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Inverse Electron Demand Diels-Alder Reactions of Indole. VI. A Fully Removable Tether for Intramolecular Reactions with 1,2,4-Triazines.

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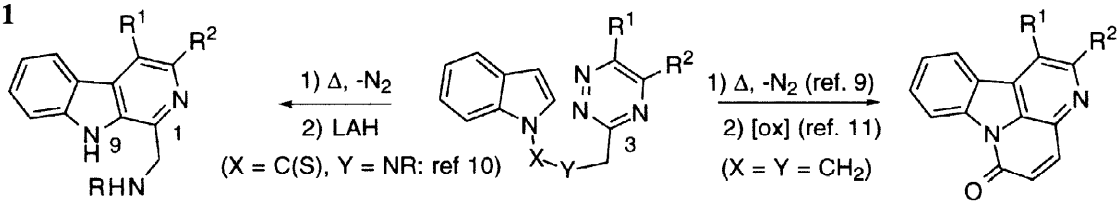
Abstract: The use of the fully removable β-sulfonoacetyl tether to link indole with 1,2,4-triazines allows for the preparation of β-carbolines unsubstituted at C1 and N9 via an intramolecular inverse electron demand Diels-Alder reaction. Mechanistic studies using 2- and 3-deuterated indole derivatives suggest involvement of a [1,5]-hydride shift following the cycloaddition and loss of N_2 that precedes desulfination. © 1998 Elsevier Science Ltd. All rights reserved.

The dienophilicity of latent enamine functions within relatively electron-rich heteroaromatic systems in inverse electron demand Diels-Alder reactions with other, electron-poor heteroaromatic azadienes has proven to be a valuable strategy in the synthesis of a variety of heterocycles.[1] We have been particularly interested in the reactions of indole,[2] pyrrole,[3] and imidazole[4] in such chemistry, as have other groups.[5,6,7] Since the intermolecular cycloadditions of indole with 1,2,4-triazines produced a variety of products depending upon the triazines substituents,[2b] we turned to intramolecular strategies[8] for the preparation of canthines[9] and β-carbolines[10] whereby a 1,2,4-triazine was linked from its 3-position to the indole nitrogen via a trimethylene or thiourea tether, respectively (Scheme 1). Subsequent to the cycloaddition, the canthine D-ring could be oxidized to the canthin-6-one alkaloidal skeleton,[11] while the thiourea tether could be cleaved by LAH reduction, or reduced to a tetrahydropyrimidine D-ring with $NaBH_4$ in refluxing pyridine.[10] This LAH reduction leads to β-carbolines substituted at C1 with an aminoalkyl group which is originally derived from the amino acid used in forming the triazine C3 as well as the thiourea tether.

Scheme 1



Adaptation of this intramolecular cycloaddition strategy to the synthesis of C1-unsubstituted β-carbolines requires the development of a fully removable tether with no vestige of the linker left as a C1 substituent. We now report the successful use of a β-sulfonoacetyl linker which allows for the intramolecular cycloaddition under relatively mild conditions (refluxing toluene compared to 170 - 180 °C with the thiourea linkage) and is easily removed to provide the C1,N9-unsubstituted β-carboline.

Reaction of N-(α-bromoacetyl)indole [**2a**], prepared from indole and α-bromoacetyl bromide in 58% yield, with readily available triazin-3-thiones[12] produced the triazinyl-tethered indoles **3** in quantitative yields (Scheme 2).[13] Not surprisingly, intramolecular cycloadditions of **3** were not achieved under any conditions attempted. Presumably electron donation from the linking sulfur electron lone pairs into the triazine ring,

