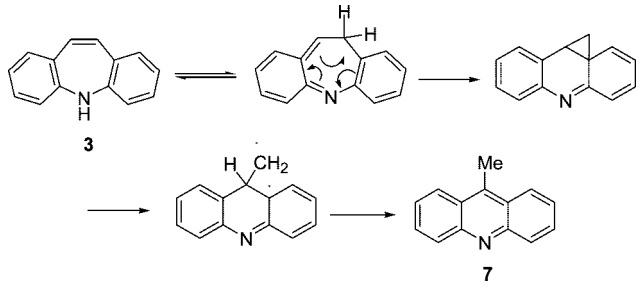
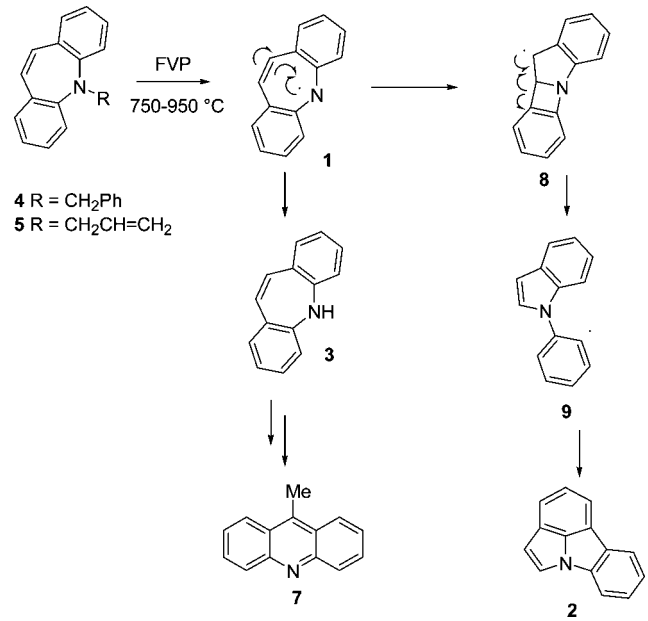


SCHEME 5



conditions[2]) is able to compete with other processes at this temperature. In addition, two ring contraction products were obtained. The first, a trace of 9-methylacridine **7** (2%), is likely to be formed by ring contraction of 5*H*-dibenz[*b*,*f*]azepine **3**; a control pyrolysis of **3** under more vigorous conditions (950 °C) gave 9-methylacridine **7** as the sole product in 60% isolated yield. Ring contractions of this type are known to provide acridine byproduct in the commercial synthesis of **3** by catalytic gas-phase dehydrogenation of its 10,11-dihydro derivative, particularly at higher temperatures.[4,5] A 1,5-shift, electrocyclization, ring cleavage, hydrogen shift sequence is the most likely mechanism (Scheme 4).

However, the major product formed from FVP of the *N*-benzyl compound **4** was pyrrolo[3,2,1-*jk*]carbazole **2** (ca. 35%), identified by comparison of its melting point and ^{1}H NMR spectrum with those previously reported.[6,7] On a preparative scale, the use of the *N*-benzyl precursor **4** proved to be inconvenient because it was difficult to separate **2** from the bibenzyl coproduct **6**. Pyrolysis of the *N*-allyl compound **5** was therefore studied; volatile coproducts (allene and/or biallyl) were expected to be generated, thus eliminating any separation issues. In this case, only the pyrrolocarbazole **2**, the dibenzazepine **3**, and the acridine **7** were obtained in 56:43:1 relative yields at 750 °C. The temperature of the pyrolysis proved to have a dramatic effect on the product distribution, with the amount of pyrrolocarbazole **2** increasing with temperature (Figure 1). The optimum temperature for formation of **2** proved to be 950 °C and on a preparative scale (>1.0 g) a 63% yield of pure **2** was obtained after workup and chromatography.

