Facile One-Pot Synthesis of Novel 6-Monosubstituted 5,11-Dihydroindolo[3,2-*b*]carbazoles and Preparation of Different Derivatives

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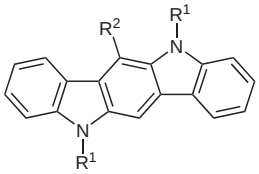
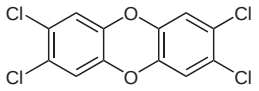
Abstract: The synthesis of novel 6-monosubstituted 5,11-dihydroindolo[3,2-*b*]carbazoles was accomplished by a three-stage one-pot procedure involving condensation of indole and an aldehyde affording 3,3′-bis(indolyl)methanes, followed by isomerization to the 2,3′-analogues and acid-catalyzed intramolecular reaction with triethyl orthoformate to give the corresponding 6-monosubstituted indolo[3,2-*b*]carbazoles in good overall yield. Different substitution patterns, such as N-alkylation, N-arylation, formylation and bromination, were successfully introduced, leading to the formation of novel substituted 5,11-dihydroindolo[3,2-*b*]carbazole derivatives.

Key words: three-stage one-pot synthesis, 6-monosubstituted 5,11-dihydroindolo[3,2-*b*]carbazole, N-substitution, formylation, bromination

Indolo[3,2-*b*]carbazole (ICZ) (**1a**, Figure 1), which is formed in the acidic environment of the stomach after intake of indole-3-carbinol, is a molecule with considerable biological significance.[1] ICZ shares the biological activity with TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin, **2**). It has been demonstrated that 6-formylindolo[3,2-*b*]carbazole (**1b**) has a strong affinity to the TCDD receptor (aryl hydrocarbon receptor, Ah receptor), binding 5–8 times as strong to the receptor as TCDD itself.[2] Moreover, 5,11-disubstituted indolo[3,2-*b*]carbazoles **1c**–**e** are a new class of high-performance organic semiconductors suitable for organic thin film transistor (OTFT) applications.[3]





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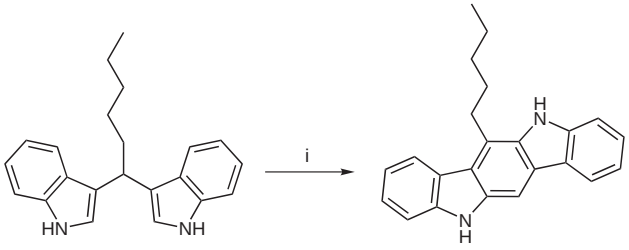
1a $R^1 = R^2 = H$
1b $R^1 = H$, $R^2 = CHO$
1c $R^1 = octyl$, $R^2 = H$
1d $R^1 = 4\text{-octylphenyl}$, $R^2 = H$
1e $R^1 = 4\text{-methylphenyl}$, $R^2 = H$

Figure 1

Several synthetic methods towards the synthesis of symmetrical and unsymmetrical indolo[3,2-*b*]carbazoles have been developed, showing the great interest in these nitrogen-containing heterocycles, such as (1) Pt-mediated cyclodehydrogenation of *N*,*N*′-diphenyl-*p*-phenylenediamine,[4a] (2) double Fischer indolization of cyclohexane-1,4-dione bis(phenylhydrazone),[4b] (3) condensation of indole and formaldehyde in the presence of strong acid, air and sensitizers,[4c] (4) Lewis acid catalyzed dimerization of 1-(1-benzotriazol-1-yl-alkyl)indoles,[4d] (5) intramolecular cyclization of 2-(1*H*-indol-3-yl-methyl)-1*H*-indole-carbaldehyde,[4e] (6) condensation of indole with aliphatic aldehydes under acidic conditions,[4f] and (7) cyclization of 3,3′-bis(indolyl)methanes[4g] or 2,3′-bis(indolyl)methanes[4h] via acid-catalyzed reaction in the presence of triethyl orthoformate. However, most of these methods involve multistep routines starting from indoles and afford the target ICZs in low total yield.