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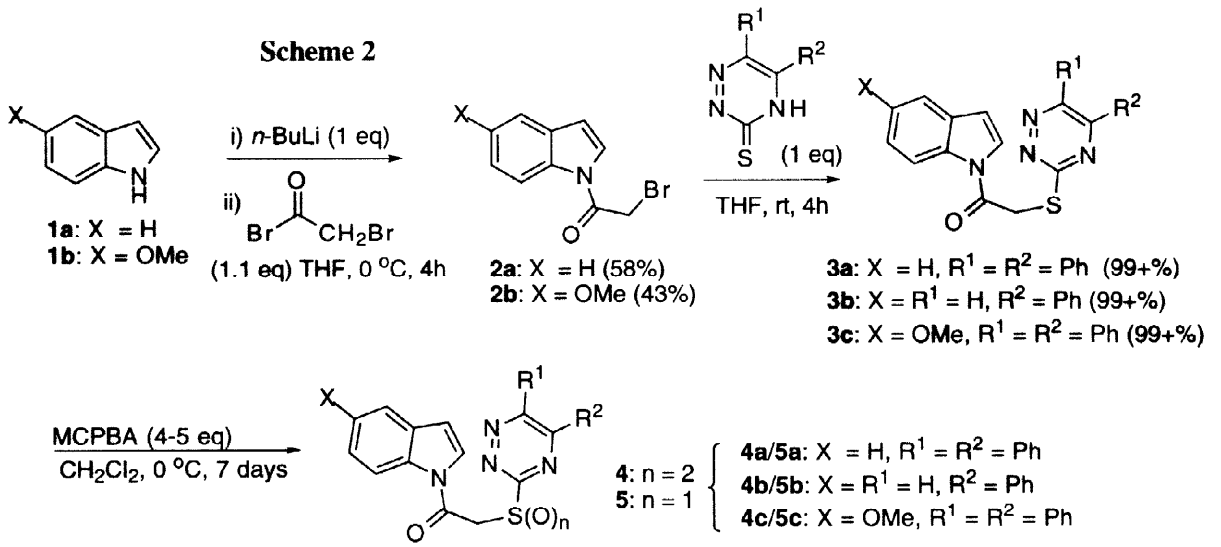
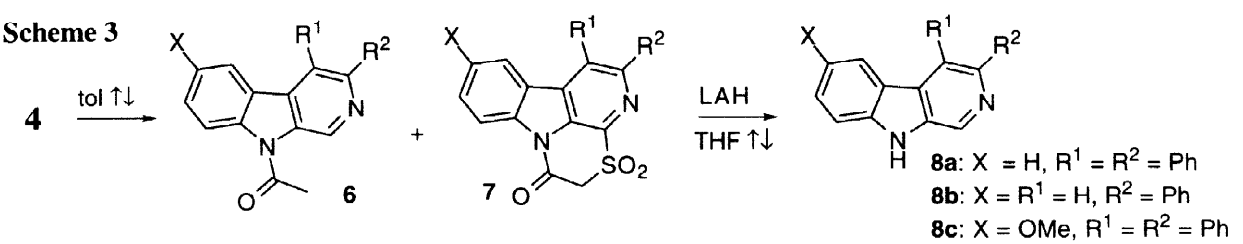
together with electron withdrawal by the acyl group on the indole nitrogen, generate an unfavorable $HOMO_{dienophile}/LUMO_{diene}$ match. Oxidation to sulfones **4** was achieved in excellent crude yields with MCPBA in CH_2Cl_2 with considerable patience (0 °C, 7 days). Shorter reaction times (0 °C for 8 hr, then 4 °C for 24 hr, CH_2Cl_2) gave up to 80% conversion to sulfones **4**, with the remainder of the material balance accounted for by the corresponding sulfoxides **5**, but these could be chromatographically separated only with difficulty and with considerable loss of the desired sulfones which were unstable to silica gel. The sulfones and sulfoxides were easily distinguished by their ^1H NMR spectrum since the sulfur of the sulfoxides is a stereogenic center that renders the adjacent methylene protons nonequivalent, forming two doublets as part of an AB-pattern around δ 5.2 and 4.8 (J = 16 Hz). In contrast, the methylene protons of the sulfones are equivalent, giving rise to a 2H singlet at lower field: δ 5.3. Analogous chemistry beginning with 5-methoxyindole [**1b**] was also successful.

Scheme 2



The crude sulfones **4** underwent cycloadditions in refluxing toluene producing a mixture of N-acetyl-β-carbolines **6** and adducts **7** with the original tether forming an additional D-ring in the latter products (Scheme 3). When **4a** and **4c** were purified prior to the cycloaddition, in highly variable yields (40 - 55%) due to their instability, then refluxed in toluene, **6a/7a** (1:1) and **6c/7c** (1:1.4) were obtained in yields of 98% and 95%, respectively; **4b** could not be purified due to its instability. In contrast, the purified sulfoxides **5** did not undergo thermal or Lewis acid-promoted cycloadditions under any conditions examined. Both **6** and **7** provided β-carbolines **8** upon treatment with LAH; thus, separation of **6** and **7** prior to reduction was not necessary and the crude cycloadduct mixture was conveniently carried through to **8** without purification.

