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Inverse Electron Demand Diels-Alder Reactions of Indole V. Reactions of 3-Substituted Indoles with Heteroaromatic Azadienes.

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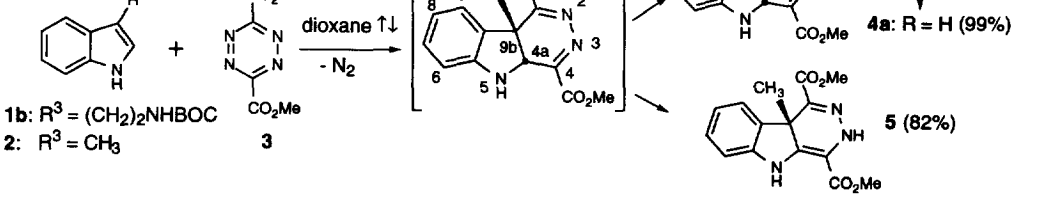
Abstract: The inverse electron demand Diels-Alder reactions of 3-substituted indoles with 1,2,4-triazines and 1,2,4,5-tetrazines proceeded in excellent yields both inter- and intramolecularly. The cycloaddition of tryptophan with a tethered 1,2,4-triazine produced a diastereomerically pure cycloadduct. Copyright © 1996 Elsevier Science Ltd

Considerable work amply demonstrates the ability of indole to serve as a 2π-component in a variety of cycloadditions.[1] Following preliminary studies,[2] we have utilized indole as the electron-rich dienophilic unit in intramolecular inverse electron demand Diels-Alder reactions to construct the canthine skeleton,[3] which was subsequently oxidized to the canthin-6-one alkaloidal system,[4] as well as to prepare other β-carbolines.[5]

Cycloadditions of dienophilic 3-substituted indoles[6] such as tryptophan and tryptamine offer a means to heteroannulate a non-aromatized ring onto the 2,3-double bond of the indole nucleus as a step to forming the Aspidosperma alkaloidal skeleton. We now report preliminary results which confirm the dienophilicity of 3-substituted indoles and probe this chemistry in both inter- and intramolecular fashion. Initial work began with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate [**3**], one of the more reactive electron deficient azadienes.[7]

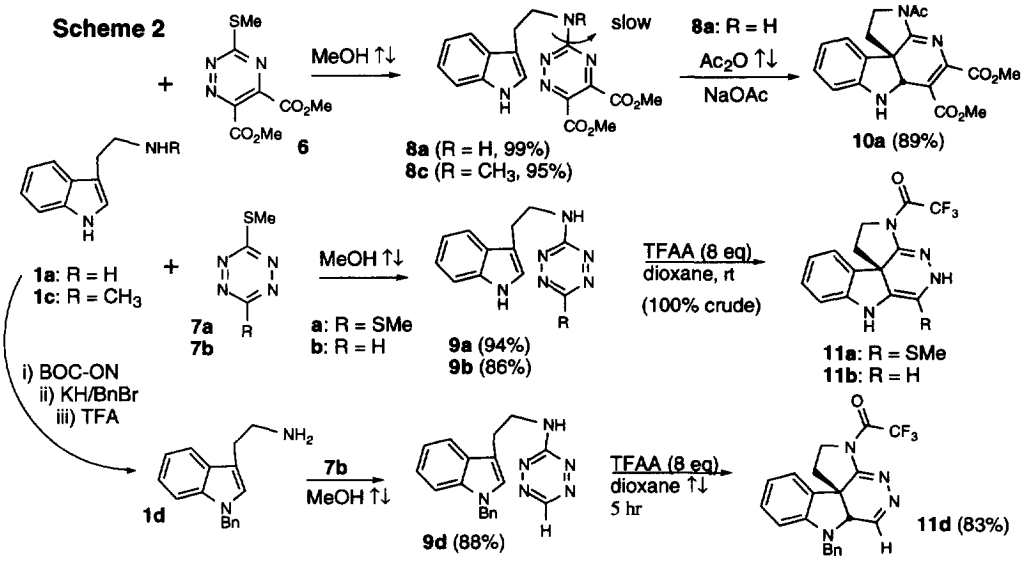
The reactions of N$^{\omega}$-BOC–tryptamine [**1b**] and skatole [**2**] with **3**[8] in refluxing dioxane (101 °C, 3 hr) provided cycloadducts **4b** and **5**, respectively, in excellent yields (80% and 82%, Scheme 1). The structure of **4b** was difficult to assess due to the presence of slowly interconverting rotamers.[9] Deprotection of **4b** produced **4a** (TFA, 99+%), whose NMR spectra were free of the complications of interconverting rotamers. The appearance of the individual protons of both methylene pairs of the original tryptamine side chain as widely distinct resonances (δ 1.97, 2.40, 3.23, and 3.46, all 1H m's),[10] along with the relatively low field resonance (δ 78.5) assignable to the C1 aminal carbon[11] suggested that cyclization to a fourth ring had occurred. Coupling between the H11 protons and C1 (δ 78.5) in the HMBC spectrum, confirmed the D-ring cyclization in the adduct.[12] The ^{1}H and ^{13}C NMR spectra of **5** revealed the 3,9b-dihydro-5*H*-pyridazino[4,5-*b*]indole structure.[13] These cycloadditions confirmed the ability of 3-substituted indoles to participate in inverse electron

