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1,3-Dipolar cycloaddition of 2- and 3-nitroindoles with azomethine ylides. A new approach to pyrrolo[3,4-*b*]indoles

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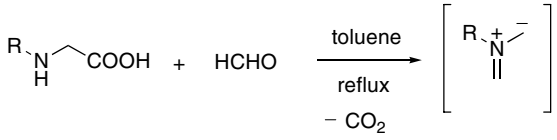
Abstract—The 1,3-dipolar cycloaddition of unstabilized azomethine ylides with 2- and 3-nitroindoles furnishes the expected hexahydropyrrolo[3,4-*b*]indole cycloadducts in good to excellent yields. The cycloadducts can be denitrated with Bu_3SnH/AIBN, and cycloadduct **5** was oxidized with MnO_2 to yield the known pyrrolo[3,4-*b*]indole **13**.

Although there are many examples of the indole π bond functioning as a dienophile in Diels–Alder reactions,[1] there are fewer examples of successful 1,3-dipolar cycloaddition reactions of indole.[2–9] Apart from the spectacular carbonyl ylide applications to the synthesis of *Aspidosperma* alkaloids by Padwa[6,7] and Boger,[8] most examples of 1,3-dipolar cycloaddition reactions with the indole π bond afford either low-yielding mixtures or unstable products.[2–5]

In our ongoing interest in the synthesis and chemistry of fused indoles,[10] we previously reported that 1,3-dipolar cycloaddition reactions between 2- and 3-nitroindoles and mesoionic münchnones is an efficient one-step synthesis of pyrrolo[3,4-*b*]indoles,[11] which can be viewed as stable synthetic analogues of indole-2,3-quinodimethane. Although there are several routes to pyrrolo[3,4-*b*]indoles,[12] one obvious approach that has apparently not been described is the 1,3-dipolar cycloaddition between 2- and 3-nitroindoles and azomethine ylides. Indeed, the 1,3-dipolar cycloaddition of azomethine ylides with alkenes is a powerful reaction since it results in the formation of a pyrrolidine ring and has been widely used for the synthesis of innumerable nitrogen heterocycles and natural products.[13]

We now report our initial results on the 1,3-dipolar cycloaddition reaction between 2- and 3-nitroindoles and unstabilized azomethine ylides. We chose the α-amino acid decarboxylative route that was discovered independently by Joucla[14] and Tsuge,[15] and was based on the inaugural work by Rizzi,[16] for the generation of azomethine ylides derived from amino acids and formaldehyde (Scheme 1). This extremely simple method utilizes commercially available compounds and is performed under almost neutral conditions. For example, the azomethine ylide derived from sarcosine and paraformaldehyde reacts with β-nitrostyrenes to give the corresponding pyrrolidines in good yield.[17]

Thus, treatment of 3-nitro-1-(phenylsulfonyl)indole (**1**)[18] with the azomethine ylide generated in situ from sarcosine and paraformaldehyde in refluxing toluene affords the desired hexahydropyrroloindole cycloadduct **2** in 61% yield (Scheme 2).[19] Although we somewhat anticipated the loss of nitrous acid from the initial cycloadduct **2** to furnish **3** as the final product, as we experienced in similar cases,[11] this path is not observed in any of our reactions, and the initially formed nitro cycloadducts **2** are quite stable. No reaction occurs



Scheme 1.

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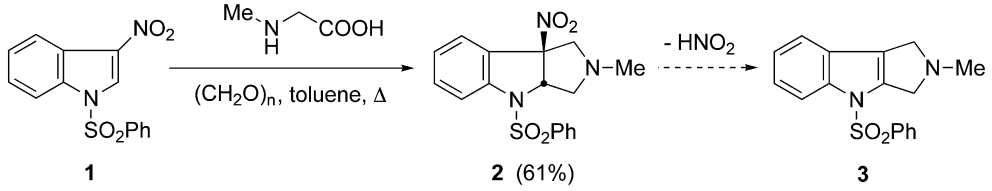


Scheme 2.

between the azomethine ylide from sarcosine and paraformaldehyde and 1-(phenylsulfonyl)indole,[20] 3-cyano-1-(phenylsulfonyl)indole,[21] and 1-benzyl-3-nitroindole[18] under the conditions that give **2**. Consistent with our earlier münchnone cycloadditions,[11] the presence of an electron-withdrawing protecting group on the indole nitrogen increases the dipolarophilic reactivity of the nitroindole toward the azomethine ylide. The reaction of sarcosine/paraformaldehyde with *tert*-butyl 3-nitroindole-1-carboxylate[18] results in deprotection of the Boc group under the reaction conditions and no cycloadduct is isolated.

