Reaction of 5-Acetyl-10,11-didehydro-5*H*-dibenz[*b*,*f*]azepine with Pyrrole, *N*-Methylpyrrole, Imidazole and *N*-Methylimidazole: Cycloaddition Versus Michael Addition

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Reaction of 5-acetyl-10-bromo-5*H*-dibenz[*b*,*f*]azepine **1** with potassium *t*-butoxide results in the reactive intermediate 5-acetyl-10,11-didehydro-5*H*-dibenz[*b*,*f*]azepine (**2**). The intermediate **2** reacts with *N*-methylpyrrole to give a mixture of the Michael addition adduct 10-(2-*N*-methylpyrrolyl)-5*H*-dibenz[*b*,*f*]azepine (**9**) and the Diels-Alder/retro Diels Alder adduct 8*H*-(*N*-methylpyrrolo[3,4-*d*]dibenz[*b*,*f*]azepine (**8a**). Reaction of **2** with pyrrole gives a mixture of two Michael addition adducts 10-(1-pyrrolyl)-5*H*-dibenz[*b*,*f*]azepine (**16**) and 10-(2-pyrrolyl)-5*H*-dibenz[*b*,*f*]azepine (**18**). Reaction of **2** with imidazole results in the Michael addition adduct 10-(1-imidazolyl)-5*H*-dibenz[*b*,*f*]azepine (**21**).

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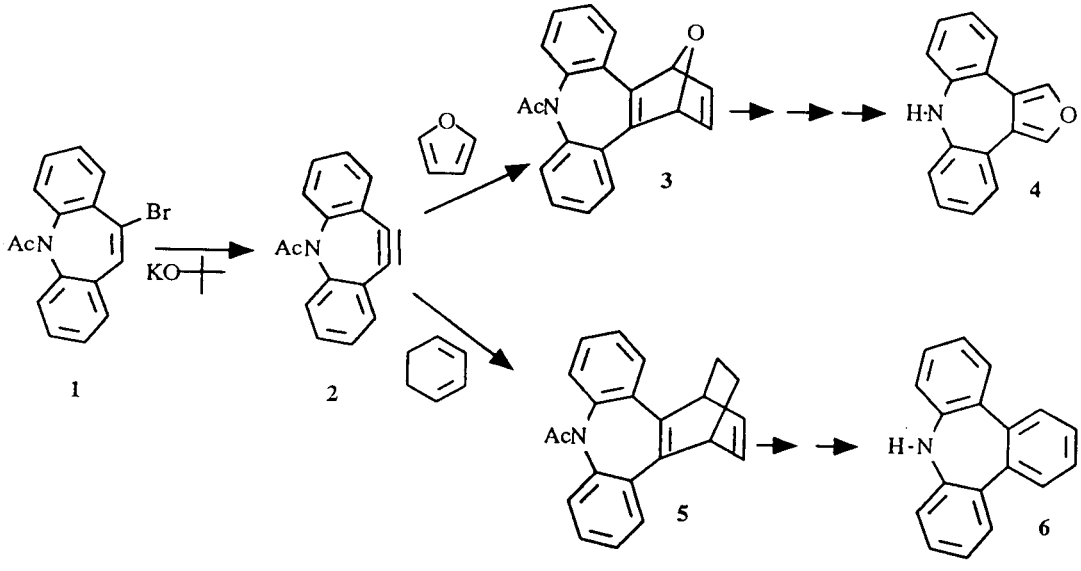
Previously it has been shown that the reactive intermediate 5-acetyl-10,11-didehydro-5*H*-dibenz[*b*,*f*]azepine (**2**), generated by dehydrohalogenation of 5-acetyl-10-bromo-5*H*-dibenz[*b*,*f*]azepine (**1**) with potassium *tert*-butoxide, reacts as a dienophile in Diels-Alder reactions with furan [1] and cyclohexadiene [2] (Scheme I). The Diels-Alder adducts, **3** and **5**, from these reactions can be converted to 8*H*-furo[3,4-*d*]dibenz[*b*,*f*]azepine (**4**) [3] and 9*H*-tribenz-[*b*,*d*,*f*]azepine (**6**) [2]. In this study we report on the reactions of **2** with the dienes *N*-methylpyrrole (**7**), pyrrole (**13**), imidazole (**19**) and *N*-methylimidazole. Our interest in these reactions was in part motivated by the potential synthesis of the tetracyclic azepine **8**. Intense interest in this heterocyclic system was displayed in the past because of its central nervous system depressant activity [4].

