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Insight into the offbeat electrochemical methoxylation of isatin

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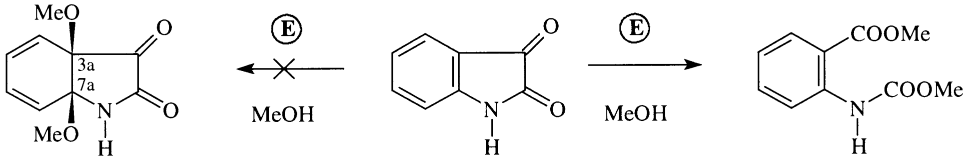
Abstract

A claim by Kazimierczuk and co-workers to have synthesized the diene **1** by electrochemical *vic*-dimethoxylation of isatin **2** is wrong. The product is now shown by a careful analysis of spectral data and synthesis to be in reality methyl *N*-(methoxycarbonyl)anthranilate **3**. © 2000 Elsevier Science Ltd. All rights reserved.

Kazimierczuk and co-workers[1] recently showed that anodic methoxylation of isatin **2** gave a stable and strongly fluorescent main product to which they assigned the structure of (*Z*)-3a,7a-dihydro-3a,7a-dimethoxy-1*H*-indole-2,3-dione **1**.[2] Needless to say, this result is surprising as no such oxidation pattern (i.e. 1,2-dimethoxylation across a fused double bond) has been previously observed in any electro-oxidation of benzenoid systems.[3] If confirmed, this reaction would provide a one-step method for the synthesis of a novel class of compounds that have thus far remained inaccessible by classical routes.



1 **2** **3**

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Because of our general interest in indole chemistry and intrigued by these findings, we were prompted to reexamine this reaction. Thus, isatin **2** was oxidized at room temperature in an undivided cell equipped with a nitrogen inlet using two Pt wire electrodes, a 0.9 M AcONa in MeOH–AcOH (15:1) electrolyte solution and a constant current of 25.4 mA cm^{-2}. The reaction proceeds exactly as the Polish workers described and, after a total of 6 F mol^{-1} of charge has passed, a 35% isolated yield of the methoxylation product was obtained. An increase in the number of F mol^{-1} did not improve the yield of this product, but did reduce the amount of starting material recovered.

Chemical behaviour and a careful analysis of this product raise questions about the proposed structure. Accordingly, we were surprised to find the cisoid 1,3-diene subunit in **1** was reluctant to give either η^4(diene)–$Fe(CO)_3$ complex with $Fe_2(CO)_9$[4] or [4+2]-cycloadducts with strong dienophiles [i.e. 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD), tetracyanoethylene (TCNE)].

Of particular concern, upon examination of the ^1H and ^{13}C NMR data, was the downfield shift ($\approx$6 ppm) noted for C(4) and C(7) resonances in **1** vis-à-vis isatin **2**.[5] In the ^1H NMR spectra the chemical shifts for H(4)–H(7) (between 7.1 and 8.2 ppm) are the most diagnostic resonances, typically falling below 6.1 ppm in similar systems,[2,6] with a noticeable (and somewhat inexplicable) downfield shift. In order to clarify the issues raised above, we undertook a thorough investigation of this product by 1D and 2D NMR experiments. Application of H,H-relayed COSY, heteronuclear multiple bond correlations (HMBC) and INADEQUATE experiments to the electro-oxidation product resulted in structure **3** as most consistent with the spectral data.[7]

The probable course of the electro-oxidation process of **2** would involve the ring-opening of the radical cation of **2**, during or after electron transfer, followed by rapid nucleophilic capture, whose product undergoes further oxidation.[8]

Quantum-mechanical calculations on **2** and its radical cation, the latter presumably formed in the first step of the electrochemical oxidation, were performed using semiempirical methods (AM1 and PM3) from the SPARTAN package.[9] The optimised structure of $\mathbf{2}^{+\bullet}$ indicated a substantial weakening of the C(2)–C(3) bond with most of the spin density confined to the NH–C(2)=O site. This could reasonably indicate that the fate of the radical cation is the C(2)–C(3) bond fission, without involving the aromatic ring.

