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A Facile Preparation of Pyrrolo[3,4-b]indoles

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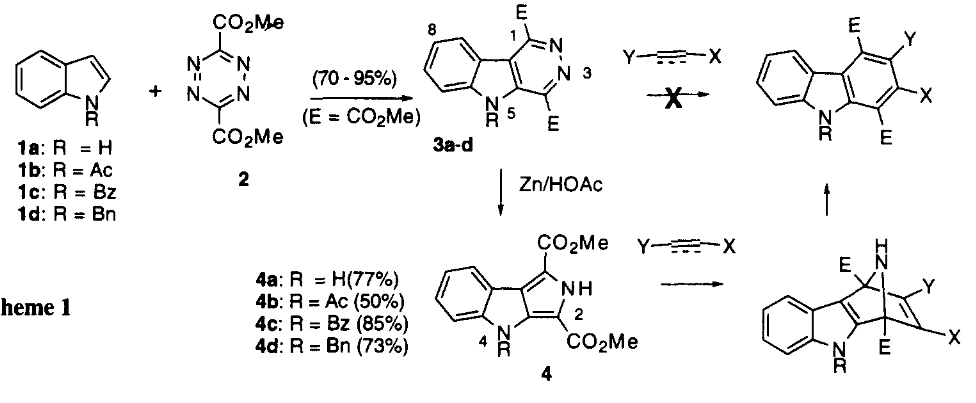
Abstract: Reductive ring contraction of dimethyl 5*H*-pyridazino[4,5-b]indole-1,4-dicarboxylate produced dimethyl 2,4-dihydropyrrolo[3,4-b]indole-1,3-dicarboxylate. © 1997 Elsevier Science Ltd.

The intermediacy of indole-2,3-quinodimethanes and related stable equivalents in efficient routes to a variety of carbazole alkaloids has been exploited for more than two decades.[1] Notable among the numerous examples, Magnus has trapped these reactive intermediates by intramolecular cycloadditions in his now classic syntheses of Apsidosperma alkaloids.[2] Gribble and Moody have developed the stable indole-2,3-quinodimethane equivalents 4*H*-furo[3,4-b]indoles and 4*H*-pyrano[3,4-b]indoles, respectively, and utilized these compounds as key intermediates for cycloadditions in a variety of carbazole syntheses including ellipticene[3] and the staurosporine aglycone[4]. More recently, Sha has disclosed success in the preparation of 1,3-unsubstituted, 1-methyl-, and 1,3-dimethyl-2,4-dihydropyrrolo[3,4-b]indoles via either a 1,3-dipolar cycloaddition/cycloreversion[5] or intramolecular Staudinger chemistry[6] and their utilization also in the synthesis of ellipticene and structural analogues.[7]

The reaction of indole [**1a**] and its N-acylated derivatives [**1b-c**] with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate [**2**] provided pyridazino[4,5-b]indoles **3** in excellent yields,[8] but to-date we have been unable to affect an intermolecular cycloaddition of **3a-d** with any dienophile (Scheme 1).[9] Thus, **3** has not been successfully employed as a stable indole-2,3-quinodimethane equivalent in intermolecular inverse electron demand Diels-Alder reactions, though Haider has had more success with the analogous 1,4-bis(trifluoromethyl)pyridazinoindole.[10] With the hope of generating a more reactive diene that would produce carbazoles upon cycloaddition with dienophiles, reductive contraction of the pyridazine system to the pyrrolo[3,4-b]indoles was explored. Ring contraction of pyridazines to pyrroles[11] has been extensively exploited by Boger,[12] notably in his synthesis of prodigiosin.[13] Application of similar chemistry to pyridazinoindoles **3** would produce pyrrolo[3,4-b]indoles **4** in very simple fashion (two steps from **1** and **2**).

