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A convergent approach to 2-substituted-5-methoxyindoles. Application to the synthesis of melatonin†

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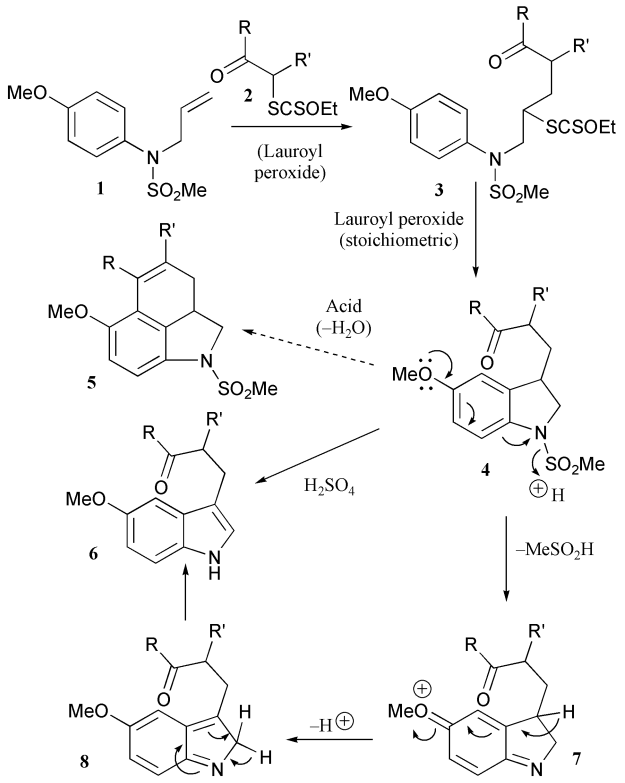
A convergent, radical based synthesis of 5-methoxyindoles including melatonin is described

The indole nucleus is a key structural feature in a large number of alkaloids and related compounds, many of which exhibit a potent pharmacological activity.[1] It is not therefore surprising that numerous routes have been devised over the years to construct the indole ring.[2] In the present communication, we describe a simple approach to 2-substituted-5-methoxyindoles and its application to the synthesis of melatonin, a hormone mainly secreted by the pineal gland and known to play a key role in the regulation of sleep and temperature rhythms in mammals.[3]

We recently found that a convergent access to indolines (*e.g.* **4**) could be achieved by a combination of an intermolecular radical addition of a xanthate (*e.g.* **2**) to a suitably protected *N*-allylaniline (*e.g.* **1**), followed by radical ring closure to the aromatic ring.[4] The first process in the sequence is a radical chain, requiring only a small amount of peroxide initiator, whereas the second is not a radical chain and therefore stoichiometric in peroxide. In the case of indoline **4**, the presence of the ketone group suggested the possibility of constructing a third ring by a Friedel–Crafts type reaction. However, when we subjected an indoline of type **4** to the action of cold concentrated sulfuric acid, a clean reaction ensued but the product turned out to be indole **6** instead of the expected tricyclic derivative **5** (Scheme 1).‡



Scheme 1 Synthesis of indoles.

Some examples of this transformation are collected in Table 1. The best conditions we found were 10 equiv. of 95% sulfuric acid for 30 min. Lower temperatures resulted in long reaction times and higher temperatures or a longer exposure caused the formation of unwanted side-products. Various functional groups capable of resisting cold concentrated sulfuric acid for a short time such as amides, ketones and, to a lesser extent, esters are tolerated and the yields are generally good. Moreover, under such conditions, it is reported that the indole ring is not sulfonylated.[5]

It is necessary to have the electron-donating *p*-methoxy group for the reaction to occur. In its absence, no reaction took place. Substituents such as halides or (not surprisingly) a nitro group were not suitable. This observation is in keeping with the mechanism shown in the lower part of Scheme 1, where the

Table 1 Synthesis of indolines **4** and indoles **5**[a]

Xanthate **2**	Adduct **3**	Indoline **4**	Indole **6**
2a	**3a** 72%	**4a** 62%	**6a** 96%
2b	**3b** 65%	**4b** 66%	**6b** 90%
2c	**3c** 36 (70%)[a]	**4c** 60%	**6c** 45%(55%)[a]
2d	**3d** 73% (88%)[a]	**4d** 66%	**6d** 80%

[a] (X = SCSOEt; Ar = *p*-methoxyphenyl); yields in parenthesis are based on recovered starting material.

† Dedicated to the memory of our friend, Dr Jean-Claude Barrière.

