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GENERATION AND CYCLOADDITION REACTIONS OF INDOLE-2,3-QUINODIMETHANES

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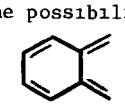
ABSTRACT: N-methyl and N-*tert*-butoxycarbonylindole-2,3-quinodimethanes (2 and 3) have been generated and observed to undergo intermolecular cycloaddition reactions with dienophiles.

The utilization of orthoquinodimethane intermediates, e.g. 1, for the annulation of aromatics is now of practical importance and has been applied to efficient syntheses of alkaloids, steroids, and terpenes.[1] Extension of this method to heteroaromatic systems would be significant. For example, many polycyclic organic compounds containing the indole nucleus possess important pharmacological properties and have been target compounds for synthetic chemists.[2] Development of the orthoquinodimethane method for the synthesis of polycyclic indoles would provide a new approach to this class of compounds.

A survey of the literature reveals that due to the types of reactions employed, few of the routes leading to precursors of 1 will be applicable to the synthesis of their heteroaromatic analogs [3]

Magnus has recently reported the intramolecular cycloadditions of indole-2,3-quinodimethanes which he has utilized in an efficient and elegant approach to Aspidospermidine.[4] This report has prompted us to disclose our preliminary results concerning the generation and intermolecular cycloadditions of the indole-2,3-quinodimethanes 2 and 3. We were intrigued with the possibility of generating indole-2,3-quinodimethane intermediates 2 and 3 via fluoride



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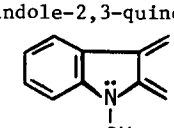

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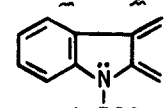

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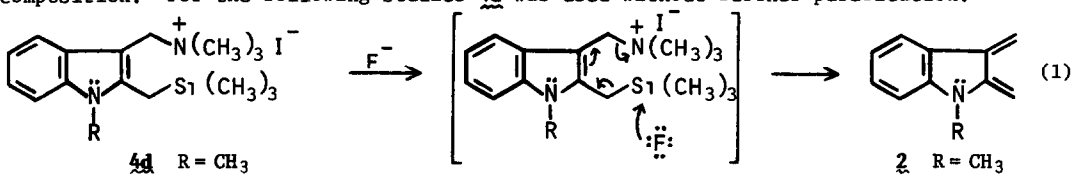
ion induced 1,4 elimination from the ammonium salts 4d and 5c (eq. 1).[5] The salt 4d was prepared beginning with the Mannich reaction of 1,2-dimethylindole (AcOH, $NH(CH_3)_2$, CH_2O),[6] which gave 4a in 65% yield, b.p. 108-118°C (0.04-0.07 mm Hg) Lithiation ($BuLi/Et_2O$, 10-20°C, 15 min) gave the colorless precipitate 4b which was quenched (1.1 equiv $ClSi(CH_3)_3$, -78°C, 3 h, then H_2O) to give 4c in 92% yield (97% purity by GLC and ^1H NMR). Quaternization[7] of 4c (1.1 equiv CH_3I in EtOH, 0°C, 10 min followed by r.t., 1 h) gave the salt 4d in 89% yield. The

salt contained impurities and attempted purification by recrystallization resulted in its decomposition. For the following studies 4d was used without further purification.



(1)

4d R = CH_3
5c R = t-BOC

2 R = CH_3
3 R = t-BOC

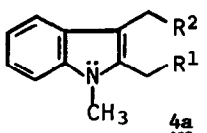
Studies using the ammonium salt 5c were motivated by two considerations· 1) any important synthesis of indoles requires a removable N-substituent; 2) an electron withdrawing N-substituent should stabilize both the salt 5c (relative to 4d) and the intermediate 3. In view of our earlier work with N-protected indoles and pyrroles,[8] we decided to use the N-*tert*-butoxycarbonyl group in the present studies.

The salt 5d was prepared as follows. The Mannich reaction of 2-methylindole (AcOH, $HN(CH_3)_2$, CH_2O),[6] gave, after recrystallization (Et_2O/Hexanes), a 75% yield of 2-methylgrammine as a pale green solid, m.p. 115-120°C [lit.[6] 116-117°C], which was pure by ^1H NMR and TLC. Acylation using 1.1 equiv of sodium dimsylate in DMSO followed by t-BOC azide in ether gave, after purification by silica gel chromatography, a 71% yield of 5a as an oil Lithiation of 5a at the methyl group (1.02 equiv of LTMP/THF,[8] -78°C, 37 min) gave a red-orange solution which was quenched (1.1 equiv of $ClSi(CH_3)_3/Et_2O$, inverse addition, -78°C, 4 h) yielding 73% of 5b after silica gel chromatography. Quaternization[7] (1.1 equiv CH_3I/EtOH, 0°C, 30 min; r.t. 5 h) proceeded smoothly affording 82% of the salt 5c.