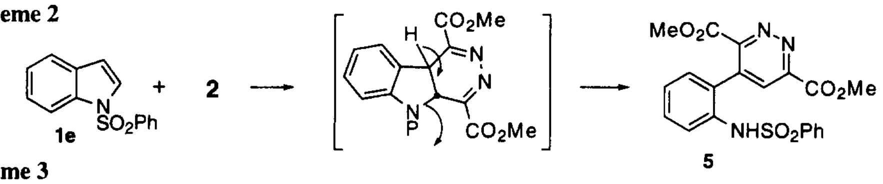
The Zn/HOAc ring contraction of **3a** and various N^5-protected derivatives **3b** - **3e** was explored in order to optimize the yields of the pyrroloindoles **4** as well as to determine which protecting group would best survive the reaction and purification conditions (Scheme 1).[14] With the exception of the benzenesulfonyl group, best yields of N^5-protected pyridazinoindoles **3b** - **3d** were obtained beginning with N-protected indoles **1b** - **1d**, protection of the cycloadduct **3a** being more troublesome. N^1-Benzenesulfonylated **1e**, however, reacted with tetrazine **2** to produce ring opened **5** subsequent to the cycloaddition (Scheme 2). Similar results had also been reported by Haider in the cycloaddition of **1e** with 3,5-bis-trifluoromethyl-1,2,4,5-tetrazine.[10b,15] Sulfonylation of **3a**, however, to produce **3e** was successful under rigorously anhydrous conditions, with subsequent reductive ring contraction giving **4e** in modest yield (51%) due to loss of the sulfonyl group during chromatography (15 - 20% unprotected **4a** was typically also produced, Scheme 3).



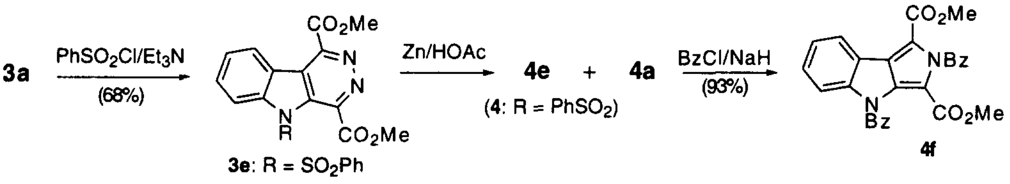
Scheme 1

Protection of pyrroloindole **4a** to-date has not been selective for either N^2 or N^4, and only good yields of diprotected products such as N^2,N^4-dibenzoylated **4f** have been achieved. Thus, N^4-monoprotected **4b** - **4e** were available only from protected **3** prior to ring contraction.

Scheme 2



Scheme 3



Since the mechanism of the ring contraction presumably involves a two electron reduction,[16] we examined the possibility of generating **4** from **3** electrochemically.[16b,16c] Cyclic voltammetric studies on **3a** - **3e** were performed in CH_2Cl_2 with Bu_4NPF_6 (TBAPF) as supporting electrolyte. In all cases, two well-formed reduction peaks were observed which coupled with oxidation peaks on the reverse sweep (Figure 1). When the electrochemical reduction was performed with **3a** (0.01 M, 1 g, 0.2 M HOAc in CH_2Cl_2), ring contracted **4a** was the only product observed (22% conversion).[17] Isolation of **4a** from the reaction mixture, however, was tedious due to the difficulty in removing the TBAPF, and we currently

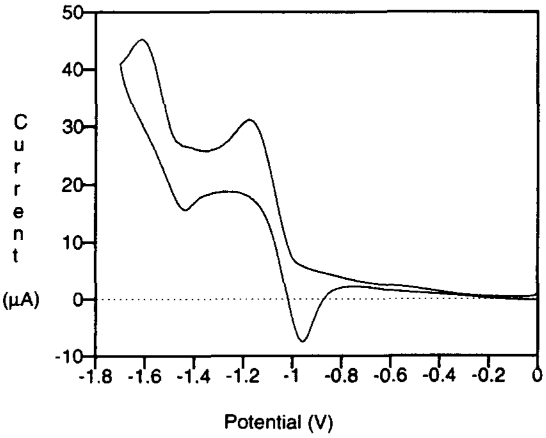
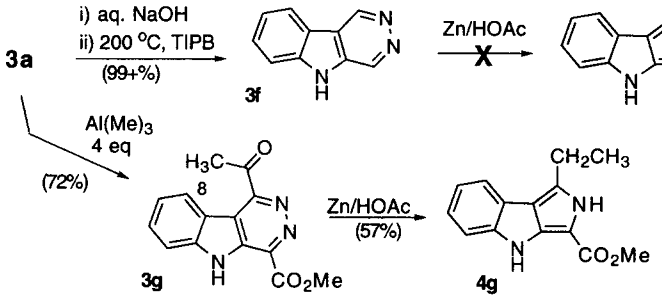


Figure 1. Cyclic voltammogram of **3b**.[18]