Scheme 1



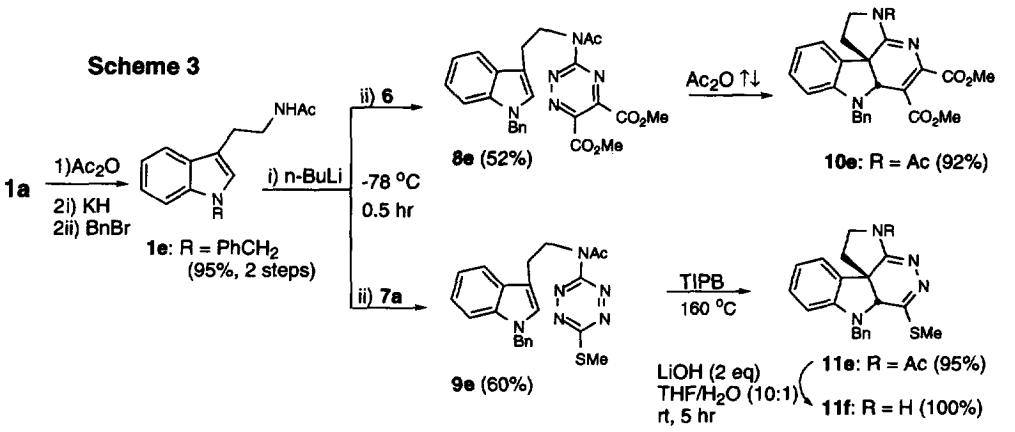
demand Diels-Alder reactions and the stability of the resultant cycloadducts.[14]

Our attention then turned to 1,2,4-triazines and 1,2,4,5-tetrazines directly tethered to the tryptamine [**1a**] amino group (Scheme 2). 3-Thiomethyltriazine **6**,[15] as well as 3-thiomethyltetrazines **7a**[16] and **7b**,[17] underwent displacements with **1a** in refluxing MeOH to produce tethered triazine **8a** and tetrazines **9a-b**. Neither **8a** nor **9a-b** produced cycloadducts upon refluxing in any solvent, even at 232 °C (triisopropylbenzene, TIPB), presumably due to the electron donation from the tethering nitrogen into the azadiene ring which raises the diene LUMO beyond the reactive level. This donation was evidenced by the observation of rotamers in the ^{1}H NMR spectra of the triazine **8a** due to slow rotation about the tethering linkage. However, refluxing **8a** in acetic anhydride (138 °C, NaOAc 10 eq)[18] produced cycloadduct **10a** (89%) with the tethering nitrogen acetylated. In contrast, refluxing **8c** (prepared from N$^{\omega}$-methyltryptamine **1c**) in acetic anhydride (or any other solvent) with the tethering amino group methylated did not produce a cycloadduct. Even more remarkable, simply stirring **9a-b** with trifluoroacetic anhydride (TFAA, 8 eq. in dioxane) at room temperature (2-3 hr) produced cycloadducts **11a-b** in quantitative crude yields, which were unstable to chromatography. Tethered tetrazine **9d** with the indole nitrogen benzylated, produced cycloadduct **11d** in 83% yield upon treatment with TFAA (8 eq) in refluxing dioxane. While the cycloaddition of this derivative was slower (no cycloaddition occurred at rt), adduct **11d** only suffered some deacylation upon chromatography, but was otherwise quite stable.



On the assumption that the cycloadditions of **8a** and **9a-d** were preceeded by acylations of the tethering nitrogens which greatly reduced lone pair donation into the azadiene ring, N^1-benzyl-N$^{\omega}$-acetyltryptamine [**1e**] was tethered with triazine **6** and tetrazine **7a** to give **8e** and **9e**, respectively (Scheme 3). Heating **9e** in TIPB (160 °C, 45 min, 95%), or in refluxing Ac_2O (72%) produced cycloadduct **11e** in excellent yield (stable to chromatography). Basic deacylation produced **11f** quantitatively. Interestingly, **11d-f** preferred the 4a,9b-dihydro tautomer while with **11a-b** the 3,9b-dihydro tautomer dominated.[12] Refluxing **8e** in TIPB did not produce a cycloadduct, but in refluxing Ac_2O, **10e** was produced in good yield (92%).