In the present work, we report the synthesis of novel 6-monosubstituted 5,11-dihydroindolo[3,2-*b*]carbazoles involving a three-stage one-pot procedure with moderate overall yield. Furthermore, several N,N′-disubstituted, formylated and brominated compounds have been prepared.

In 2003, Bandgar et al. reported fast reactions of indoles with various aldehydes and ketones using I_2 in acetonitrile to afford the corresponding 3,3′-bis(indolyl)methanes in excellent yields.[5] 3,3′-Bis(indolyl)hexane (**3**) was obtained in 70% yield by condensation of indole and hexanal with a catalytic amount of iodine for 30 minutes at room temperature. We treated compound **3** with triethyl orthoformate in MeOH using sulfuric acid or methanesulfonic acid as a catalyst (Scheme 1). We observed that 6-pentyl-5,11-dihydroindolo[3,2-*b*]carbazole (**4c**) was formed only in trace amounts from mass spectral analysis of the reaction mixture.



3 **4c**

Scheme 1 *Reagents and conditions*: (i) $(EtO)_3CH$, MeOH, H_2SO_4 or CH_3SO_3H (cat.), r.t.

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We found that if the condensation of indole and commercial aldehydes with iodine as a catalyst was carried out for longer time (14 h) the 3,3′-bis(indolyl)alkanes were isomerized to 2,3′-bis(indolyl)alkanes **5a**–**d** (monitored by ^{1}H NMR spectroscopy). Because of their instability, we did not purify compounds **5a**–**d** after work-up. The acid-catalyzed intramolecular cyclization of crude compounds **5a**–**d** in the presence of triethyl orthoformate produced the corresponding ICZs in acceptable overall yield (45–50%, Scheme 2, Table 1).

Table 1 Three-Stage One-Pot Synthesis of 6-Monosubstituted Indolo[3,2-*b*]carbazoles

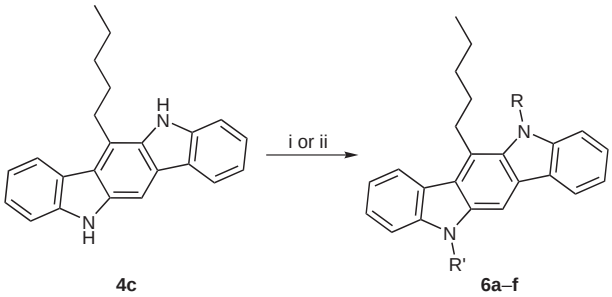
Entry	Compound	R	Reaction time (h) of the first step	Total yield (%)
1	**4a**	Methyl	14	46
2	**4b**	Isobutyl	14	50
3	**4c**	Pentyl	3	20
4	**4c**	Pentyl	14	47
5	**4c**	Pentyl	48	18
6[a]	**4d**	Undecyl	14	36
7	**4e**	Phenyl	0.5	20

[a] Using CH_2Cl_2 as the solvent.

The second step of the synthesis was carried out in MeOH under acidic conditions using a catalytic amount of methanesulfonic acid (0.2 equiv). To optimize the isomerization of the 3,3′-isomer, alternative reaction times of 3 hours (entry 3) and 48 hours (entry 5) were tried but afforded much lower yields compared with entry 4 (14 h). With this optimal condition, the other 6-monoalkylated ICZs were obtained in comparable yield, except for **4e** (20%). Thus, aromatic aldehydes are less suited for this formation of ICZs because the corresponding intermediates of type **3** and **5** are much less stable, quickly forming an insoluble precipitate which is difficult to characterize (entry 7).

Comparing with the reported symmetrically 6,12-disubstituted ICZs,[2,4f,6] the better solubility in apolar organic solvents of these asymmetrical analogues **4** of ICZ allows for an easy further structural modification. The N-alkylation of compound **4c** using sodium hydride in DMF and 4 equivalents of bromoethane at 70 °C afforded the corresponding N,N′-diethylated compound **6a** in 50% yield. On the other hand, tosylation of **4c** under similar reaction conditions using 4 equivalents of *p*-toluenesulfonyl chloride was found to occur at only one nitrogen atom to produce selectively monotosylated derivative **6b** in 60% yield. Thus, the protection of **4c** with *p*-toluenesulfonyl chloride is regioselective. This result is very interesting and could be employed to prepare the N-monoarylated or asymmetrically N,N′-diarylated ICZ derivatives.