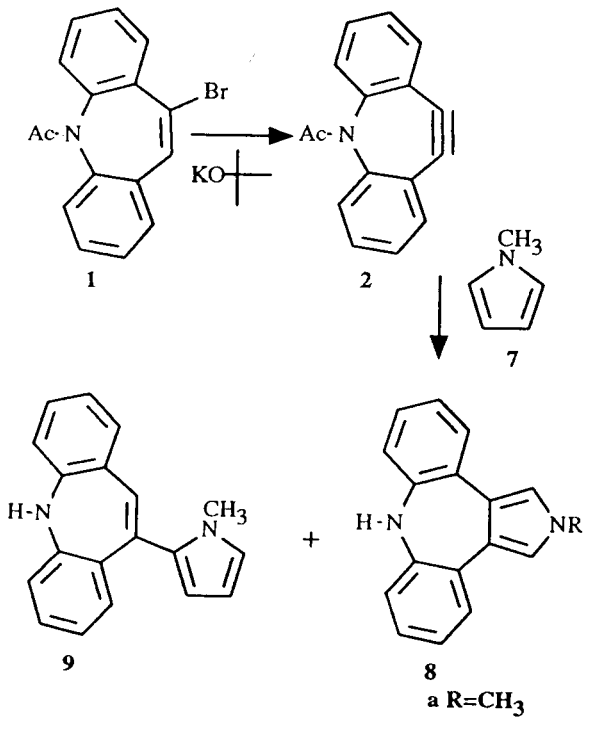
Generation of **2** (by reaction of **1** with potassium *tert*-butoxide) in refluxing *N*-methylpyrrole produces 8*H*-*N*-methylpyrrolo[3,4-*d*]dibenz[*b*,*f*]azepine (**8a**) (31%) and 10-(2-*N*-methylpyrrolyl)-5*H*-dibenz[*b*,*f*]azepine (**9**) (26%) (Scheme II). Formation of **8a** likely occurs *via* a three step process (Scheme III) involving a Diels-Alder reaction of **2** with **7** to produce **10**, followed by a retro Diels-Alder reaction of **10** to produce **11** and ethylene, and finally hydrolysis to yield **8a**. We believe compound **9** is the result of a Michael type addition between **2** and **7** (as shown in Scheme IV) followed by hydrolysis.

Reaction of **1** with potassium *tert*-butoxide in refluxing pyrrole (**13**) produces a mixture of addition products **16** (46%) and **18** (25%) (Scheme V). We suggest that the reaction of the intermediate **2**, with pyrrole initially produces