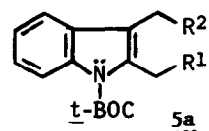
Preliminary experimentation with 4d was undertaken and proved only moderately encouraging. Treatment of an acetonitrile solution of 4d and N-phenylmaleimide with TBAF (1.0 equiv, slow addn., r.t. 3 h) resulted in a 35% yield of the 9-methyltetrahydrocarbazole 6 (m.p. 134°C) after laborious purification by thick-layer chromatography and recrystallization (Et_2O/Pentane). A similar reaction of 4d with 40 equiv of methylacrylate gave a mixture of at least two products (by TLC) in low yield. Examination of the deep red crude by ^1H NMR revealed the presence of two carbomethoxy groups with resonances at 3.46 δ and 3.64 δ.

The results with the *tert*-butoxycarbonyl derivative 5c were more encouraging. Treatment of an acetonitrile solution of 5c and 1 equiv of N-phenylmaleimide gave, after silica gel chromatography and recrystallization (Et_2O/Pentane), a 57% yield of tetrahydrocarbazole 7 as colorless crystals (m p. 113-114°C). A similar reaction with 1 equiv of methylacrylate gave a single compound whose structure we have tentatively assigned as 8 (35%, m p. 168-170°C) The enamide structure was verified by removal of the protecting groups to give indolenine 11 while the regiochemistry of the reaction is assumed to be as shown due to the regiochemistry of the subsequent reaction with excess methylacrylate [9] That the dimer 8 is indeed derived from the reaction of the putative intermediate 3 with itself was shown by treatment of an acetonitrile solution of 5c with TBAF (r.t. 3 h) TLC analysis showed that the reaction was complete after the addition of TBAF (5 min) attesting to the high reactivity of the proposed intermediate 3. The spectral data for the product obtained (80% yield) were identical to that found for the previously isolated 8 The use of 40 equiv of methylacrylate resulted in the

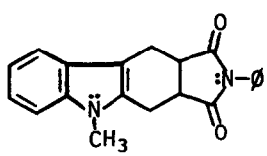
isolation of a 3:1 mixture of **9a** and **9b** as a clear oil in 63% yield after silica gel chromatography (**8** was isolated in 16% yield). The mixture **9** was homogeneous using CH_2Cl_2/Hexanes or EtOAc/Hexanes as solvents for TLC analysis but ^{13}C NMR revealed the presence of two regioisomers with ester carbonyl resonances for **9a** and **9b** in the above mentioned ratio. Removal of the *tert*-butoxycarbonyl group (CH_3ONa/CH_3OH in THF, 0-7°C, 3 h) gave a gum which was a 3:1 mixture of **10a** and **10b** (^{13}C NMR) in 82% yield. Recrystallization (Et_2O/Hexanes) afforded a 50% yield of **10a**, m.p. 110-112°C [lit.[12a] 111-114°C]. The residue from the mother liquors was a 1:1 mixture of **10a** and **10b** by ^{13}C NMR. This allowed the assignment of **9a** as the major isomer of **9**. That the mixture **10** was composed only of **10a** and **10b** was established as follows. The compound **10b** was obtained by an independent synthesis.[12b] The ^{13}C NMR of a mixture of pure **10a** and pure **10b** gave only the resonances displayed by the ^{13}C NMR spectra of both the reaction mixture of **10a** and **10b** prior to recrystallization and the residue from the previously mentioned recrystallization.[13]



4a $R^1 = H$, $R^2 = N(CH_3)_2$
b $R^1 = Li$, $R^2 = N(CH_3)_2$
c $R^1 = Si(CH_3)_3$, $R^2 = N(CH_3)_2$
d $R^1 = Si(CH_3)_3$, $R^2 = \overset{+}{N}(CH_3)_3 I^-$



5a $R^1 = H$, $R^2 = N(CH_3)_2$
b $R^1 = Si(CH_3)_3$, $R^2 = N(CH_3)_2$
c $R^1 = Si(CH_3)_3$, $R^2 = \overset{+}{N}(CH_3)_3 I^-$



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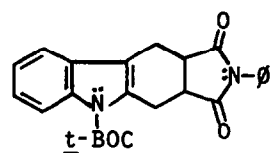

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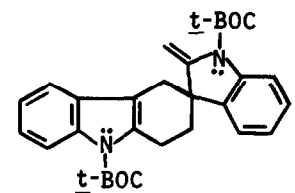