The pyrolysis results can be rationalized by the proposed mechanisms shown in Scheme 5. The dibenzazepin-5-yl radical **1** may undergo hydrogen capture (a comparatively low energy process, favored at low temperatures) to give the dibenzazepine **3** (and hence the low levels of the acridine **7**). Alternatively, a trans-annular interaction of the aminyl center of **1** with its 10,11-double bond leads via the tetracyclic transition state (or intermediate) **8** to the phenyl radical **9** which can cyclize to provide the strained pyrrolo[3,2,1-*jk*]carbazole **2**. Many examples of phenyl radical cyclizations to provide strained ring systems are known,[8] and it is not surprising that this process is relatively favored at the higher temperatures.

It is clear from the proposed mechanism that the phenyl radical **9** is the key intermediate in pyrrolocarbazole formation, and we sought to obtain supporting evidence by generating such radicals by an independent route. In previous work,[9] we have used FVP of allyl esters as a source of substituted phenyl radicals, and the required precursor **11** of the phenyl radical **9** was made by the method shown in Scheme 6. The carboxylic acid **10** was not isolated but was esterified in situ to provide **11** in 47% yield for the two steps.

FVP of the allyl ester **11** at 950 °C provided pyrrolo[3,2,1-*jk*]carbazole **2** in 42% isolated yield as essentially the only product (Scheme 6). This result is consistent with the mechanism proposed in Scheme 5 and with the involvement of the phenyl radical **9** in the process.

Because of the availability of the starting materials, the phenyl radical cyclization route to pyrrolo[3,2,1-*jk*]carbazoles is more general in principle than the dibenzazepine ring contraction. As

(4) Kricka, L. J.; Ledwith, A. *Chem. Rev.* **1974**, *74*, 101–123.
(5) Inoue, M.; Itoi, Y.; Enomoto, S.; Ishizuka, N.; Amemiya, H.; Takeuchi, T. *Chem. Pharm. Bull.* **1982**, *30*, 24–27.
(6) Brown, R. F. C.; Choi, N.; Coulston, K. J.; Eastwood, F. W.; Ercole, J. M.; Horvath, J. M.; Mattinson, M.; Mulder, R. J.; Ooi, H. C. *Liebigs Ann. Recl.* **1997**, 1931–1940.
(7) Klingstedt, T.; Hallberg, A.; Dunbar, P.; Martin, A. *J. Heterocycl. Chem.* **1985**, *22*, 1547–1550.
(8) For example: Peng, L.; Scott, L. T. *J. Am. Chem. Soc.* **2005**, *127*, 16518–16521.
(9) Cadogan, J. I. G.; Hutchison, H. S.; McNab, H. *Tetrahedron* **1992**, *48*, 7747–7762.

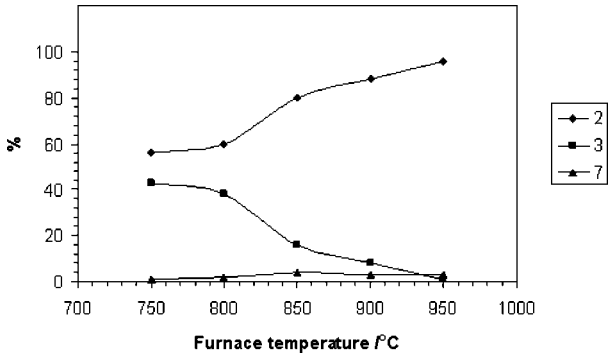
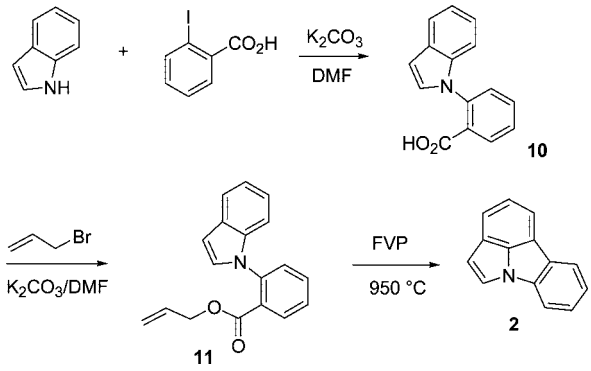
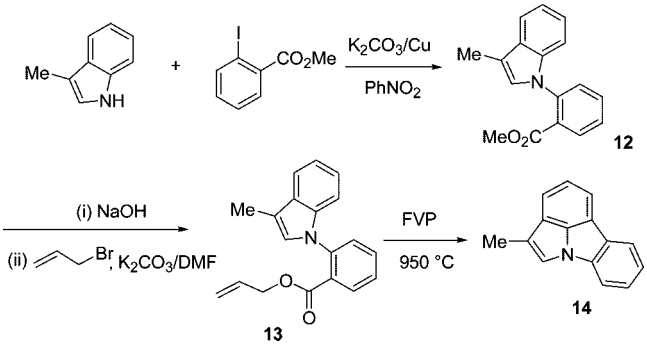