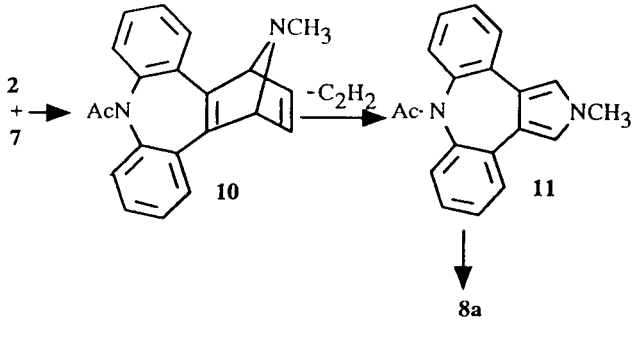
Scheme I



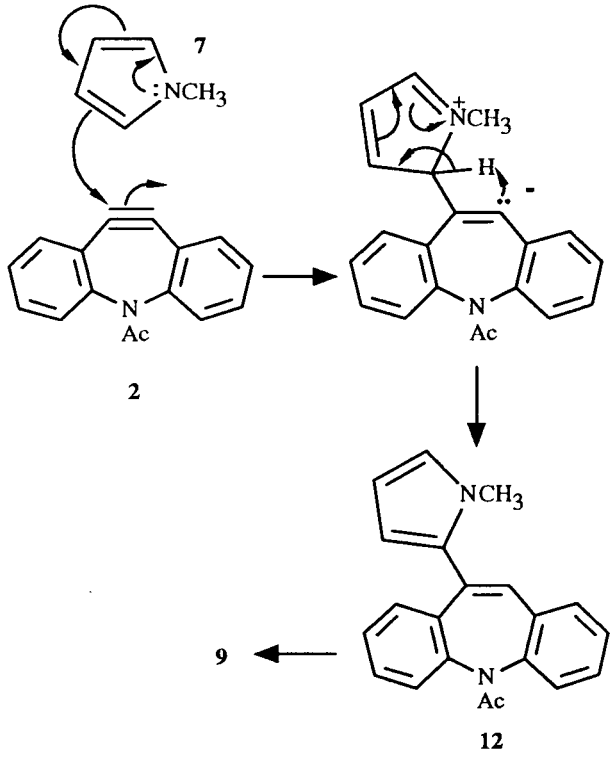
Scheme II



Scheme III



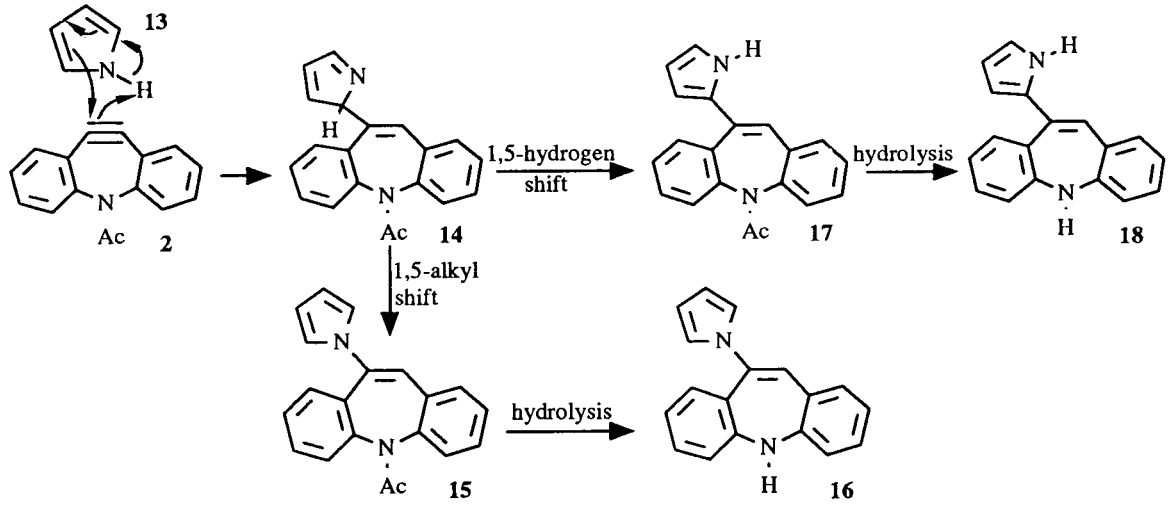
Scheme IV



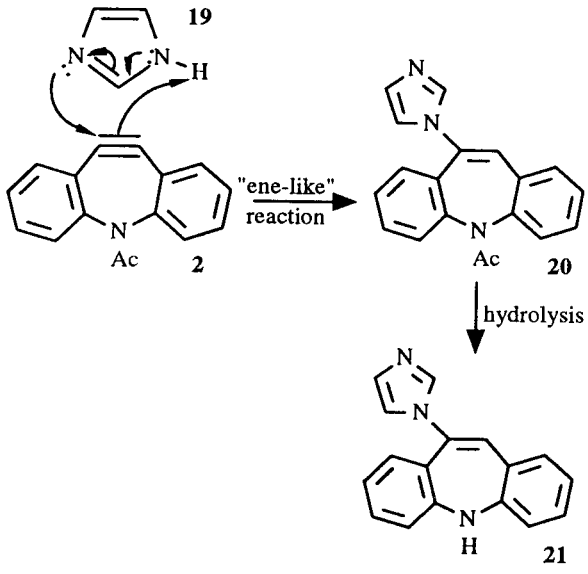
14 by a Michael addition. Regeneration of the aromaticity of the pyrrole ring can take place by two competing pathways: rearrangement of **14** *via* a 1,5-hydrogen shift produces **17**; the competing rearrangement of **14** by a 1,5-alkyl shift results in the formation of **15**. Subsequent hydrolysis of **15** and **17** under the reaction conditions produces **16** and **18**.

Generation of **2** in imidazole (**19**) at 105° results in the formation of **21** (67%). We believe the mechanism of this reaction occurs *via* an ene like reaction as shown in Scheme VI.

Scheme V



Scheme VI



Reaction of **1** with potassium *tert*-butoxide in *N*-methylimidazole at 100-110° allows for a cursory evaluation of the potential of this imidazole as a diene. Monitoring the reaction by gc/ms indicates that the Diels-Alder/retro Diels-Alder adduct **11** forms in moderate amounts however unlike the *N*-methylpyrrole reaction, further reaction does not lead to the hydrolysis product **8a** but to decomposition to numerous unidentified products.

Others have found that the electron withdrawing acetyl group makes *N*-acetylpyrrole a much better diene in Diels-Alder reactions than pyyrole or *N*-alkylpyrroles [5]. In light of this fact we believed *N*-acetylpyrrole and *N*-acetylimidazole might serve as reactive dienes in Diels-Alder reactions with **2**. Since *N*-acetylimidazole is commercially available we performed an evaluation of this molecule first. However we found that reaction of acetylimidazole with potassium *tert*-butoxide resulted in rapid cleavage of the amide to yield imidazole. It is likely that *N*-acetylpyrrole would react in a similar manner.