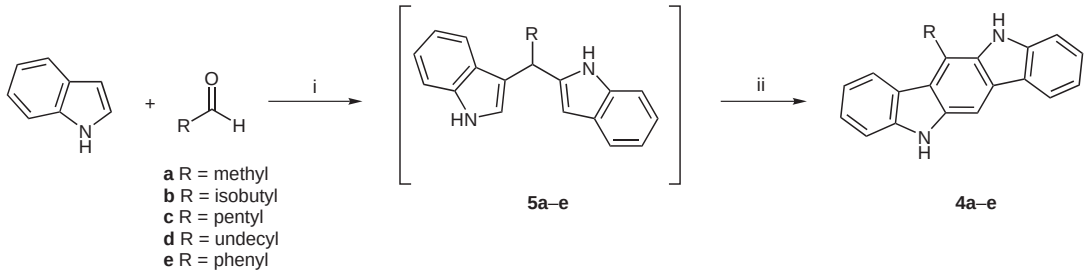
The Ullmann-type coupling of aryl halides with ICZ is a straightforward, inexpensive approach to obtain N-arylated ICZ. Under the conditions of Ullmann coupling we have previously reported for the synthesis of oligocarbazoles,[7a–d] the desired N-disubstituted products **6c**–**f** were obtained in good yield (Scheme 3). The results for these N-substituted derivatives of 6-pentyl indolo[3,2-*b*]carbazole (**4c**) are summarized in Table 2.



Scheme 3 *Reagents and conditions*: (i) compounds **6a**–**b**: NaH, DMF, 70 °C, bromoethane or *p*-TsCl; (ii) compounds **6c**–**f**: Cu (bronze), iodoarene, *o*-dichlorobenzene, 190 °C.

An N-monoarylated derivative of **4c** was not obtained when 1 equivalent of iodobenzene was used under the same Ullmann coupling conditions as described above. The reaction gave in all cases only the completely N-arylated derivative **6c**.

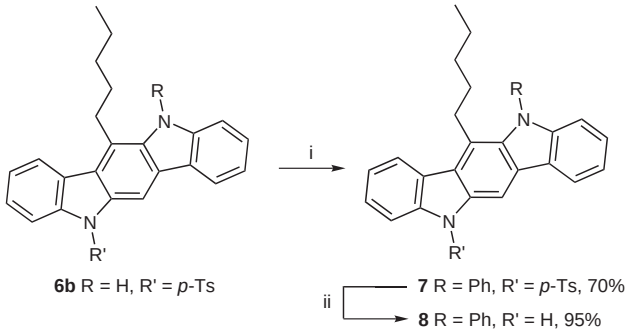
To solve this problem, we designed an alternative synthetic route. First, N-arylation of **6b** afforded the corresponding monoarylated product **7** in 70% yield. Deprotection of the *p*-tosyl group of **7** under basic conditions gave compound **8** in 95% yield (Scheme 4).



Scheme 2 *Reagents and conditions*: (i) 0.2 equiv I_2, MeCN, r.t., 14 h; (ii) $(EtO)_3CH$, MeOH, 0.2 equiv CH_3SO_3H, r.t., 14 h.

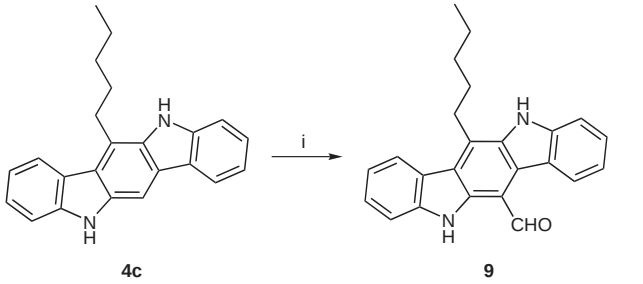
Table 2 N-Substituted Derivatives of Compound **4c**