FIGURE 1. Temperature profile for the pyrolysis of **5**.

SCHEME 6



SCHEME 7



a second example, 4-methylpyrrolo[3,2,1-*jk*]carbazole **14** was obtained via the esters **12** and **13** by the route shown in Scheme 7. This appears to be the first substituted pyrrolo[3,2,1-*jk*]carbazole recorded in the literature.

In practice, the preparation of allyl esters such as **11** proved less robust than we had hoped, and we therefore sought an alternative generator of the phenyl radical **9** which could be readily made from indole by S_NAr methodology. The nitro compound **16** was an attractive possibility synthetically, though the literature reveals conflicting evidence on the FVP reactions of aromatic nitro compounds. Under flow conditions,[10] (later extended to FVP[11]) nitro compounds have been shown to give phenols by rearrangement and cleavage of NO. However, Marty and De Mayo presented good evidence that aryl nitro groups could undergo C−N cleavage to give phenyl radical intermediates;[12] this route has been used to generate diradicals for matrix isolation[13] and appears to be the best explanation of certain cyclization reactions observed by Rees and co-workers.[14] In our case, 1-(2-nitrophenyl)indole**16** was readily made in 90% yield by reaction of indole **15** with 2-fluoronitrobenzene, and FVP of **16** provided pyrrolo[3,2,1-*jk*]carbazole **2** (60%) after chromatography (Scheme 8). The effect of the coformation of reactive NO_x species as pyrolysis byproducts from the nitrophenylindole method could be minimized by using a coldfinger, cooled by a dry ice−acetone mixture, in place of our usual U-tube trap.

SCHEME 8

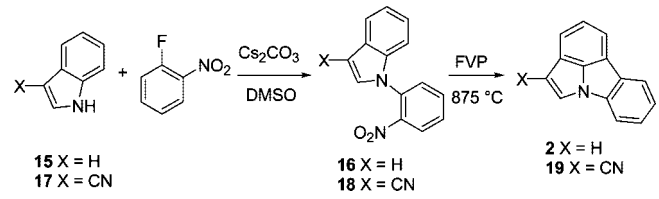


TABLE 1. ^{1}H and ^{13}C NMR Data for Pyrrolo[3,2,1-*jk*]carbazole 2 (Numbering Scheme Shown in Scheme 3)

position	δ_C	δ_H	J_{HH}/Hz	pattern
1	117.84	7.90	^3J 7.4, ^4J 0.5	dd
2	123.91	7.51	^3J 7.4	t
3	121.54	7.79	^3J 7.4, ^4J 0.5	dd
4	109.86	6.86	^3J 3.1	d
5	122.93	7.73	^3J 3.1	d
7	111.91	7.68	^3J 8.0, ^4J 1.0,^5J 0.7	ddd
8	127.01	7.47	^3J 8.0, ^4J 1.2	td
9	122.63	7.32	^3J 7.8, ^4J 1.0	td
10	123.62	8.08	^3J 7.8, ^4J 1.2,^5J 0.7	ddd