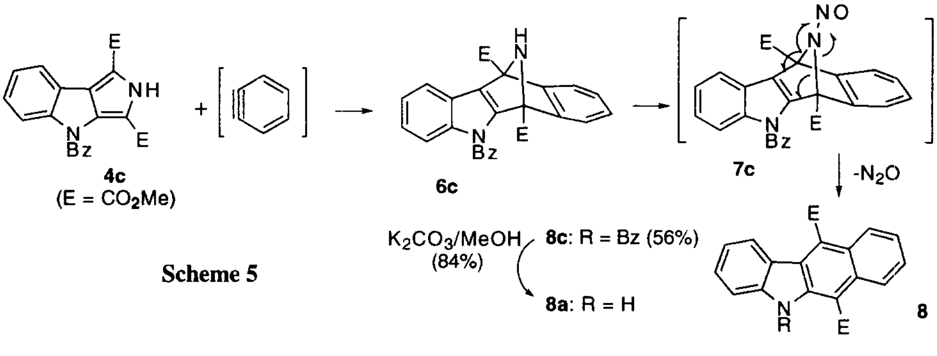
employ the Zn/HOAc procedure to prepare **4a**.

Saponification of **3a** followed by thermal decarboxylation in 1,3,5-triisopropylbenzene (TIPB/200 °C) produced the parent pyridazinoindole **3f** in near quantitative yield; however, **3f**, which no longer bears the electron withdrawing ester substituents as in **3a** - **3e**, did not undergo the Zn/HOAc ring contraction. Treatment of **3a** with Me_3Al (4 eq) gave monoketone **3g** (72%) as the sole regioisomer, which underwent Zn/HOAc ring contraction to produce **4g** (Scheme 4). The importance of the adjacent, electron-deficient pyridazine ring for this apparently unprecedented direct conversion of the methyl ester to a methyl ketone with $AlMe_3$[19] was demonstrated by the lack of similar reactivity of **4a** toward $AlMe_3$, which did not produce a reaction under the same conditions. The regioselectivity of the methylations were established by the observation of an NOE between the methyl ketone and H8 of **3g** in DNOE spectra upon saturation of the methyl singlet.

Scheme 4



Good to excellent yields of cycloadducts have been reported in the reactions of N^2,N^4-diprotected pyrrolo[3,4-b]indoles with benzyne, though not with the unprotected pyrroloindoles.[5,20] We briefly examined the reaction of pyrroloindole **4c** with benzyne (Scheme 5) generated from anthranilic acid and isoamylnitrite (6.4 eq); a modest yield (56%) of fully aromatized adduct **8c** was obtained. Presumably excess diazotizing reagent isoamylnitrite removes the bridging amine by N-nitrosation of bridged intermediate **6c**, which was not detected under the reaction conditions, producing **7c** followed by N_2O extrusion.[21] Removal of the benzoyl group from **8c** to give **8a** was routinely accomplished in 84% yield by basic methanolysis (K_2CO_3/MeOH).



Scheme 5

In conclusion, a facile preparation of pyrrolo[3,4-b]indoles from pyridazino[4,5-b]indole **3a** using a Zn/HOAc reductive contraction has been described. Since **3a** is easily prepared in 95% yield from the inverse electron demand cycloaddition of indole with tetrazine **2**, this represents a simple, two-step sequence to prepare the pyrroloindoles **4**. Further work is in progress to explore the scope of the cycloaddition chemistry of the pyrroloindoles with a variety of dienophiles in order to prepare several carbazole targets.

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[14] In a typical reaction (adapted from ref. 12), activated zinc dust (3.24 mmol) was added to a solution of **3** (0.18 mmol) in glacial acetic acid (2 mL, rt) under argon, and the mixture was stirred for 20 min. After filtration, the insoluble material was washed with CH_2Cl_2, and the combined acetic acid filtrate/CH_2Cl_2 wash was extracted with water (4 X 50 mL), dried over Na_2SO_4, and then the solvent removed in vacuo. Flash chromatography on silica gel provided the desired pyrroloindole.

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[17] Electrolysis: 2 mA for 21 hr at rt; supporting electrolyte was TBAPF (0.1M).

[18] Recorded with a platinum working electrode in CH_2Cl_2 (5 mM **3b**) with TBAPF as supporting electrolyte (0.1 M), -78 °C, sweep rate 0.0125 V/s. The return oxidation peaks are not observed if HOAc is added.

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