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Formal [4+2] cycloaddition reactions of *N*-sulfonyl-2,2′-biindoles: synthesis of indolo[2,3-*a*]carbazoles and indigo azines

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Abstract—The formal [4+2] cycloaddition reactions of readily available *N*-sulfonyl-2,2′-biindoles with various dienophiles is reported. The reaction with carbon-centered dienophiles leading to indolo[2,3-*a*]carbazoles is facilitated by the sulfonyl group, which is lost as part of the aromatization process. Reaction with aza-dienophiles gives access to indigo azines.

The indolocarbazole ring system constitutes the core skeleton of a family of structurally unique natural products possessing a wide range of biological activity.[1] Due to the pronounced physiological activities of many of the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles such as staurosporine (**1**) and rebeccamycin (**2**), interest in this class of compounds continues to attract the synthetic efforts of both academic and pharmaceutical researchers (Fig. 1).[2] The selectivity and potency of many of the indolocarbazoles depends on the substituents about the aglycon as well as the nature of the carbohydrate moiety. Often the aromatic substituents are displayed in an unsymmetrical manner, which presents formidable challenges to current synthetic methods. To fully define biological profiles, strategies are required, which allow access to highly functionalized indolocarbazoles not accessible through available methods. Recently, we reported an effective two-step strategy for the preparation of unsymmetrical 2,2′-biindoles from readily available *O*-nitrostryrenes (Scheme 1) and utilized these intermediates for the synthesis of tjipanazole indolocarbazole aglycon and glycoside alkaloids.[3] In connection with these investigations, we discovered that *N*-sulfonyl-2,2′-biindoles **7** undergo formal [4+2] cycloadditions with various dienophiles. In this *Letter*, we disclose our initial observations in this area leading to uniquely substituted indolocarbazole aglycons and indigo azines.

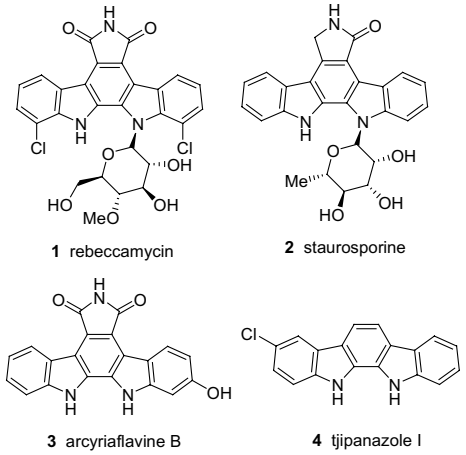
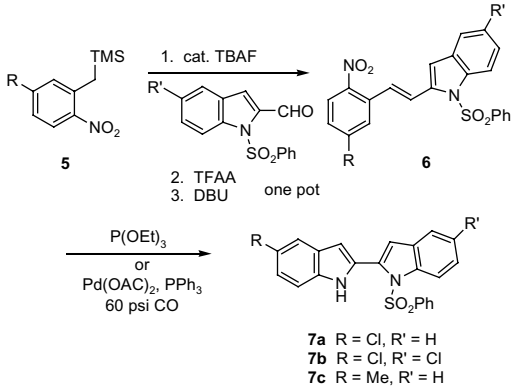


Figure 1.



Scheme 1.

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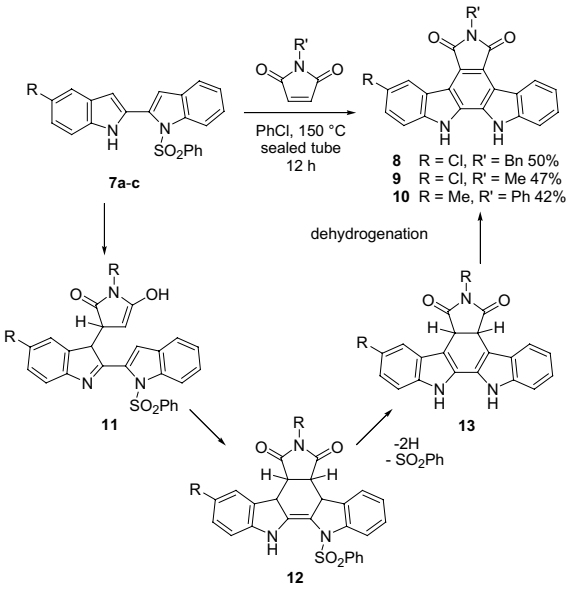
The [4+2] cycloaddition reactions of unsubstituted 2,2′-biindoles with maleimides has been reported to give indolocarbazoles of type **8–10** in low isolated yields.[4,5] The major reaction products are typically identified as Michael addition products suggesting that the indolocarbazole products are the result of a stepwise, rather than a concerted, process. Somei et al. recently reported that the [4+2] cycloaddition reactions of *N*-mono-alkylated 2,2′-biindoles proceeded in yields up to 64% in refluxing nitrobenzene.[6] These results imply that introduction of an appropriate substituent onto the nitrogen atom of 2,2′-biindoles may improve the isolated yield of the corresponding indolocarbazole cycloaddition products.

