Preparation of 9*H*-Tribenz[*b*,*d*,*f*]azepine and Its 1-Methoxy Derivative

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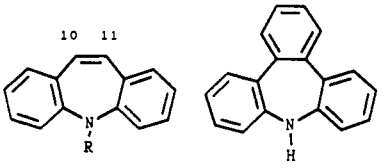
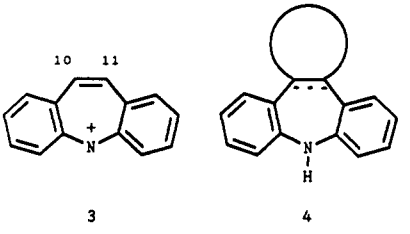
Two convenient routes to 9*H*-tribenz[*b*,*d*,*f*]azepine (2) have been developed. The first method involves the deoxygenation and hydrolysis of 1,4-dihydro-1,4-epoxy-9-acetyl-9*H*-tribenz[*b*,*d*,*f*]azepine (8) employing low-valent titanium. The second method employs the reactive intermediate 10,11-didehydro-5-acetyl-5*H*-dibenz[*b*,*f*]azepine (7) in a Diels–Alder reaction with 1,3-cyclohexadiene. The resulting cycloadduct 13 upon undergoing a retro-Diels–Alder reaction and hydrolysis yields 2. 1-Methoxy-9*H*-tribenz[*b*,*d*,*f*]azepine (11) was prepared from ring opening of 8 to 1-hydroxy-9-acetyl-9*H*-tribenz[*b*,*d*,*f*]azepine (10) followed by methylation with dimethyl sulfate and hydrolysis.

Although 5*H*-dibenz[*b*,*f*]azepine (1a) and its derivatives are very well-known and well-studied compounds,[1,2] the 9*H*-tribenz[*b*,*d*,*f*]azepine ring system (as in the parent compound 2) has curiously only been cited once in the



chemical literature. Hellwinkel and Seifert reported the formation of the *N*-phenyl derivative in poor yield via a multistep synthesis from diphenylamine and 2-nitro-2′-iodobiphenyl.[3]

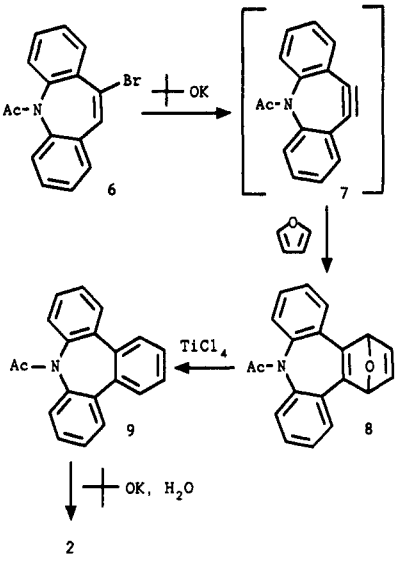
Our interest in both 5*H*-dibenz[*b*,*f*]azepine (1a) and 9*H*-tribenz[*b*,*d*,*f*]azepine (2) relates to our efforts in preparing an aromatic nitrenium ion. We have studied the reactions of 1a with *tert*-butyl hypochlorite[4] and with silver trifluoroacetate[5] in attempts to form the 14π electron dibenz[*b*,*f*]azatropylium ion (3). However, in both cases,



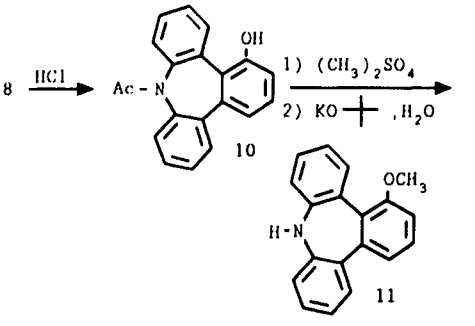
we observed major amounts of acridine products resulting from ring contraction of the central azepine ring.[6] Thus, due to the propensity of the dibenz[*b*,*f*]azepine system to undergo this contraction, it appears that the generation and observation of 3 is unlikely. We have therefore embarked upon an effort to prepare derivatives of 1a whereby the 10,11 double bond is incorporated in an additional ring as in 4. This structural modification should prevent the ring contraction and allow for the preparation and observation of tetracyclic derivatives of 3.