These results indicate that the nitrogen heterocycles with an available N-H (**13** and **19**) react with **2** to give exclusively Michael addition. However, *N*-methylpyrrole **1** reacts with **2** *via* both cycloaddition and Michael addition resulting in a mixture of **8** and **9**.

It is interesting to note that in all cases (that is reaction of **1** with potassium *tert*-butoxide and **7**, **13** or **19**) hydrolysis of the azepine acetyl amide to yield the free amine occurs under these reaction conditions. This is in stark contrast with the reactions in cyclohexadiene [3] and furan [1,2]. We found the *N*-acetyl amides of **4** and **6** to be very resistant to hydrolysis even using Gassman's method for hydrolysis of amides [6]. Gassman's method employs potassium *tert*-butoxide in THF as the solvent. From our results it appears that nitrogen heterocycles as solvents in combination with potassium *tert*-butoxide may in general provide a facile method for difficult to hydrolyse amides.

EXPERIMENTAL

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. The 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 (^{1}H, 300 MHz; ^{13}C, 75 MHz) and done in deuteriochloroform. Elemental analyses were carried out by Oneida Research Services, Inc., Whitesboro, NY. 5-*H*-Acetyl-10-bromodibenz[*b*,*f*]azepine (**1**) was prepared according to the literature [1].

Preparation of 8*H*-(*N*-Methylpyrrolo)[3,4-*d*]dibenz[*b*,*f*]azepine (**8a**) and 10-(2-*N*-Methylpyrrolyl)-5*H*-dibenz[*b*,*f*]azepine (**9**) from the Reaction of 5-Acetyl-10-bromo-5*H*-dibenz[*b*,*f*]azepine (**1**) with Potassium *tert*-Butoxide and *N*-Methylpyrrole (**7**).