Compound	R	R′	Method	Yield (%)
6a	Ethyl	Ethyl	i	50
6b	H	Tosyl	i	60
6c	Phenyl	Phenyl	ii	70
6d	2-Thienyl	2-Thienyl	ii	53
6e	4-Nitrophenyl	4-Nitrophenyl	ii	65
6f	4-[3,6-Bis(*tert*-butyl)carbazol-9-yl]phenyl	4-[3,6-Bis(*tert*-butyl)carbazol-9-yl]phenyl	ii	70



Scheme 4 *Reagents and conditions*: (i) iodobenzene, Cu (bronze), *o*-dichlorobenzene, 190 °C; (ii) KOH–MeOH, THF, 55 °C.

The formylation of **4c** was accomplished by the well-known Vilsmeier reaction ($POCl_3$/DMF). By using an excess of the reagent, the 6-formyl-12-pentyl-5,11-dihydroindolo[3,2-*b*]carbazole (**9**) was formed selectively and isolated in 50% yield (Scheme 5), opening an entry to potential ligands for the Ah receptor.



Scheme 5 *Reagents and conditions*: (i) $POCl_3$, DMF, 1,2-dichloroethane, 85 °C.

In contrast to the formylation, the bromination of compound **4c** was not selective and the brominated products depended on the reaction conditions, such as the amount of the halogenation reagent and the reaction temperature. When the reaction was carried out in dichloromethane at room temperature in the presence of 1–2 equivalents of *N*-bromosuccinimide (NBS), a complex product pattern of mono-, di- and tribrominated compounds was observed. However, by using 3 equivalents of NBS, we succeeded to isolate the corresponding 2,6,8-tribrominated compound **10** in 20% yield. Moreover, by using 5 equivalents of bromine in acetic acid and under reflux, the 2,4,6,8,10-pentabrominated compound **11** was isolated in 40% yield.

On the other hand, the 2,8-dibrominated compound **12** was synthesized with our three-stage one-pot approach with 5-bromoindole as the starting material, but initially the reaction failed due to very slow isomerization of the corresponding 3,3′-bis(indolyl)hexane to the 2,3′-isomer. However, when instead of iodine, the more active hydroiodic acid was used as the catalyst for the condensation reaction, the final dibrominated compound **12** was obtained in 26% overall yield (Scheme 6).

In summary, an easy and efficient three-stage one-pot synthetic approach towards various 6-monosubstituted 5,11-dihydroindolo[3,2-*b*]carbazoles has been developed. Iodine was found to be a highly convenient catalyst for promoting the electrophilic reaction, under mild condition, of indole with aliphatic aldehyde to afford 2,3′-bis(indolyl)alkanes, which are used as intermediates to synthesize the corresponding 6-monosubstituted ICZs with methanesulfonic acid as a catalyst. Enhanced solubility and stability towards oxidative degradation allows for easy modification. Thus, the ICZ **4c** was substituted under different conditions, including N-alkylation, N-tosylation, copper-catalyzed Ullmann coupling, Vilsmeier reaction and bromination. In the case of N-tosylation and C-formylation, monofunctionalized compounds are selectively obtained.

All synthesized compounds were fully characterized by the usual techniques including ^{1}H NMR, ^{13}C NMR and mass spectrometry.[8]