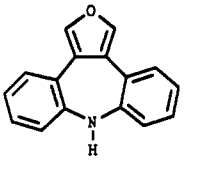
We have previously reported the synthesis of 8*H*-furo[*3*,*4d*]dibenz[*b*,*f*]azepine (5)[7] and report here our preparation of 9*H*-tribenz[*b*,*d*,*f*]azepine (2) and its 1-methoxy derivative 11.

Scheme I



Scheme II





Our synthesis of 5[7] utilized the 3,6-epoxy-3,6-dihydrotribenzazepine 8, which in turn was prepared from the reaction of the unstable alkyne 7 with furan.[8] It also appared that 8 could act as a precursor to 9 by deoxygenation. As illustrated in Scheme I, we first attempted

(1) For a review, see: Kricka, L. J.; Ledwith, A. *Chem. Rev.* **1974**, *74*, 101.
(2) For a recent reference, see: Pindur, V.; Flo, C. *J. Heterocycl. Chem.* **1989**, *26*, 1563.
(3) Hellwinkel, D.; Seifert, H. *Chem. Ber.* **1972**, *105*, 880.
(4) Cann, M. C.; Lezinsky, D. *J. Heterocycl. Chem.* **1988**, *25*, 863.
(5) Cann, M. C. *J. Org. Chem.* **1988**, *53*, 1112.
(6) Others have also reported the ring contraction of 1. See, for example: Bendall, M. R.; Bremner, J. B.; Fay, J. F. W. *Aust. J. Chem.* **1972**, *25*, 2451.
(7) McHugh, K. B.; Howell, W. M.; Doran, J. J.; Cann, M. C. *J. Heterocycl. Chem.* **1990**, *27*, 1839.
(8) Das, B. P.; Boykin, D. W. *J. Med. Chem.* **1971**, *14*, 1839.

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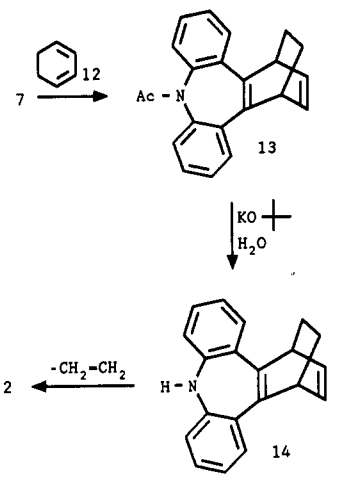
Scheme III



the deoxygenation of 8 using low-valent titanium according to the procedure of Wong ($TiCl_4$, THF, $LiAlH_4$, $(C_2H_5)_3N$).[9] Removal of an aliquot from this reaction mixture and analysis by GC/MS indicated the deoxygenation to 9 was successful. However, efforts to separate and purify 9 from the reaction mixture were hampered by contamination with a high-boiling liquid. The liquid has been tentatively identified (through NMR) as 4-chloro-1-butanol, presumably formed from ring opening of THF. However, substitution of methylene chloride for THF allowed for the isolation of crude 9. Subsequent hydrolysis of 9 with potassium *tert*-butoxide[10] gave 2 in 79% yield from 8.

In addition to the deoxygenation of 8, we also found that ring opening of 8 to the phenol 10 occurred upon reaction with hydrochloric acid (Scheme II). The phenol was then methylated with dimethyl sulfate and subsequently hydrolyzed to yield 1-methoxy-9*H*-tribenz[*b*,*d*,*f*]azepine (11) in 39% overall yield from 8.