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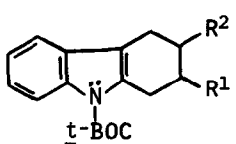
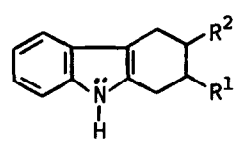
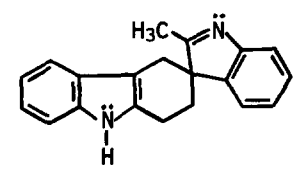


9a $R^1 = CO_2CH_3$, $R^2 = H$
b $R^1 = H$, $R^2 = CO_2CH_3$



10a $R^1 = CO_2CH_3$, $R^2 = H$
b $R^1 = H$, $R^2 = CO_2CH_3$



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In summary, we have demonstrated the generation, reactivity patterns and the utilization of indole-2,3-quinodimethane intermediates to give substituted tetrahydrocarbazoles. Other heteroaromatic orthoquinodimethane intermediates will be the subject of future studies.

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9. Ammonium salts **4d** and **5c** were prepared on a 1-10 gram scale. All cycloadditions were performed on a 1-2 mmol scale. Deprotection experiments were performed on a 0.015-1.0 mmol scale. All compounds had IR, ^{1}H NMR and low and high resolution mass spectra consistent with the assigned structures We assume compounds **6** and **7** to be the cis isomers. A simple Huckel calculation for **2** and **3** gives HOMO symmetry that predicts suprafacial addition of the dienophile to the diene system of **2** and **3**. This is consistent with the "cis" principle for cycloadditions of this type.[14] Compound **8**: IR ($CDCl_3$) 3050, 2980, 2925, 2850, 1740, 1718, 1645, 1604, 1484, 1465, 1400, 1365, 1330, 1295, 1255, 1235, 1155, 1095, 1022, 995 cm^{-1}, ^{1}H NMR ($CHCl_3$ 80 MHz) δ 1.63 (s, 9 H), 1.65 (s, 9 H), 1.80-2 00 (t, 2 H, J = 6 Hz), 2.65-2.95 (br t, 2 H, J = 6 Hz), 3.35 (br s, 2 H), 4.68 (d, 1 H, J = 1 3 Hz), 5 73 (d, 1 H, J = 1.3 Hz), 6.65-7.00 (m, 2 H), 7.00-7.50 (m, 4 H), 7 75-7.85 (d,1 H, J = 8 Hz), 8.00-8 15 (br t, 1 H, J = 5 Hz), ^{13}C NMR ($CDCl_3$, 20 MHz), δ 154.1, 151 9, 150.6, 141.1, 136.5, 136.3, 134.4, 129.2, 128 0, 124.0, 123 4, 123.2, 122.8, 118.0, 116 3, 115.7, 93 5, 83.7, 82.7, 47.1, 38.3, 35 4, 28.5, 28.4, 18 2, low resolution mass spectrum m/e (relative intensity), 487 (1), 486 (3), 386 (7), 316 (9), 287 (7), 286 (27), 285 (7), 271 (23), 188 (8), 187 (52), 186 (8), 145 (7), 144 (37), 143 (100), 142 (7), 128 (8), 115 (12), 100 (7), 57 (50) Cleavage of the carbamate moieties,[10] (8 equiv of CH_3Li/THF-Et_2O, inverse addition, -10 to -7°C, 51 min), followed by rapid workup and crystallization from CH_2Cl_2 gave a 45% yield of a pale yellow solid (mp 257-259°C) which was shown to be the major product (TLC, ^{1}H NMR of crude and purified material). The spectral data are consistent with the indolenine structure **11**.[11] Had addition occurred at the enecarbamate moiety the resulting 3-methyleneindoline would exhibit ^{1}H NMR resonances at ca 4 90 δ and 5 40 δ for the remaining exomethylene unit.[11] The ^{1}H NMR shows no olefinic resonances The relevant spectral data are listed below. IR ($CDCl_3$) 3575, 3520, 3200, 3065, 2945, 2860, 1600, 1585, 1540, 1480, 1462, 1438, 1385, 1370, 1340, 1315, 1260, 1245, 1215, 1162, 1145, 1015 cm^{-1}, ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.40-1.75 (m, 2 H), 2 35 (s, 3 H), 2 00-2 50 (m, 2 H), 2 80-3.25 (m, 2 H), 7 00 (d, 2 H, J = 5 Hz), 7.05-7 40 (m, 4 H), 7 45-7 70 (m, 2 H), 7 83 (br s, 1 H), low resolution mass spectrum (70 ev) m/e (relative intensity), 287 (3), 286 (13), 144 (26), 143 (100), 142 (7), 125 (3), 128 (3), 120 (4), 115 (8), 100 (6)

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