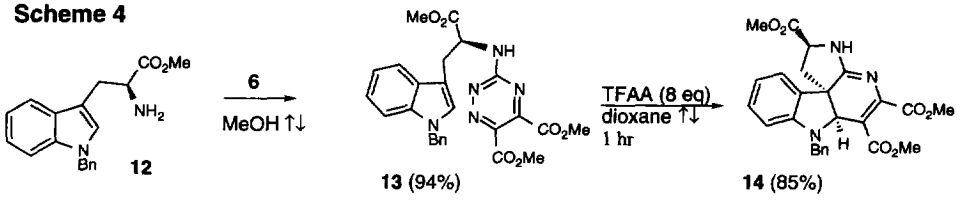
Scheme 3



These observations suggested that N^{ω}-acylated tethered tetrazines such as **9e** have sufficiently low LUMO's to allow for the thermal cycloaddition, but the requirement of Ac_2O as "solvent" for the reactions of the N-acylated tethered triazine **8e** indicated that further activation by in situ acylation of a triazine ring nitrogen may be necessary. Once the ring nitrogen is acylated, the cycloadditions proceed smoothly at temperatures considerably lower in comparison to those employed (232 °C) in the attempted cycloaddition of the N-acylated tethered **8e** in a nonacylating medium, which failed. Supporting this interpretation that both acylation of the tethering nitrogen and a triazinyl nitrogen are required for a cycloaddition of the tethered triazine, the N-methylated analogue **8c** did not undergo a cycloaddition in refluxing Ac_2O (Scheme 2). Presumably no reaction occurred because the tethering nitrogen cannot be acylated.

N^{ω}-Acetyl-N^{1}-benzyltryptophan-tethered triazine **13** similarly underwent a cycloaddition (TFAA, 8 eq in refluxing dioxane, 1 hr) to produce a single adduct **14** (85%) with no other diastereomer detectable. Deacylation of the presumed N-trifluoroacetate adduct apparently occurred during work-up. Thus, the chiral center exerted excellent stereocontrol in the facial approach of the azadiene and indole double bond (Scheme 4, relative stereochemistry assignment by diagnostic NOE's).

Scheme 4



Two key conclusions were drawn from these studies. First, 3-substituted indoles undergo inverse electron demand cycloadditions with 1,2,4,5-tetrazines and 1,2,4-triazines. With triazines and tetrazines tethered to tryptamine via the terminal nitrogen, N-acylation is required to reduce electron donation into the heteroaromatic ring. In the reactions with tethered triazines, further activation of the triazine is necessary and can be achieved by in situ acylation. Second, the use of tryptophan chirality imparts excellent stereocontrol in the cycloaddition, at least in the example examined here. Efforts are now focused on utilizing the azadiene ring of cycloadducts **10** and **11** in a second Diels-Alder reaction as to access the Aspidosperma alkaloidal skeleton.

ACKNOWLEDGMENT. We thank the National Science Foundation for financial support (CHE-9501069).

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12. The 4a,9b-dihydro tautomers (**4b**, **11d-f**) were also identified by a nonexchangeable ^1H singlet (δ 4.0 - 4.7) bonded to a methine sp^3 carbon (δ 66.8 - 67.4). In the spectra of **5** and **11a-b**, 3,9b-dihydrotautomers, the ^1H and ^{13}C resonances of this methine were missing and replaced by a second exchangeable NH resonance (typically δ 8.1 - 8.2, see ref 13) and an sp^2 carbon δ 140 – 142. All new compounds were characterized by ^1H and ^{13}C NMR and HRMS.
13. The ^1H spectrum of **5** at 24 °C showed only a single, broad exchangeable NH resonance (δ 8.38, 1H), and a very broad sp^2 ^{13}C signal at δ 141. At -50 °C, four exchangeable NH resonances appeared (δ 8.70, 8.51, 8.45 and 7.70) in a 0.4:0.6:0.6:0.4 ratio, and one of the methoxy singlets also split into two resonances (3.96 and 3.86, 1.2:1.8 ratio). These observations suggested **5** was a slowly equilibrating mixture of rotamers about the C4/CO_2Me bond. Low temperature ^{13}C spectra supported this conclusion.
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