A second approach to the parent 9*H*-tribenz[*b*,*d*,*f*]azepine (2) is outlined in Scheme III. Since the alleged alkyne intermediate 7 acts as a dienophile in the Diels–Alder reaction with furan, we decided to substitute 1,3-cyclohexadiene (12) for furan. Reaction of 6 with potassium *tert*-butoxide in refluxing 12 followed by reaction of the crude product with potassium *tert*-butoxide in refluxing THF produced a mixture of 14 and 2. Partial separation of the products was achieved by column chromatography. Compound 14 decomposes at 158 °C with bubbling to 2 via a retro-Diels–Alder reaction. In order to avoid the mixture of 14 and 2, in subsequent preparations of 2, 13 was reacted with potassium *tert*-butoxide in refluxing diglyme (bp 161 °C). Overall, the yield of 2 from 6 was 39%.

In conclusion, we have presented three attractive routes to the 9*H*-tribenz[*b*,*d*,*f*]azepine ring system 2. Each route provides respectable yields from readily available starting materials. The Diels–Alder/retro-Diels–Alder route (Scheme III) offers the possibility for the synthesis of many substituted derivatives of 2 by simply employing substituted cyclohexadienes. The ring-opening route (Scheme I) provides an opportunity for the preparation of some interesting azepine/quinone fused ring systems through oxidation of the phenol 10. We are presently investigating the formation of aromatic nitrenium ions from 2 and 11 and the formation of the azepine/quinone fused ring system from 10.

Experimental Section

Melting points were determined on a Mel-Temp capillary apparatus and are uncorrected. All chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, and were used without further purification. GC/MS were obtained on a Hewlett-Packard Model 5995C equipped with a 25-m fused silica capillary column OV101; nuclear magnetic resonance spectra were recorded on a Varian Gemini 300 (^1H, 300 MHz; ^{13}C, 75 MHz) or a Varian T60. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, TN. 5-Acetyl-10-bromo-5*H*-dibenz[*b*,*f*]azepine (6) and 1,4-dihydro-1,4-epoxy-9-acetyl-9*H*-tribenz[*b*,*d*,*f*]azepine (8) were prepared according to the literature.[8]

Preparation of 9-Acetyl-9*H*-tribenz[*b*,*d*,*f*]azepine (9) from 1,4-Dihydro-1,4-epoxy-9-acetyl-9*H*-tribenz[*b*,*d*,*f*]azepine (8) and Low-Valent Titanium. Methylene chloride (15 mL) was added dropwise to 3 mL (24 mmol) of titanium(IV) chloride at 0 °C under nitrogen. Lithium aluminum hydride (0.075 g, 2.0 mmol) and triethylamine (0.51 mL, 3.7 mmol) were added, and the mixture was refluxed for 15 min; 8 (0.20 g, 0.66 mmol) was added, and the reflux was continued for another 3 h. The reaction mixture was washed with water and dried over anhydrous sodium sulfate, and the methylene chloride was evaporated under vacuum to yield the crude product 9. The crude product was used in the next step without further purification. 9: ^1H NMR ($CDCl_3$, 60 MHz) δ 1.9 (s, 3 H), 7.3–7.8 (m, 12 H); MS *m*/*z* (relative intensity) 285 (M^+, 52), 243 (100), 215 (8).

