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Synthesis of 6-Formylindolo[3,2-b]carbazole, an Extremely Potent Ligand for the Aryl Hydrogen (Ah) Receptor

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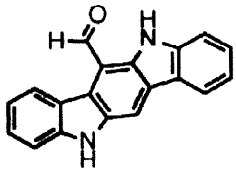
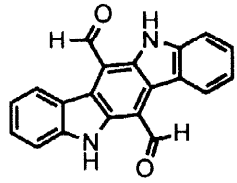
Abstract: Dichloroacetylation of 2,3-diindolylmethane followed by a tandem cyclization–hydrolysis reaction under acidic conditions gave the title compound.

It has previously been reported that very small amounts of two extremely efficient ligands for the aryl hydrocarbon (Ah) receptor can be isolated from the very complex mixture obtained when UV-irradiatiating (200 nm) aqueous L-tryptophan solutions[1,2]. Interpretation of the spectra of the compounds in question has led to the conclusion that the two ligands are **1** and **2**, i.e. derivatives of indolo[3,2-b]carbazole[2], a good Ah receptor ligand itself[3]. The monoformyl derivative **1** is the stronger ligand of the two, showing affinity at picomolar concentrations (K_d= $7x10^{-11}$), which is 5-8 times higher than that of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) **3**, an environmental contaminant binding infamously strong to the receptor. In fact, this strong binding of TCDD has given the Ah receptor its sometimes used second name: the TCDD receptor. The indolocarbazoles **1** and **2** have been suggested to be endogenous ligands for the Ah receptor (the receptor is certainly not there for TCDD) and should therefore be powerful tools for understanding receptor function[1,2].



1



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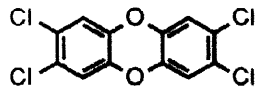

3

As a means both to confirm the assigned structure and to obtain amounts sufficient for animal tests, we set out to develop a synthesis of **1**, something which has now been achieved.

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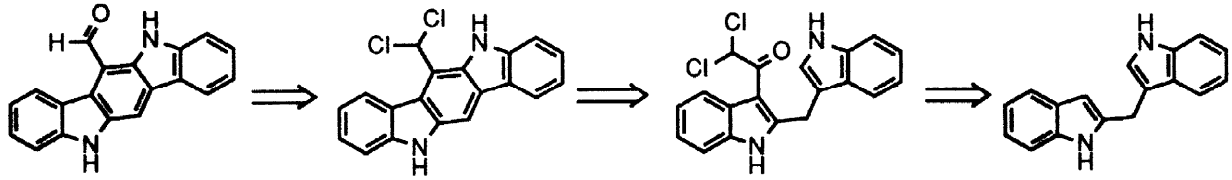
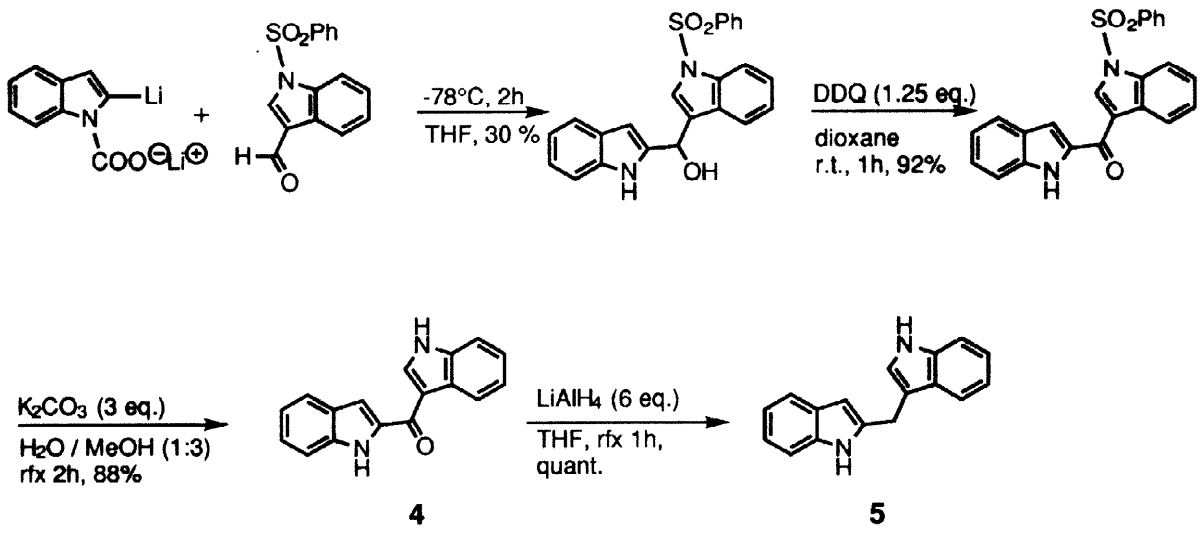
As indolo[3,2-b]carbazole itself is readily available via Fischer indolization of the bis-phenylhydrazone of 1,4-cyclohexanedione[4], direct formylation would seem to be a method of choice. Neither Vilsmeier reagents (several variants) nor more powerful Duff conditions (hexamethylene tetramine-trifluoroacetic acid) showed any signs of the desired product, however, so we therefore decided to employ a different strategy involving construction of the indolocarbazole ring system on the way (Scheme 1).