Compound **1** (500 mg, 1.56 mmoles) and potassium *tert*-butoxide (211 mg, 1.88 mmoles) in 7 ml of **7** were refluxed. The reaction was monitored by gc/ms. Formation of **11** and **12**, and subsequent hydrolysis to **8a** and **9** is observed. An additional 500 mg of potassium *tert*-butoxide is added in portions over a two day period until the reaction was complete. *N*-Methylpyrrole is evaporated under vacuum and the residue was dissolved in 30 ml of methylene chloride and washed with 5% sodium thiosulfate (1 x 20 ml) and water (1 x 20 ml). The methylene chloride solution was dried over sodium sulfate and evaporated to yield 506 mg of residue. Column chromatography of the residue on 5 g of silica gel with toluene followed by methylene chloride yields 114 mg (0.50 mmole, 31%) of **8a**, mp 270° dec; ^{1}H nmr: δ 3.73 (s, 3H, CH_3), 5.20 (s, 1H, NH), 6.78 (s, 2H), 6.82 (d, 2H), 6.95 (t, 2H), 7.07 (t, 2H), 7.32 (d, 2H); ^{13}C nmr: 36.5, 119.5, 120.1, 122.6, 123.1, 127.0, 127.2, 127.6, 146.4; ms: m/z 246 (100, M$^+$), 231 (12), 204 (16), 123 (6).

Anal. Calcd. for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 83.09; H, 5.71; N, 11.19.

Further elution produced 123 mg (0.42 mmole, 26%) of crude **9**; ^{1}H nmr: [7] 3.29 (s, 1.5H), 3.72 (s, 1.5H), 5.2 (s, 1H, NH), 6.2 (m, 1H), 6.3 (m, 1H), 6.7-7.3 (m, 11H); ^{13}C nmr: 34.6, 36.5, 107.2, 109.4, 119.3, 119.5, 120.1, 122.9, 123.1, 123.4, 123.5, 127.0, 127.2, 127.6, 128.0, 129.1, 129.6, 130.2, 130.5, 133.7, 135.3, 146.2, 148.6; ms: m/z 273 (20, M + 1), 272 (100, M$^+$), 271 (65), 270 (16), 256 (18), 255 (18), 204 (5), 193 (3), 135 (5), 128 (7). Various attempts to purify **9** did not lead to an analytically pure sample.

Preparation of 10-(1-Pyrrolyl)-5*H*-dibenz[*b*,*f*]azepine (**16**) and 10-(2-Pyrrolyl)-5*H*-dibenz[*b*,*f*]azepine (**18**) from the Reaction of 5-Acetyl-10-bromo-5*H*-dibenz[*b*,*f*]azepine (**1**) with Potassium *tert*-Butoxide and Pyrrole (**13**).

Compound **1** (303 mg, 0.96 mmole) and potassium *tert*-butoxide (160 mg, 1.4 mmoles) in 5 ml of **13** were refluxed for 20 hours; additional potassium *tert*-butoxide (160 mg, 1.4 mmoles) was added and reflux was continued for another 2 hours; additional potassium *tert*-butoxide (480 mg, 4.2 mmoles) was added and reflux was continued for another 12 hours. Monitoring of the

reaction mixture with gc/ms indicated that formation of **16** and **18** is complete. During the monitoring process the decrease in **1** with concomitant formation of the *N*-acetylamides **15** and **17** followed by their hydrolysis to **16** and **18** is observed. Pyrrole is evaporated under vacuum, and the residue was dissolved in 50 ml of methylene chloride and washed with water (2 x 50 ml). The methylene chloride solution was dried over sodium sulfate and evaporated under vacuum to yield 310 mg of residue. Column chromatography of the residue on 5.5 g of silica gel with toluene yields 113 mg (0.44 mmole, 46%) of **16**, mp 141° (ethanol); ^{1}H nmr: δ 5.2 (broad s, 1 H, exchanges with deuterium oxide), 6.3 (s, 2 H), 6.6-7.3 (m, 11 H); ^{13}C nmr: 109.1, 119.6, 120.4, 121.9, 123.5, 123.7, 124.9, 127.9, 128.1, 128.5, 129.2, 129.4, 130.4, 130.8, 148.7, 148.9; ms: m/z 259 (18), 258 (M^+, 100), 257 (71), 256 (31), 255 (12), 243 (3), 230 (7), 204 (4), 190 (14), 179 (15), 165 (17), 128 (25); hrms Calcd. for $C_{16}H_{14}N_2$: 258.1157, found 258.1157.