Preparation of 9*H*-Tribenz[*b*,*d*,*f*]azepine (2) by Hydrolysis of 9-Acetyl-9*H*-tribenz[*b*,*d*,*f*]azepine (9). The crude 9-acetyl-9*H*-tribenz[*b*,*d*,*f*]azepine (9) was dissolved in 10 mL of THF. To this solution was added 0.11 g (0.99 mmol) of potassium *tert*-butoxide and 0.01 mL of H_2O.[10] The mixture was refluxed for 3 h and an aliquot removed and analyzed by GC/MS. GC/MS revealed 2 and unreacted 9. An additional 0.2 g of potassium *tert*-butoxide was added and the mixture refluxed for 48 h. GC/MS analysis indicated the reaction had gone to completion. The THF was evaporated under vacuum, and the residue was dissolved in 50 mL of methylene chloride and washed with 50 mL of 1 N sodium hydroxide. The methylene chloride solution was dried over anhydrous sodium sulfate and evaporated under vacuum, yielding 0.13 g (0.53 mmol, 79% from 8) of 9*H*-tribenz[*b*,*d*,*f*]azepine (2). See the subsequent preparation of 2 (from 6 and 12) for elemental analysis and physical and spectral properties of 2.

Ring Opening of 1,4-Dihydro-1,4-epoxy-9-acetyl-9*H*-tribenz[*b*,*d*,*f*]azepine (8) to 1-Hydroxy-9-acetyl-9*H*-tribenz[*b*,*d*,*f*]azepine (10). A suspension of 8 (1.01 g, 3.3 mmol) in 100 mL of 6 N hydrochloric acid was refluxed for 3 h and filtered. The solid was dried under vacuum to yield 0.81 g (2.7 mmol, 80% yield) of the phenol 10. The crude phenol was used in the next step without further purification. 11: ^1H NMR ($CDCl_3$, 60 MHz) δ 1.9 (s) and 2.0 (s)[11] (3 H), 5.9 (s, broad, 1 H), 7.2–7.8 (m, 11 H); MS *m*/*z* (relative intensity) 301 (M^+, 72), 259 (100), 228 (17).

Methylation and Hydrolysis of 1-Hydroxy-9-acetyl-9*H*-tribenz[*b*,*d*,*f*]azepine (10) To Form 1-Methoxy-9*H*-tribenz[*b*,*d*,*f*]azepine (11). The crude phenol 10 (0.81 g, 2.7 mmol) was placed in 10 mL of dimethyl sulfate and heated to 80–90 °C for 20 min with stirring. Aqueous sodium hydroxide (20 mL, 6 M) was added, and the reaction mixture was stirred at room temperature for 10 min and extracted with methylene chloride (3 × 20 mL). the organic layer was dried over anhydrous sodium sulfate and evaporated under vacuum to yield crude 1-methoxy-9-acetyl-9*H*-tribenz[*b*,*d*,*f*]azepine: ^1H NMR ($CDCl_3$, 60 MHz)

(9) Wong, H. N. C. *Synthesis* **1984**, 787.

(10) We have in general experienced that *N*-acetyl derivatives of dibenz[*b*,*f*]azepines and similar compounds are difficult to hydrolyze by more conventional methods (either acid or base catalyzed). Witness, for example, in this paper, the ring opening of 8 to 10 in refluxing 6 N hydrochloric acid has no effect on the amide group. We have thus resorted to the method of Gassman, employing *tert*-butoxide and water in THF for these hydrolyses. Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275.

(11) Data (unpublished) from temperature dependent NMR performed in our laboratory indicate a significant barrier to rotation about the C–N amide bond in 1b. We believe the appearance of two peaks for the methyl in the NMR of the acetyl group in both 10 and its methyl ester is due to a similar restricted rotation. The methoxy methyl of the methyl ether of 10 also has two peaks due to this restricted rotation.

