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TETRAHEDRON
LETTERS

Swern Oxidation of Tryptamine Derivatives

Patrick D. Bailey,[a]* Philip J. Cochrane,[a] Frances Irvine,[a] Keith M. Morgan,[a]
David P.J. Pearson,[b] and Kenneth T. Veal[c]

[a] *Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh, UK EH14 4AS*
[b] *Zeneca Agrochemicals, Jealott's Hill Research Station, Bracknell, Berkshire, UK RG42 6EY*
[c] *SmithKline Beecham Pharmaceuticals, Synthetic Chemistry, Coldharbour Road, The Pinnacles, Harlow, Essex, UK CM19 5AD*

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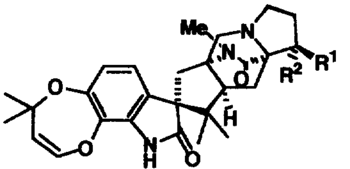
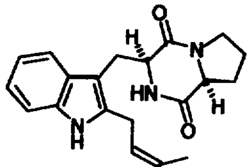
Abstract
The Swern oxidation of various indolic substrates is described, and a range of products resulting from overall oxidation at the 2-position were observed. In particular, depending on the substrate and reaction conditions, it was possible to achieve direct oxidation to α,β-unsaturated systems at the 2-position, to introduce a nucleophile at the 2-position, and to introduce a CH_3-S-CH_2 group at the indole 4-position *via* an unprecedented rearrangement of a Swern intermediate.

Keywords: indoles, oxidation, rearrangements, Swern

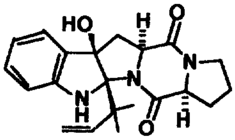
There are a wide range of indolic natural products that possess oxidized indole rings at the 2-position (e.g. **1** [1]) or at the 3-position (e.g. **2** [2]); there are also many examples of 2-alkylated indole alkaloids (e.g. **3** [3]) for which the 2-substituent can be introduced *via* an oxidized intermediate, whilst okaramine A **4** [4] has two derivatized indole rings. We decided to explore routes to such compounds *via* the oxidation shown in Scheme 1. However, despite specific cases in which this reaction can be effected in high yield [5-8], the transformation is, in general, difficult to achieve reliably and efficiently, and we were conscious of the need for improving the methodology.



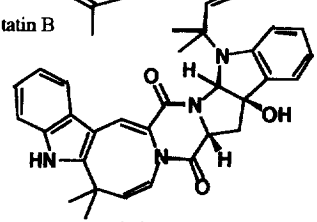
1a paraherquamide A (R^1 = OH, R^2 = Me)
1b paraherquamide B (R^1 = H, R^2 = H)



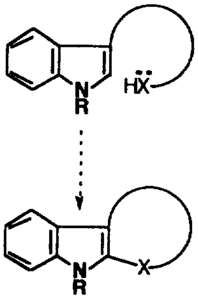
3 tryprostatin B



2 brevianamide E



4 okaramine A



Scheme 1
The required nucleophilic cyclization at the indolic 2-position

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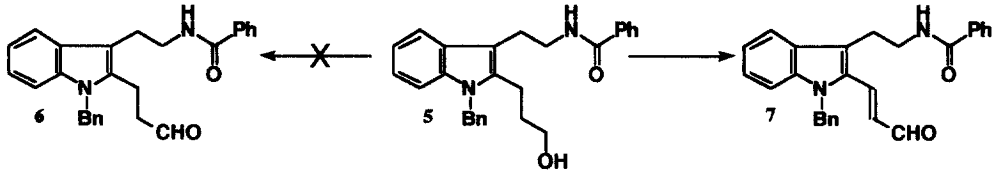
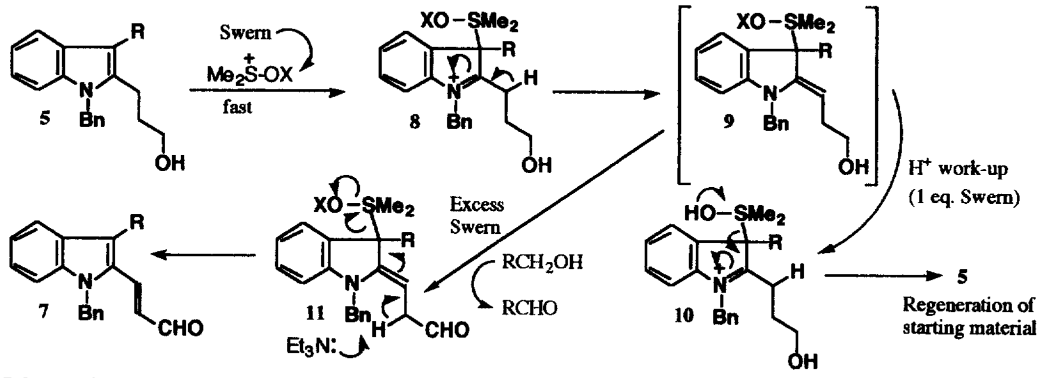
However, it was during work on an apparently unrelated problem that a possible solution became apparent. Whilst attempting to oxidize the indolic alcohol **5** to the aldehyde **6**, we were surprised to discover that Swern oxidation [9,10] (using excess oxidant) yielded only the α,β-unsaturated aldehyde **7** in high yield, with no trace of the desired product (Scheme 2). When the reaction was conducted with 1 equivalent of Swern reagent, complete consumption of the starting material was observed by TLC; however, after acidic work-up, almost quantitative recovery of starting material was achieved. The involvement of the indolic ring in the formation of the α,β-unsaturated system was confirmed by carrying out the Swern oxidation of 3-phenylpropanol, which generated the expected 3-phenylpropanal with excess reagent.