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.84. Found: C, 83.84; H, 5.44; N, 10.74.

Further elution with toluene yielded 62 mg (0.24 mmole, 25%) of **18**, mp 238° dec (from toluene); ^{1}H nmr: [7] δ 5.1 (broad s, 1H, exchanges with deuterium oxide), 6.3 (s, 1H), 6.4 (s, 1H), 6.8-7.3 (m, 10H), 8.2 (broad s, 1H, exchanges with deuterium oxide); ^{13}C nmr: 104.3, 104.8, 113.4, 115.0, 116.4, 118.9, 119.1, 123.5, 124.2, 125.4, 125.6, 125.7, 126.0, 126.4, 129.0, 131.0, 144.9, 145.9; ms: m/z 259 (19), 258 (M^+, 100), 257 (69), 256 (10), 255 (17), 230 (7), 228 (6), 227 (3), 204 (3), 180 (3), 128 (9).

Anal. Calcd. for $C_{18}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.84. Found: C, 83.24; H, 5.60; N, 10.50.

Preparation of 10-(1-Imidazolyl)-5*H*-dibenz[*b*,*f*]azepine (**21**) from the Reaction of 5-Acetyl-10-bromo-5*H*-dibenz[*b*,*f*]azepine (**1**) with Potassium *tert*-Butoxide and Imidazole (**19**).

Compound **1** (202 mg, 0.64 mmole), potassium *tert*-butoxide (174 mg, 1.55 mmoles) and **19** (1.0 g) were heated to 100-105° for two days during which time the reaction was monitored (by gc/ms) for formation of **21** and an additional 168 mg (1.50 mmoles) of potassium *tert*-butoxide was added. The mixture was allowed to cool and the resulting solid is combined with 15 ml of water and stirred. The resulting suspension was filtered leaving 105 mg (0.41 mmole, 64%) of **21**, mp 186° dec; ^{1}H nmr δ 5.25 (s, 1H, NH), 6.5-7.3 (m, 11H), 7.24 (s, 1H); ^{13}C nmr [7] 115.4, 115.7, 116.2, 119.3, 119.4, 119.7, 123.0, 123.4, 124.0, 125.3, 125.7, 126.3, 126.9, 132.4, 133.1, 144.5, 144.8; ms: m/z 260 (20), 259 (M^+, 100), 231 (12), 204 (18), 190 (14), 180 (56), 165 (22); hrms Calcd. for $C_{17}H_{13}N_3$: 259.1109. Found: 259.1113.

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REFERENCES AND NOTES

[1] B. P. Das and D. W. Boykin, *J. Med. Chem.*, **14**, 1839 (1971).

[2] H. C. Axtell, W. M. Howell, L. G. Schmid and M. C. Cann, *J. Org. Chem.*, **56**, 3906 (1991).

[3] K. B. McHugh, W. M. Howell, J. J. Doran and M. C. Cann, *J. Heterocyclic Chem.*, **27**, 1839 (1990).

[4] B. Renfroe, C. Harrington and G. R. Proctor, The Chemistry of Heterocyclic Compounds. Azepines, Vol **48**, Part 1, A. Rosowsky, ed, John Wiley and Sons, New York 1989, p 411 and references therein.

[5] K. Saito, K. Ito and K. Takahashi, *Heterocycles*, **29**, 2135 (1989) and references therein.

[6] P. G. Gassman, P. K. G. Hodgson and R. J. Balchunis, *J. Am. Chem. Soc.*, **98**, 1275 (1976).

[7] Both the ^{1}H and ^{13}C nmr of **9** and **18**, and the ^{13}C nmr of **21** are complicated by the hindered rotation about the pyrrole (or imidazole) and azepine rings.