δ 1.9 (s) and 2.1 (s)[11] (3H), 3.8 (s) and 3.9 (s)[11] (3H), 7.2-7.8 (m, 11 H); MS m/z (relative intensity) 315 (M^+, 66), 273 (100), 257 (26), 241 (19), 228 (22). The crude product was dissolved in 50 mL of THF to which was added 0.1 mL (6 mmol) of H_2O and 0.93 g (8.3 mmol) of potassium *tert*-butoxide, the mixture was refluxed for 24 h, and an additional 0.3 g (2.7 mmol) of potassium *tert*-butoxide was added followed by refluxing for 48 h. The THF was evaporated under vacuum and the residue taken up in 50 mL of methylene chloride and 50 mL of H_2O. The layers were separated, and the organic layer was dried over anhydrous sodium sulfate and the methylene chloride evaporated under vacuum. Column chromatography of the residue using carbon tetrachloride on 15 g of silica gel gave 0.35 g of 11 (1.3 mmol, 39% from 8): mp 157-159 °C (heptane); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.78 (s, 3 H), 5.12 (s, 1 H), 6.87 (d, J = 8.4 Hz, 1 H), 6.94 (d, J = 7.5, 1 H), 7.00 (d, J = 8.4 Hz, 1 H), 7.0-7.3 (m, 5 H), 7.38 (dd, J = 8.4 Hz, 1 H), 7.53 (d, J = 8.4 Hz, 1 H), 7.65 (d, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 55.95, 110.69, 119.36, 120.19, 122.58, 123.09, 123.83, 127.53, 127.74, 128.01, 128.38, 129.99, 132.32, 133.39, 141.44, 151.45, 151.70, 156.23; MS m/z (relative intensity), 273 (M^+, 100), 258 (12), 257 (14), 230 (9) 228 (8), 202 (5). Anal. Calcd for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.12; O 5.85. Found: C, 83.61; H, 5.87; N, 5.04; O, 5.39.

Preparation of 9*H*-Tribenz[*b*,*d*,*f*]azepine (2) from Reaction of 5-Acetyl-10-bromo-5*H*-dibenz[*b*,*f*]azepine (6) with Potassium *tert*-Butoxide and 1,3-Cyclohexadiene (12) Followed by Hydrolysis with Potassium *tert*-Butoxide and Water. 5-Acetyl-10-bromo-5*H*-dibenz[*b*,*f*]azepine (6; 3.0 g, 9.5 mmol) and 1.47 g (13 mmol) of potassium *tert*-butoxide were placed in 24 mL of 1,4-cyclohexadiene (12), and the mixture was refluxed for 21 h. The cyclohexadiene was distilled from the reaction mixture. The residue was dissolved in 20 mL of 2-methoxyethyl ether (diglyme), 2.4 g (21 mmol) of potassium *tert*-butoxide was added, and the mixture was refluxed for 18 h.[12] Water (50 mL) was added to the reaction mixture, and the mixture cooled in an ice bath to yield one large piece of black solid. The black solid was dissolved in methylene chloride, the solution dried over anhydrous sodium sulfate, and the solvent was removed under vacuum. Column chromatography of the residue using toluene on 40 g of silica gel yielded 0.89 g (3.6 mmol, 39% from 6) of 9*H*-tribenz[*b*,*d*,*f*]azepine (2): mp 220 °C (ethanol); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.29 (s, 1 H), 6.89 (d, J = 7.6 Hz, 2 H), 7.12 (dd, 2 H), 7.22 (dd, 2 H), 7.4-7.8 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 119.71, 124.09, 127.72, 128.43, 130.08, 130.15, 132.68, 139.34, 150.99; MS m/z (relative mass), 243 (M^+, 100), 215 (11), 202 (3), 189 (3), 120 (9). Anal. Calcd for $C_{18}H_{13}N$: C, 88.85; H, 5.38; N, 5.75. Found: C, 88.94; H, 5.48; N, 5.53.

If the hydrolysis was performed in refluxing THF (in place of diglyme), a mixture of 14 and 2 was obtained. No attempts were made to maximize the yield of 14. Column chromatography of this mixture using toluene on silica gel resulted in partial separation. 14: mp 158 °C from ethanol (decomposes with bubbling to 2 as evidenced by ^1H and ^{13}C NMR of decomposition product); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.65 (m, 4 H), 4.08 (s, 2 H), 4.99 (s, 1 H), 6.54 (dd, 2 H), 6.69 (d, 2 H), 7.01 (dd, 2 H), 7.08 (dd, 2 H), 7.25 (d, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 25.95, 42.55, 119.80, 123.57, 126.47, 128.02, 131.74, 134.98, 142.42, 148.41; MS m/z (relative intensity), 243 (100), 215 (12), 202 (3), 189 (4), 120 (10). Anal. Calcd for $C_{20}H_{17}N$: C, 88.52; H, 6.31; N, 5.16. Found: C, 88.28; H, 6.58; N, 5.06.