Scheme 1

The 2,3-diindolylmethane **5** has previously been prepared by Jackson[5] starting from isatin and 3-chloroacetylindole, but in our hands this method was in many ways troublesome. An alternative approach was therefore developed (Scheme 2), where the first step is according to the Katritzky protocol[6], using CO_2 as an easily removed protecting/directing group for lithiation of the indole 2-position.



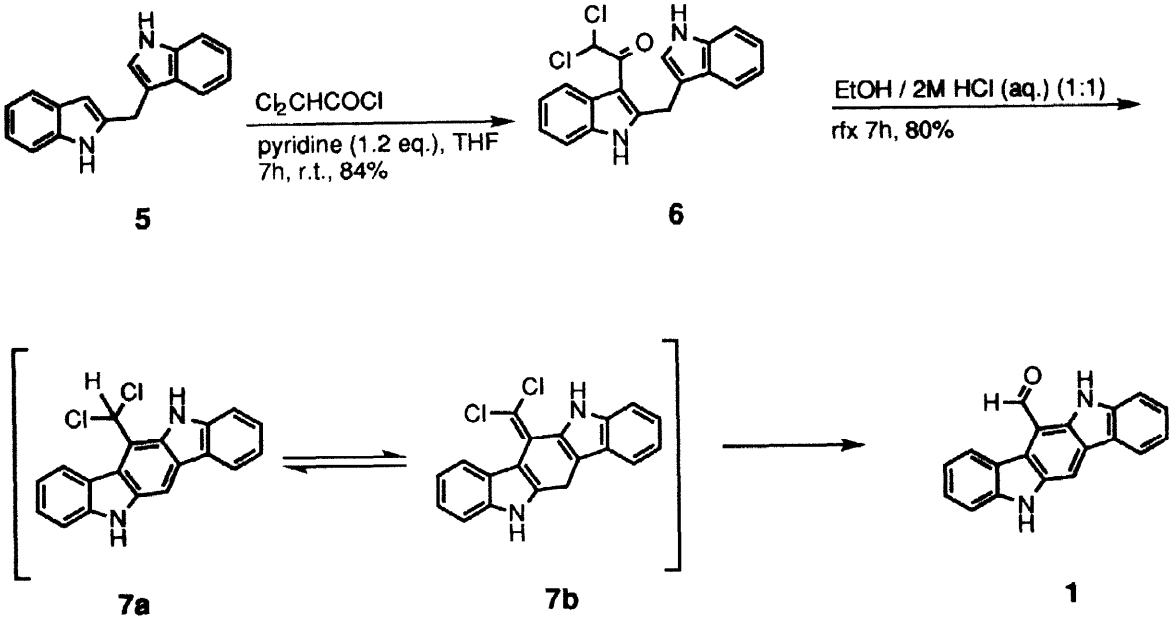
4 **5**

Scheme 2

The spectral data of **4** and **5** were in agreement with those reported[5].