We believe that this method is generally the most efficient of our new synthetic routes to the pyrrolo[3,2,1-*jk*]carbazole ring system so that the parent compound **2** is now readily made in two steps from indole, on a gram scale, in 54% overall yield. Other published routes suffered from low overall yields,[6] mixtures of products,[6] and/or inconvenient starting materials,[6,7] such that only milligram quantities were previously available. On the other hand, the reactive NO_x coproducts are the main drawback of the route involving the nitro precursors, especially for the preparation of electron rich species such as **14**, for which the allyl ester method remains preferable (see the Supporting Information).

Pyrrolo[3,2,1-*jk*]carbazole **2** is an unusual heterocyclic skeleton which is significantly strained, owing to the presence of the bis-fused benzene ring spanning two bonds of a pyrrolizine system. With quantities of **2** now available, a brief examination was made of its spectroscopic and chemical properties. The previous assignment of its ^{1}H NMR spectrum[7] was fully confirmed by NOESY methods and extension to the ^{13}C dimension was made by HSQC (see the Supporting Information). The full assignments are shown in Table 1.

Despite the inherent ring strain, pyrrolo[3,2,1-*jk*]carbazole **2** was found to behave as a 1-substituted indole in its reactions with electrophiles. Thus, treatment with oxalyl chloride provided

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(11) Wiersum, U. E. *Polycyclic Aromat. Compd.* **1996**, *11*, 291–300.
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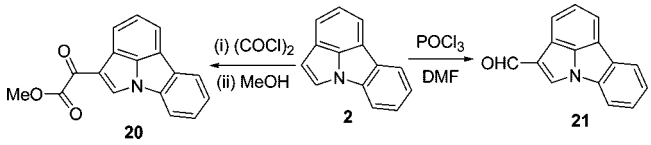
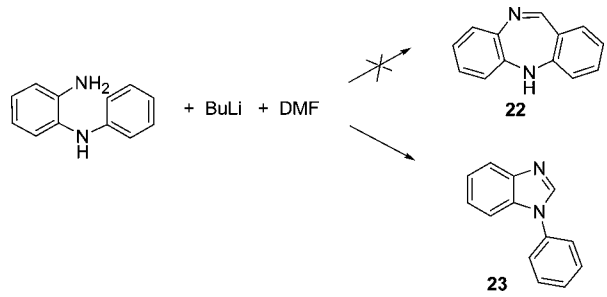
SCHEME 9



SCHEME 10



the 4-substituted product **20** in 48% yield; the position of substitution was confirmed by NOESY correlation of the 1-proton singlet (δ_H 8.89) to a doublet of doublets of doublets (δ_H 7.74) belonging to the 4-spin system (see the Supporting Information). Similarly, Vilsmeier formylation of pyrrolo[3,2,1-*jk*]carbazole **2** gave its 4-carboxaldehyde derivative **21** in 24% (unoptimized) yield (Scheme 9).

In an attempt to extend the ring contraction work to the previously reported diazepine **22**, the one-step literature synthesis of this compound was repeated (Scheme 10). In our hands, the sole product isolated in moderate yield from this procedure, had an identical ^{1}H NMR spectrum and compatible melting point with those reported for **22**,[15] but it was clear from its ^{13}C NMR spectrum that the compound contained an unchanged phenyl group. This product proved to be 1-phenylbenzimidazole **23** (see the Supporting Information), formed by *N*-formylation instead of *C*-formylation, followed by cyclization.