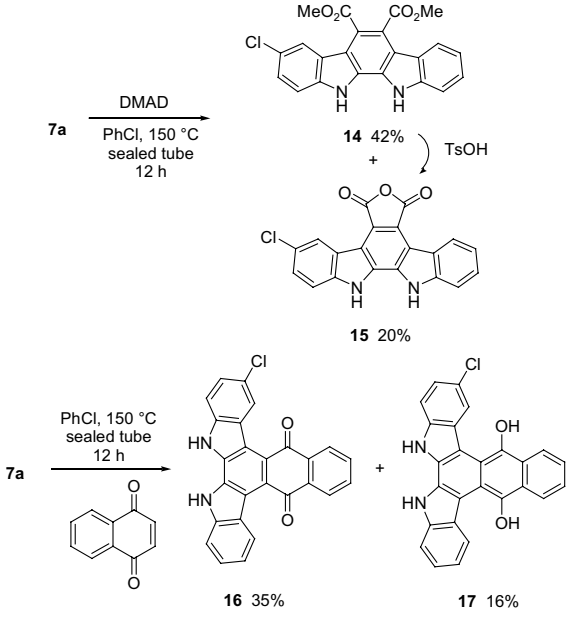
We reasoned that *N*-sulfonylbiindoles of type **7** would provide significant advantages in [4+2] cycloaddition reactions due to the electron withdrawing nature of the sulfonyl group, which would facilitate the formation of the [4+2] adducts by accelerating the rate of cyclization after the initial Michael addition (i.e., **11** to **12**). To this end the cycloaddition reactions of 2,2′-biindoles **7** were examined (Scheme 2). Reaction of **7a** with *N*-benzylmaleimide in chlorobenzene (150 °C, sealed tube, 12 h) provided the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole **8**[7] as the single reaction product, which crystallized from the cooled reaction mixture in 50% yield. There were no significant amounts of Michael addition products observed in the NMR of the mother liquors of the crude reaction mixture. Interestingly, the phenylsulfonyl group was absent from the isolated product. Due to the propensity of 2,2′-biindoles to undergo stepwise [4+2] processes with dienophiles,[4] we speculate that addition of the dienophile to the 3-position of the unsubstituted indole ring to give **11** is followed by rapid cyclization to **12**, a process, which is facilitated by the sulfonyl group. Subsequent loss of the phenylsulfonyl group as part of the aromatization process leads to **13**, which undergoes dehydrogenation[4,8] to **8**. In similar fashion, reaction of **7a** with *N*-methylmaleimide afforded **9** in 47% isolated yield, and reaction of **7b** with *N*-phenylmaleimide gave **10** in 42% yield.

Indolocarbazoles of type **9** have served as useful precursors for the construction of the arcyriaflavin and staurosporine class of alkaloids through hydrolysis of the *N*-methylimide functionality followed by ammonolysis of the corresponding anhydride.[9] In addition, this approach has been employed from diesters of type **14**.[4b,f,g,10] When biindole **7a** was reacted with dimethylacetylene dicarboxylate (DMAD), a mixture of diester **14** and anhydride **15** was obtained in 42% and 20% yields respectively (Scheme 3). The formation of anhydride **15** was unexpected as a minor reaction product and revealed that dehydration to the anhydride was extremely facile under the reaction conditions. When *p*-toluenesulfonic acid was added to the crude mixture and heated at 100 °C for 3 h, anhydride **15** became the sole product of the reaction and could be isolated in 52% overall yield from **7a**. The [4+2] cycloaddition reaction of **7a** with 1,4-naphthoquinone gave a separable mixture of quinone **16** (35%) and the fully aromatized product **17** (16%).[11] Evidently, the dehydrogenation of the reaction intermediate of type **13** leading to **16** was competitive with aromatization leading to **17**. In each case, the [4+2] cylcoaddition reactions between **7a–c** and *N*-substituted maleimides, DMAD, and 1,4-nathphoquinone yielded products, which lacked the phenylsulfonyl group and were devoid of any significant levels of Michael-addition products.