Acylation of **5** (Scheme 3) was performed using a modification of an existing technique[7]. To our joy, the cyclization of **6**[8] did not only work as planned, but also resulted in hydrolysis of the presumed intermediate

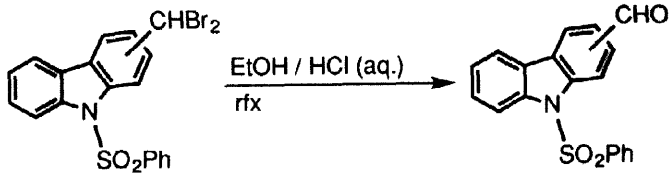
dichloromethyl compound **7a**, which we so far have been unable to isolate. A possible explanation might be that **7a** to a considerable extent exists as its exocyclic tautomer **7b**, which should undergo ready hydrolysis.



Scheme 3

The synthesized compound **1** was in all respects identical with the sample obtained by UV-irradiation (200 nm)[9].

A hydrolysis of a dibromomethyl group to an aldehyde in a similar carbazole system is described in the literature (Scheme 4)[10]:



8a, 2-$CHBr_2$
b, 3-$CHBr_2$
c, 4-$CHBr_2$

Scheme 4

It is worth noting that the dibromomethyl groups in the 2- and 4-positions are more susceptible to hydrolysis than the one in the 3-position. Thus, hydrolysis of **8a** and **8c** was complete after 5 h in a 3:1 EtOH / 0.5 M HCl (aq.) mixture, whereas **8b** required 24 h in a double as acidic medium.

In conclusion, we have verified by synthesis a previous assignment: that the extremely potent ligand for the Ah receptor (also called the TCDD receptor) really is 6-formylindolo[3,2-b]carbazole. Sufficient amounts for animal tests have been produced.

References and Notes

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8. Compound **6**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.61 (br s, NH, 1H), 8.36 (br s, NH, 1H), 7.90 (d, J = 7.9, 1H), 7.47 (d, J = 8.3, 1H), 7.45 (d, J = 7.9, 1H), 7.34 - 7.08 (m, 6H), 6.91 (s, 1H), 4.76 (s, 2H);
   ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (s), 151.6 (s), 136.6 (s), 134.5 (s), 127.1 (s), 125.5 (s), 124.1 (d), 124.1 (d), 123.1 (d), 123.0 (d), 120.7 (d), 120.4 (d), 118.8 (d), 111.9 (d), 111.6 (d), 109.4 (s), 108.2 (s), 69.9 (d, $CHCl_2$), 25.8 (t, CH_2)
   IR (KBr) 3396, 1641, 1483, 1456, 742 cm^{-1};
   mp 80 °C
9. Compound **1**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.75 (s, NH, 1H), 11.63 (s, NH, 1H), 11.37 (s, 1H), 8.60 (s, 1H), 8.57 (d, J = 8.2, 1H), 8.30 (d, J = 7.7, 1H), 7.75 (d, J = 8.1, 1H), 7.60 (d, J = 8.1, 1H), 7.52 - 7.42 (m, 2H), 7.27 - 7.18 (m, 2H)
   ^{13}C NMR (DMSO-d_6, 75 MHz) δ 189.9 (d), 141.5 (s), 141.5 (s), 135.2 (s), 134.7 (s), 126.3 (d), 126.1 (d), 124.5 (d), 123.2 (s), 121.5 (s), 121.2 (s), 120.9 (s), 120.3 (d), 119.1 (d), 118.7 (d), 112.2 (s), 111.9 (d), 111.3 (d), 109.8 (d)
   IR (KBr) 3382, 1655, 1616, 1520, 1459, 1322, 1288, 741 cm^{-1};
   mp > 300 °C
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