Redox considerations further support these proposals suggesting that **2** would be readily transformed into **3** (via $\mathbf{2}^{+\bullet}$) by metal-based oxidizing agents [e.g. Ce(IV), Pb(IV)].[10] Gratifyingly, treatment of **2** with 2.1 molar equiv. of $Ce(NH_4)_2(NO_3)_6$ (CAN) in 1:1 MeCN–MeOH at room temperature for 1 h, followed by silica gel chromatography, led to clean formation of **3** in 45% isolated yield.[11]

With the exception of the chemical shifts of the four C(sp^2)H in the ^1H and ^{13}C NMR spectra, which may be a result of inadvertent inversion in the assignment, all signals and coupling constants for the alleged **1**[1] are in agreement within experimental error with those obtained for the authentic **3**[12] (prepared by treatment of commercially available methyl anthranilate with $ClCO_2Me$ in pyridine at room temperature). We are forced to conclude that the claim that isatin **2** could be converted into **1** was erroneous.

Acknowledgements

The help rendered by Drs L. Calabi and L. Paleari, Bracco S.p.A. (Milan) in the 2D NMR studies is greatly appreciated.

References

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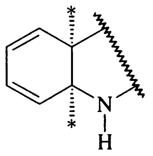
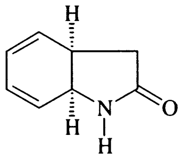
2. Search of database (Beilstein CrossFire) using the substructure **A** provided only one representative and rather unstable compound (i.e. **4**) (Kröner, M. *Chem. Ber.* **1967**, *100*, 3162–3171).



A



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3. The anodically promoted 1,4-addition of two OMe groups across a benzenoid system represents a well documented behaviour. See: Yoshida, K. In *Electro-oxidation in Organic Chemistry (The Role of Cation Radicals as Synthetic Intermediates)*; Wiley: New York, 1984; pp. 174–203.
4. For a review, see: Donaldson, W. A. In *Comprehensive Organometallic Chemistry II*; Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Elsevier Science: Oxford, UK, 1995; Vol. 12, pp. 623–637.
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6. Smith, G.; Warren, C. L.; Vaughan, W. R. *J. Org. Chem.* **1963**, *28*, 3323–3329.
7. Compound **3**: mp 57–58°C (hexane) (lit.[1] 54.5°C; lit.[12b] 56–58°C); IR (KBr) 3300, 3010, 2960, 1743, 1695, 1610, 1599, 1588, 1535 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) 3.77 (3H, s, OMe), 3.88 (3H, s, OMe), 6.99 (1H, t, J=7.6 Hz, H-5), 7.54 (1H, ddd, J=8.7, 7.9, 1.7, H-6), 7.96 (1H, dd, J=8.0, 1.7, H-7), 8.41 (1H, d, J=8.5 Hz, H-4), 10.49 (1H, br s, N-H); ^{13}C NMR (150 MHz, CDCl$_3$) 52.6 (2s, C-8 and C-9), 114.9 (C-3a), 119.1 (C-7), 121.9 (C-5), 131.2 (C-4), 134.9 (C-6), 142.1 (C-7a), 154.4 (C-2), 168.8 (C-3). HMBC C-2/H-4, H-9; C-3/H-4, H-5, H-8; C-4/H-6, H-7; C-5/H-6, H-7; C3a/N-H, H-5, H-6, H-7; C7a/H-4, H-5, H-6, H-7. EI-MS 209 (M$^{+\bullet}$, 52%), 177 (M−MeOH), 146 (M−MeOH-MeO, 100%) (for the sake of comparison, we retained the numbering scheme of the parent compound **2**).
8. The efficient C–C bond cleavage of radical cations is well documented. See, for example: Adam, W.; Casado, A.; Miranda, M. A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 797–798.
9. PC Spartan Pro, Wavefunction, Inc., Irvine, CA, 1999.
10. The peak oxidation of isatin **2** measured at a Pt anode in 0.1 M LiClO$_4$–MeCN (scan rate 50 mV s^{-1}) was +0.43 V versus SCE, whereas the reduction potential of Ce(IV) was ca. +1.7 V.
11. For the Ce(IV)-promoted bond fission of α-dicarbonyl compounds, see: Danieli, B.; Palmisano, G. *Chem. Ind. (London)* **1976**, 565–566.
12. (a) Erdmann, E. *Chem. Ber.* **1899**, *32*, 2159–2172; (b) Hoesch, L.; Dreiding, A. S. *Helv. Chim. Acta* **1975**, *58*, 980–1001.