In conclusion, the work presented in this paper has identified a new thermal ring contraction of dibenzazepin-5-yl radicals which has been extended to give the first convenient access to the pyrrolo[3,2,1-*jk*]carbazole system **2**. In reactions with electrophiles, **2** behaves as a 1-substituted indole, with substitution reactions occurring exclusively at the 4-position. Further examples of the phenyl radical route to new heterocyclic ring systems related to pyrrolo[3,2,1-*jk*]carbazoles will be reported in future publications.

Experimental Section

Alkylation of 5*H*-dibenz[*b*,*f*]azepine (3). Powdered potassium hydroxide (1.5 g, 37.5 mmol) was added to DMSO (10 cm^3) and the mixture allowed to stir for 10 min. 5*H*-Dibenz[*b*,*f*]azepine **3** (1.0 g, 5.2 mmol) was added, and the solution was stirred for 90 min. The appropriate alkyl halide (10.4 mmol) was added, and the solution was stirred for a further 90 min. The solution was added to water (100 cm^3) and extracted with DCM (3 × 100 cm^3). The organic layer was washed with water (2 × 100 cm^3) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was subjected to dry flash chromatography on silica using hexane as eluant.

5-Benzyl-5*H*-dibenz[*b*,*f*]azepine (4). Application of the general method using benzyl bromide gave 5-benzyl-5*H*-dibenz[*b*,*f*]azepine **4** (35%): mp 81−83 °C (from hexane) (lit.[16] mp 80 °C); NMR δ_H 7.03−7.63 (11H, m), 6.72−6.77 (2H, m), 6.57 (2H, s) and 4.81 (2H, s); *m*/*z* 283 (M$^+$, 6), 217 (100), 194 (14), 149 (2), and 91 (77). Anal. Calcd for $C_{21}H_{17}N$: C, 89.05; H, 6.0; N, 4.95. Found: C, 89.2; H, 6.2; N, 5.15.

5-Allyl-5*H*-dibenz[*b*,*f*]azepine (5). Application of the general method using allyl bromide gave 5-allyl-5*H*-dibenz[*b*,*f*]azepine **5** (46%): mp 55−56 °C (lit.[17] mp 55−57 °C); MS M$^+$, 233.1200, $C_{17}H_{15}N$ requires 233.1205; NMR δ_H 7.22−7.29 (2H, m), 6.96−7.10 (6H, m), 6.77 (2H, m), 5.80 (1H, m), 5.32 (1H, m), 5.12 (1H, m) and 4.40 − 4.43 (2H, m); NMR δ_C 150.5 (2 × quat), 135.1 (CH), 133.6 (2 × quat), 132.1 (2 × CH), 129.0 (2 × CH), 128.5 (2 × CH), 123.2 (2 × CH), 120.4 (2 × CH), 117.5 (CH_2), and 53.4 (CH_2); *m*/*z* 233 (M$^+$, 19), 192 (100), 165 (15), 139 (7), 89 (6), and 77 (6).

Flash Vacuum Pyrolysis (FVP) Experiments. The precursor was volatilized under rotary pump vacuum through an empty, electrically heated silica tube (35 × 2.5 cm), and the products were collected in a U-tube, cooled with liquid nitrogen, situated at the exit point of the furnace. For large scale (0.5 g and greater) pyrolyses from aromatic nitro precursors, a "coldfinger" trap, cooled by a mixture of dry ice and acetone, was used in place of the U-tube. For all pyrolyses, the pressure was measured by a Pirani gauge situated between the product trap and the pump. Upon completion of the pyrolysis, the trap was allowed to warm to room temperature under a nitrogen atmosphere. The entire pyrolysate was dissolved in solvent and removed from the trap. The precursor, pyrolysis conditions [quantity of precursor (*m*), furnace temperature (T_f), inlet temperature (T_i), pressure (*P*) and pyrolysis time (*t*)], and products are quoted below for each experiment.