Scheme 2
Oxidation of **5** under Swern conditions {DMSO + TFAA [11] or $(COCl)_2$ [12], then NEt_3, then H^+ work-up}.
TFAA = trifluoroacetic anhydride

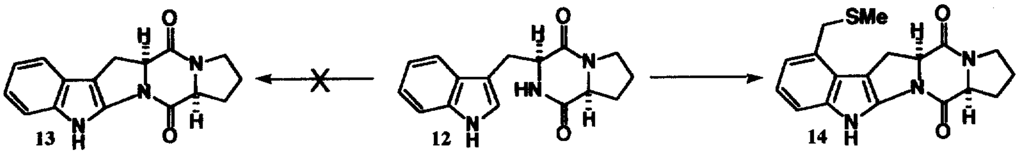
We propose the mechanism shown in Scheme 3 for the formation of the α,β-unsaturated aldehyde **7**. In the presence of only one equivalent of Swern reagent, the sulfonium reagent rapidly attacks the indole 3-position forming the intermediate **9**, which is decomposed on work-up to regenerate the starting material **5**. With excess oxidant, the same intermediate **9** undergoes standard Swern oxidation of the alcohol, to form the aldehyde **11**; the acidic α-proton can then be removed by the triethylamine (probably in a concerted elimination step) to generate the extended conjugative system of the α,β-unsaturated aldehyde **7**.



Scheme 3
Proposed mechanism for the formation of **7** with excess Swern reagent, but regeneration of **5** with 1 eq. of Swern reagent.

If similar reactions were carried out on indole derivatives in which the iminium intermediate could not rearrange to a neutral enamine, then we reasoned that nucleophilic attack at the indole 2-position might be possible, followed by elimination of dimethylsulfide to regenerate the aromatic indole system. This would provide a method of accessing targets such as **1-4**.

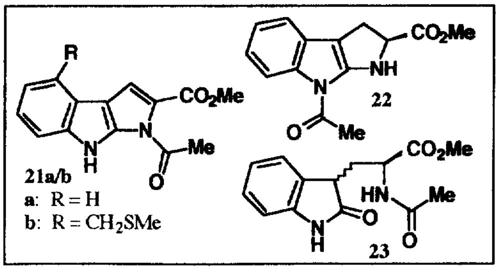
To test whether this was the case, we oxidized the diketopiperazine (DKP) derivative **12** under Swern conditions, and were surprised to obtain **14** as the major product, in 35% yield, with no trace of **13** (Scheme 4). In this transformation, the expected oxidation had clearly occurred, followed by the desired nucleophilic attack by nitrogen on the iminium intermediate; however, the Swern reagent had also led to the introduction of the CH_2SMe group into the indolic 4-position, and we decided to explore the mechanism for this overall transformation in more detail.