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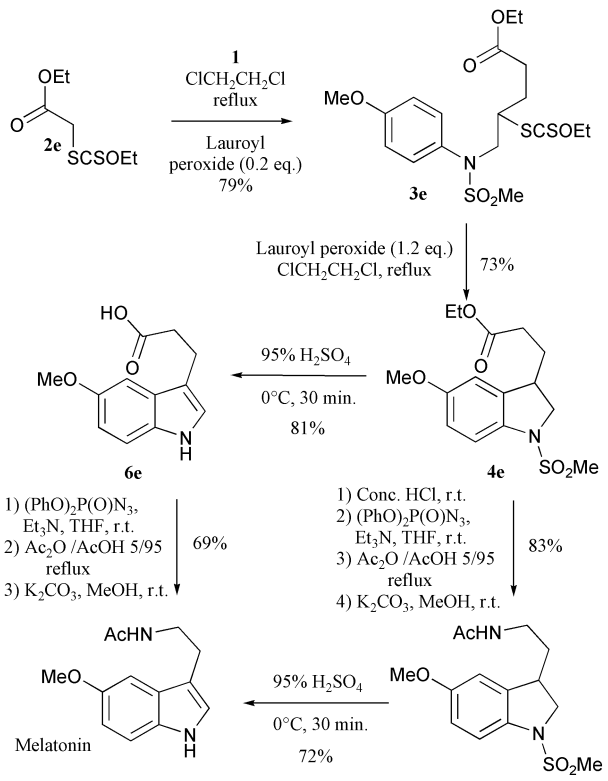
slow step is the cleavage of the nitrogen–sulfur bond, assisted by an electron push by the lone pair on oxygen. The resulting intermediate **7** first undergoes tautomerisation to **8**, then aromatisation by a [1,5] sigmatropic rearrangement or an acid catalysed prototropic shift. Although many reagents are known to oxidise indolines to indoles,[6] there is no need in our case to use an oxidant since the mesyl group serves both as a protecting group for the nitrogen and a leaving group allowing the introduction of the desired unsaturation. It interesting that in one report,[6c] a 7-methoxy-*N*-benzenesulfonylindoline was subjected to a Friedel–Crafts reaction in the presence of tin tetrachloride as the Lewis acid. The indoline portion of the molecule remained intact, even though the methoxy group is also in a favourable position to trigger the expulsion of the sulfonyl group under the strong acidic conditions typical of a Friedel–Crafts reaction.

With a good access to 2-substituted-5-methoxyindolines in hand, we considered applying this sequence to the synthesis of melatonin. Many syntheses of this molecule have been reported but none, as far as we are aware, involves free radical chemistry.[7] Our approach is outlined in Scheme 2. Addition of xanthate **2e**, prepared in 93% yield by heating ethyl bromoacetate with commercially available potassium *O*-ethylxanthate, to olefin **1**, mediated by the portion-wise addition of lauroyl peroxide (0.2 equiv.), provided the corresponding adduct **3e** in 79% yield. Exposure of this compound to stoichiometric amounts of peroxide in refluxing 1,2-dichloroethane promoted ring closure into indoline **4e** in 73% yield.

Two variants were used to convert **4e** into melatonin. The first consisted in cleaving both the ester and mesyl groups with 95% sulfuric acid at room temperature followed by a Curtius rearrangement mediated by diphenylphosphoryl azide[8] and capture of the intermediate isocyanate with a 95 : 5 mixture of acetic acid and acetic anhydride. The latter reagent was used to avoid any hydrolysis of the isocyanate by adventitious water in the medium causing the undesired formation of amine then the symmetrical urea by reaction of the amine with the isocyanate. Finally, the crude melatonin thus obtained is treated briefly with methanolic potassium carbonate to cleave a small amount of the corresponding diacetylimide, generated through overacetylation.

The second route was one step longer but gave a slightly better overall yield. It involved hydrolysing first the ester group with concentrated HCl, performing the Curtius degradation under acetylating conditions before finally removing the mesyl group and concomitant aromatisation by treatment with 95% sulfuric acid.

In summary, we have found a simple route to indoles substituted with electron donating groups. This chemistry can in principle be easily adapted to provide access to various analogues of melatonin, which may not be readily available otherwise.[9]



Scheme 2 Synthesis of melatonin.

Notes and references

‡ *Typical experimental procedure*: ice-cold 95% sulfuric acid (10 equiv.) was added to the pure indoline and the resulting mixture stirred at 0 °C for about 30 min, then poured carefully into cold distilled water and extracted with diethyl ether. The aqueous phase was neutralized with potassium bicarbonate and extracted with ether. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on silica gel.

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