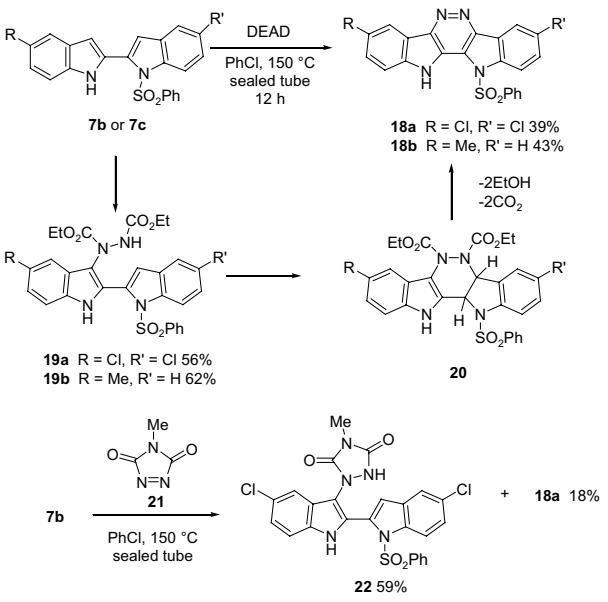
We next turned our attention to the [4+2] cycloaddition reactions of **7b** and **7c** with aza-dienophiles, which were anticipated to give access to indigo azine derivatives (Scheme 4). The closely related indolo[3,2-*c*]cinnolines have been shown to inhibit the proliferation of leukemia, lymphoma, and solid tumor-derived cell lines at micromolar concentrations.[12] In addition, these com-



Scheme 2.



Scheme 3.



Scheme 4.

pounds possess antibacterial and antifungal activity.[12] Access to indigo azines for the assessment of potential biological profiles has been limited due to the lack of synthetic methods for their preparation.[13] Reaction of symmetrically substituted 2,2′-biindole **7b** with diethylazodicarboxylate (DEAD) at 150 °C in a sealed tube for 12 h gave the 5,5′-dichloroindigo azine derivative **18a**[14] as the only identifiable product in 39% yield. Reaction of **7c** under the identical conditions afforded **18b** in 43% yield. The isolation of azine products **18** with the *N*-sulfonyl groups still attached to the indole core indicated the possibility that an alternative reaction mechanism was operating than that depicted in Scheme 2. We postulate that addition of **7b/c** to DEAD is followed by rapid re-aromatization of the indole ring to give intermediates **19**. Ring closure to intermediate **20** leads to aromatization and decarboxylation to give **18**. The primary diving force for the overall sequence from **19** to **18** is aromatization of the C-ring. When the reaction was conducted in refluxing toluene for shorter periods of time (3 h), intermediates **19a/b** could be isolated in 56% and 62% yields respectively with only trace amounts of **18a/b** (<5%) detected in the crude reaction mixture. Interestingly, reaction of **7b** with 4-methyl-1,2,4-triazoline-3,5-dione **21** in refluxing chlorobenzene for 1.5 h gave Michael-addition product **22**, which crystallized from the reaction mixture in analytically pure form in 49% yield. Analysis of the mother liquors revealed the presence of an additional 10% of **22** and azine **18a** (18%). When compound **22** was heated in refluxing chlorobenzene for 8 h, azine **18a** became the major product and was isolated in 37% yield.

In summary, we have outlined a three step protocol for the synthesis of symmetrically and unsymmetrically substituted indolocarbazoles and indigo azines from readily available nitrobenzene precursors. The formal [4+2] cycloaddition reactions with carbon-centered dienophiles is facilitated by the sulfonyl group, which is lost as part of the aromatization process. The [4+2] cycloaddition reactions with aza-dienophiles (DEAD and **21**) gives access to previously inaccessible indigo azines, which contain the sulfonyl group on the indole nitrogen, which may serve as a useful handle for further manipulation. Work is currently in progress in order to further define the overall scope of the sequence. The results of our findings will be reported in due course.

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