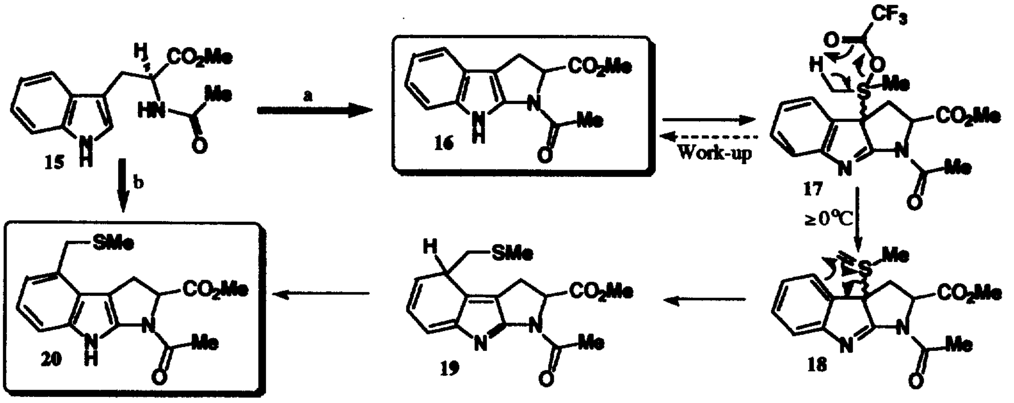


Scheme 4
The reaction of DKP derivative **12** under Swern conditions: i) DMSO/TFAA (excess); ii) NEt_3; iii) H^+ work-up. The presence of the key C-N bond in **14** was deduced from ^1H NMR, as the indole H(2) (δ7.04) and amide NH (δ5.85) signals in **12** were absent in **14**; the position of the CH_2SMe group in **14** was deduced from ^{13}C NMR (DEPT) due to the characteristic δ_C of C(4) [13], for which the CH at δ119.4 in **12** was replaced by a C at δ121.1 in **14**. The conversion of **12** → **13** has been reported [8].

We chose to study the Swern oxidation of the slightly simpler *N*-acetyl tryptophan methyl ester **15** under a range of conditions. Three key results provided insight into the mechanism: a) when the whole reaction was carried out at low temperature (-78°C) using DMSO/TFAA/NEt_3, **16** was formed (but no **20**); b) when DMSO/TFAA was used, but the reaction was allowed to warm up to room temperature, before re-cooling and adding NEt_3, the desired cyclization was always accompanied by the introduction of the CH_2SMe group (i.e. **20** formed, but no **16**); c) when DMSO/$(COCl)_2$/NEt_3 was used, cyclization occurred without the introduction of CH_2SMe under any conditions. We therefore conclude that **16** is initially formed in all cases, and that this reacts with excess Swern reagent to form intermediates such as **17**, which would be hydrolysed back to **16** on work-up. At elevated temperatures, however, an intramolecular proton transfer can occur (as in the Swern oxidation of alcohols using DMSO/TFAA [14]) to generate the sulfur ylid, which can then react further *via* a Sommelet-Hauser [15] rearrangement (Scheme 5); intramolecular proton transfer to generate the ylid is not believed to occur in the Swern oxidation of alcohols using DMSO/$(COCl)_2$ [9,10]. As far as we are aware, the Sommelet-Hauser rearrangement has not been reported for indolic systems, and this procedure provides a highly selective way of functionalising the indolic 4-position, which might be exploited in the synthesis of targets such as lysergic acid, or in the preparation of 4-substituted indolic compounds of medicinal interest.

Footnote: The conversion of **15** into **16** has been reported [8] using Bu^tOCl, in 78% yield; in our hands, this reaction proceeded at best in 33% yield. Using our Swern conditions, yields of **16** or **20** were reliably about 35%; a further 35% of by-products (each < 10%) were isolated and identified in all cases, comprising a mixture of starting material, compounds **21a/b** and **22** (c.f. ref. [16]), and **23**. The remaining by-products were base-line materials.





Scheme 5
Proposed mechanism for Swern oxidation of **15** (DMSO/TFAA then NEt_3) a) at low T or b) with warming before basification.

Finally, when the low temperature Swern conditions from Scheme 5 were applied to the DKP derivative **12**, the cyclized product **13** was obtained, albeit in low yield (12%), and there was no sign of the rearrangement product **14**.

In summary, we have used Swern oxidation conditions to derivatise indolic compounds in three ways. Firstly, to effect direct oxidation to α,β-unsaturated systems at the 2-position; secondly, to introduce a nucleophile at the 2-position; thirdly, to introduce a CH_3-S-CH_2 group at the indole 4-position *via* an unprecedented rearrangement of a Swern intermediate.

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