(12) The mixture was refluxed in a vessel open to the atmosphere, and water for the hydrolysis is presumably absorbed from the atmosphere.

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Fluoride Ion Promoted Reactions of α-Halo Silanes: Synthesis of Stilbenes, Epoxides, Cyclopropanes, Benzazepines, and Phthalidylisoquinolines

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Reaction of α-halo silanes 1 with CsF in DMF affords stilbenes 5. In the presence of added aldehydes, epoxides 6 are obtained, while with electron-deficient olefins the corresponding cyclopropanes 7 are formed. A similar reaction of 1a with iminium compounds 8 in HMPA leads to 2-phenyl-3-benzazepines 12, whereas 1b or 17 furnishes phthalidylisoquinolines 15.

We have initiated studies on synthetic utilization of organosilanes having suitably placed electrofugic groups.[1] Reactions of such substrates with a negatively charged silaphile, like F^- or OR^-, can afford carbanion equivalents of reactive intermediates; e.g., carbenoids may be obtained from α-halo silanes. This approach is useful for halogenated and vinylcarbenes,[2] but with other precursors (1, $R^1 = R^2 \neq$ halogen or doubly bonded carbon) side reactions, shown in Scheme I, tend to ingress to a large extent.[3,4] In fact, our attempts to generate and trap phenylcarbenes in this manner were unsuccessful until it was found that dipolar aprotic solvents particularly favor the desired reaction course.[1] We now report these results in detail along with a significant extension wherein iminium compounds are used for capturing the reactive intermediates.

Results and Discussion

Reaction of 1a with CsF (1.5 mmol) in solvents like DME and THF led only to protodesilylation, but in DMF the *trans*-stilbene (5a) was formed in 89% yield. The product 5a can arise by dimerization of carbene 4a or through reaction of the anion 3a with the halide 1a as

(1) Kessar, S. V.; Singh, P.; Venugopal, D. *Ind. J. Chem.* **1987**, *26B*, 605. Kessar, S. V. *Pure Appl. Chem.* **1990**, *62*, 1397.

(2) (a) Stang, P. J.; Fox, D. P. *J. Org. Chem.* **1977**, *42*, 1667. (b) Cunico, R. F.; Chou, B. B. *J. Organomet. Chem.* **1978**, *154*, C45.

(3) (a) Damrauer, R.; Yost, V. E.; Danahey, S. E.; O'Connell, B. K. *Organometallics* **1985**; *4*, 1779. (b) Damrauer, R.; Danahey, S. E.; Yost, V. E. *J. Am. Chem. Soc.* **1984**, *106*, 7633. (c) Noll, J. E.; Speier, J. L.; Daubert, B. F. *J. Am. Chem. Soc.* **1951**, *73*, 3867. (d) Speier, J. L.; Daubert, B. F.; McGregor, R. R. *J. Am. Chem. Soc.* **1948**, *70*, 1117. (e) With α-iodosilanes a different pathway involving alkyl group migration from silicon to iodine has been proposed; Chakraborty, T. K.; Reddy, G. V. *J. Chem. Soc., Chem. Commun.* **1989**, 251.

(4) (a) Corriu, R. J. P.; Guerin, C. J. *J. Organomet. Chem.* **1980**, *198*, 231. (b) Anh, N. T.; Minot, C. *J. Am. Chem. Soc.* **1980**, *102*, 103.

0022-3263/91/1956-3908$02.50/0