The crystal structure of **2** (Fig. 1) confirms the expected cis-addition of the azomethine ylide to 3-nitroindole **2**.[22]

Similarly, upon reaction with 3-nitro-1-(phenylsulfonyl)indole (**1**) the azomethine ylide generated in situ from *N*-benzylglycine and paraformaldehyde in refluxing toluene gives cycloadduct **5** in almost quantitative yield (Scheme 3).[23] Likewise, 1-carbethoxy-3-nitroindole (**4**)[18] furnishes **6** and **7** with the appropriate azomethine ylide under the same conditions.[24] In contrast, the reaction of **1** with glycine and paraformaldehyde in refluxing xylene or toluene does not furnish a cycloadduct. This lack of reactivity of glycine in these azomethine cycloadditions has precedence and may simply be due to the presence of a second acidic hydrogen on glycine that prevents generation of the azomethine ylide.[25] In general, we find that toluene is a better solvent than xylene for these cycloaddition reactions.

To investigate this 1,3-dipolar cycloaddition reaction with 2-nitroindoles, we treated 1-(phenylsulfonyl)-2-nitroindole (**8**)[26] with the azomethine ylides from both

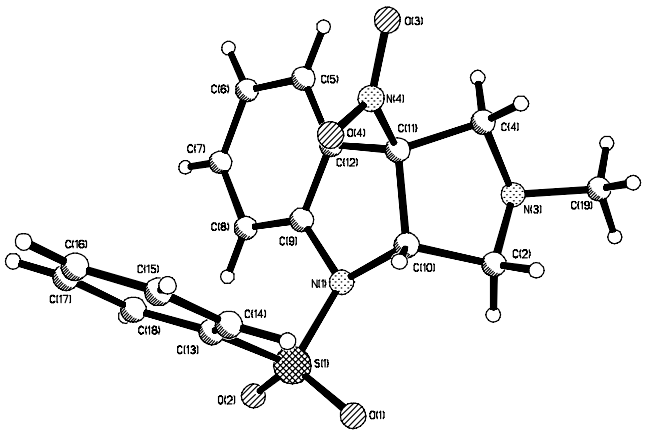
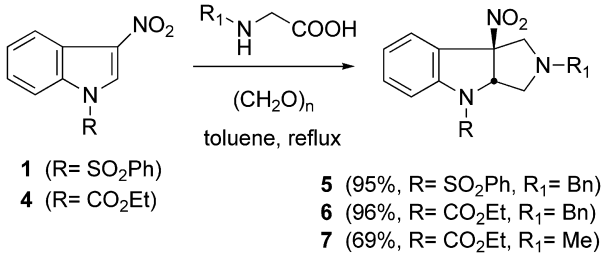


Figure 1.

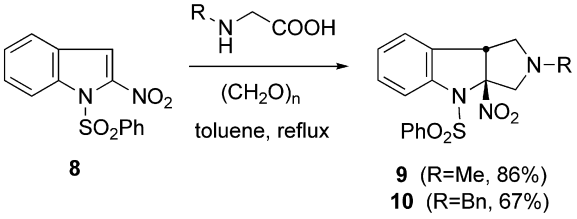


Scheme 3.

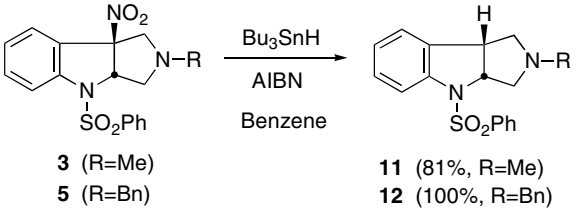
sarcosine and *N*-benzylglycine, and paraformaldehyde. To our satisfaction, the desired cycloadducts **9** and **10** were isolated in 86% and 67% yield, respectively (Scheme 4).[27] However, no cycloadduct is obtained in the reaction of 1,2-bis(phenylsulfonyl)indole[28] with these azomethines, again signifying the importance of the nitro group in these cycloaddition reactions, and perhaps also indicative of a steric effect with 1,2-bis(phenylsulfonyl)indole.

To access the pyrrolo[3,4-*b*]indole ring system, we needed to eradicate the nitro group from these cycloadducts. Although initial attempts with acid, base, or heat were unproductive, we found that treatment of **3** and **5** with Bu_3SnH[29] gives the denitrated products **11** and **12** in excellent yields (Scheme 5).[30] However, thus far, these conditions do not denitrate 2-nitroindoles.

As further structure confirmation, we treated hexahydropyrrolo[3,4-*b*]indole **12** with MnO_2 to afford pyr-



Scheme 4.



Scheme 5.