Scheme 3



The starting concentration of the tethered triazines had a dramatic impact upon the ratio **6**:**7**, as illustrated

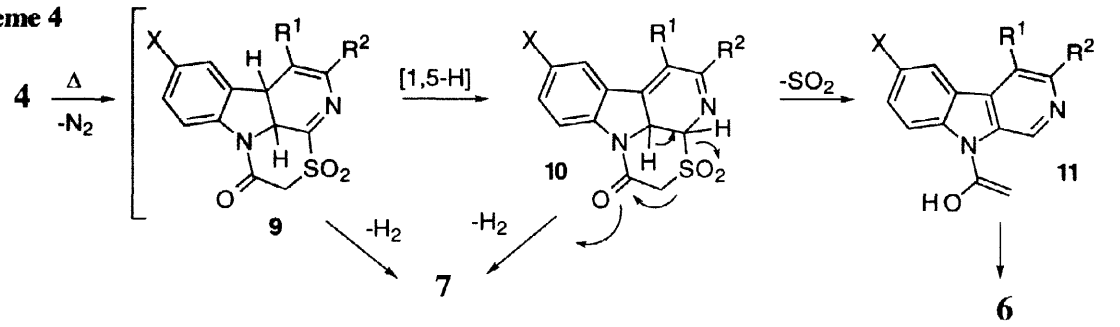
Table 1. Cycloadditions of **4** and Conversion to **8**.

Item	4	X	R^1	R^2	Concentration 4 (M)[a]	6/7[b]	3 → 8[c]
1	**4a**	H	Ph	Ph	[**4a**] = 0.009	1/1	46%
2	**4a**	H	Ph	Ph	[**4a**] = 0.018	3.6/1	d
3	**4a**	H	Ph	Ph	[**4a**] = 0.16	5.4/1	d
4	**4b**	H	H	Ph	[**4b**] = 0.009	2.3/1	41%
5	**4c**	OMe	Ph	Ph	[**4c**] = 0.009	1/1.3	42%

(a) All reactions run in refluxing toluene, 16 hrs. (b) Determined from H NMR. (c) Isolated yield of **8** from **3** (3 steps). (d) Not carried through to **8a**.

for **4a** → **6a**:**7a** in Table 1 (Items 1 - 3). Increasing the concentration of **4a** from 0.009M to 0.16M improved the ratio in favor of **6a** from 1:1 to 5.4:1. (In control experiments, both **6a** and **7a** were stable to the reaction conditions.) A mechanism to account for the products observed in the cycloaddition is proposed in Scheme 4. Cycloaddition of **4** with loss of N_2 provides pivotal intermediate **9**. Dehydrogenation of **9** leads to **7**, while a [1,5-H] shift would give new dihydro-β-carboline intermediate **10**, placing the original indole H3 proton at the carboline C1 position. While **10** could also undergo dehydrogenation to produce **7**, either sulfinic elimination[14] followed by desulfination,[15] or a direct elimination of SO_2 gives enol **11**.[16] Tautomerization then gives the observed adduct **6**. The observed increase in the **6a**:**7a** ratio with increasing concentration of **4a** suggests involvement of either **4a** (or one of the intermediates) in the pathway leading to **6a**. One likely candidate is general base catalysis of the elimination step (**10a** → **11a**).

Scheme 4



To test this proposed mechanism, both 2-[17] and 3-deuteroindole[18] were prepared, tethered to 5,6-diphenyltriazine via the β-sulfonylacetate linkage and subjected to the cycloaddition conditions maximizing the production of **6a** ([**4**] = 0.18 M, refluxing toluene). As predicted from the mechanism above, the 3-deuteroindole derivative of **4a** (50% ^2H) produced the 1-deutero-β-carboline derivative of **6a** (65% yield, 50% ^2H) along with unlabelled **7a** (18%) while the 2-deuteroindole derivative of **4a** (88% ^2H) did not lead to any observable deuterium incorporation in any of the products.

In conclusion, the β-sulfonoacetate linkage has proven to be a fully removable tether for linking indole and 1,2,4-triazines in order to prepare β-carbolines unsubstituted at C1 via intramolecular inverse electron demand Diels-Alder reactions. We are continuing to probe this strategy in two specific directions: (1) develop alternative routes to establishing this tether that avoid the use of α-bromoacetyl bromide, a very nasty reagent,[19] and (2) extend this strategy to other intramolecular cycloadditions beginning with pyrrole, which would allow for the preparation of 6-azaindoles.

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