FVP of 5-Benzyl-5*H*-dibenz[*b*,*f*]azepine (4). FVP of **4** (*m* 0.05 g, T_f 750 °C, T_i 150 °C, *P* 0.04 Torr, *t* 20 min) produced bibenzyl **6** (ca. 20%, but could not be totally separated from **2** by chromatography): NMR δ_H 7.16−7.87 (10H, m) and 2.92 (4H, s); NMR δ_C 129.3 (2 × quat), 128.3 (4 × CH), 128.2 (4 × CH), 125.8 (2 × CH) and 37.8 (2 × CH_2);[18] pyrrolo[3,2,1-*jk*]carbazole **2** (ca. 35%, but could not be separated from **6** by chromatography; see spectroscopic data below); 9-methylacridine **7** (see below) (2%) and 5*H*-dibenz[*b*,*f*]azepine **3** (20%); δ_H 7.03−7.10 (2H, m), 6.82−6.93 (4H, m), 6.51−6.55 (2H, m) and 6.35 (2H, s); NMR δ_C 148.2 (2 × quat), 132.0 (2 × CH), 130.4 (2 × CH), 129.6 (2 × quat), 129.3 (2 × CH), 122.9 (2 × CH) and 119.2 (2 × CH).

FVP of 5-Allyl-5*H*-dibenz[*b*,*f*]azepine (5). FVP of **5** [*m* 1.10 g (4.7 mmol), T_f 950 °C, T_i 150 °C, *P* 0.04 Torr, t_m 60 min] gave pyrrolo[3,2,1-*jk*]carbazole **2** (0.57 g, 63%): mp 88−89 °C (lit.[7] mp 89−90 °C), after dry flash chromatography on silica using hexane as eluant; NMR δ_H (360 MHz) 8.08 (1H, ddd, ^3J 7.8, ^4J 1.2, ^5J 0.7), 7.90 (1H, dd, ^3J 7.4, ^4J 0.5), 7.79 (1H, dd, ^3J 7.4, ^4J 0.5), 7.73 (1H, d, ^3J 3.1), 7.68 (1H, ddd, ^3J 8.0, ^4J 1.0, ^5J 0.7), 7.51 (1H, t, ^3J 7.4), 7.47 (1H, td, ^3J 8.0, ^4J 1.2), 7.32 (1H, td, ^3J 7.8, ^4J 1.0) and 6.86 (1H, d, ^3J 3.1); NMR δ_C (90 MHz) 141.3 (quat), 139.9 (quat), 131.4 (quat), 127.0 (CH), 123.9 (CH), 123.6 (CH), 122.9 (CH), 122.6 (CH), 122.1 (quat), 121.5 (CH), 119.4 (quat), 117.8 (CH), 111.9 (CH) and 109.9 (CH); MS *m*/*z* 191 (M$^+$, 78), 190 (84), 156 (100), 128 (31), 95 (6), 78 (14) and 51 (4).

Control pyrolysis of 5*H*-dibenz[*b*,*f*]azepine (3). FVP of **3** [*m* 0.35 g (1.8 mmol), T_f 950 °C, T_i 180−200 °C, *P* 0.009 Torr, *t* 30 min] gave 9-methylacridine **7** after dry flash chromatography on silica using hexane/ethyl acetate as eluant (0.21 g, 60%): NMR δ_H 8.14−8.21 (4H, m), 7.45−7.75 (4H, m) and 3.02 (3H, s); NMR δ_C

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(19) Moeller, U.; Cech, D.; Schubert, F. *Liebigs Ann. Chem.* **1990**, 1221–1225.

148.1 (2 × quat), 142.1 (quat), 129.9 (2 × CH), 129.6 (2 × CH), 125.5 (2 × quat), 125.2 (2 × CH), 124.3 (2 × CH) and 13.4 (CH_3).[19]

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Supporting Information Available: Full experimental details for all new compounds; data for the FVP temperature profile of **5**; copies of ^{1}H and ^{13}C NMR spectra of **2** and **20** and of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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