Acknowledgment

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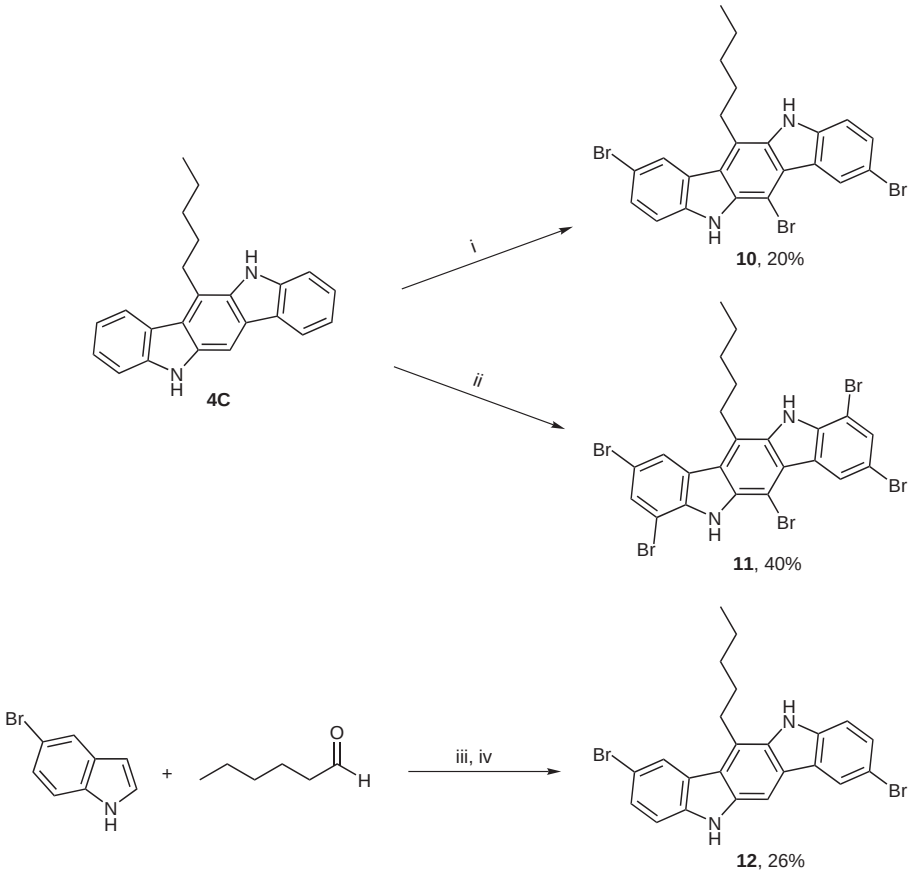

Scheme 6 *Reagents and conditions*: (i) 3 equiv NBS, CH_2Cl_2, r.t.; (ii) 5 equiv Br_2, AcOH, reflux; (iii) 0.2 equiv HI, MeCN, 60 °C; (iv) $(EtO)_3CH$, MeOH, 0.2 equiv CH_3SO_3H, r.t.

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(8) **Synthesis of Compound 4c.**
To a solution of indole (4.6 g, 40 mmol) and *n*-hexanal (2.1 g, 20 mmol) in MeCN (10 mL) was added I_2 (1 g, 4 mmol). The reaction was stirred at r.t. for 14 h. Then, aq sat. Na_2SO_3 was added until the iodine color disappeared and the solution was extracted with EtOAc (3 × 20 mL). After concentration of the organic layers, the crude product and triethyl orthoformate (2.9 g, 20 mmol) were dissolved in MeOH (4 mL). After the addition of methanesulfonic acid (0.3 mL, 4 mmol), the reaction was stirred overnight at r.t. The precipitate was filtered off and washed with MeOH. After drying the pure **4c** (2.9 g, 45%) was obtained as a light yellow solid; mp 286–289 °C. IR (KBr): ν = 3405 (s), 2923 (m), 2860 (m), 1611 (m), 1527 (s), 1460 (s), 1422 (s) cm^{-1}. ^1H NMR (DMSO): δ = 0.85 (3 H, t, CH_3), 1.39 (2 H, m, CH_2), 1.56 (2 H, m, CH_2), 1.82 (2 H, m, CH_2), 3.50 (2 H, m, CH_2), 7.12 (2 H, m, 2 ICZ-H), 7.37 (2 H, m, 2 ICZ-H), 7.47 (2 H, m, 2 ICZ-H), 7.95 (1 H, s, H-12), 8.14 (dd, 2 H, 2 ICZ-H), 10.90 (1 H, s, NH), 11.05 (1 H, s, NH). ^{13}C NMR (DMSO): δ = 14.9, 23.2, 29.3, 29.7, 32.5, 98.8, 111.2, 111.4, 118.4, 118.7, 119.1, 121.0, 121.1, 122.7, 123.1, 123.4, 123.7, 125.6, 126.3, 134.9, 136.4, 142.1. HRMS (EI): *m/z* calcd for $C_{23}H_{22}N_2$ $[M]^+$: 326.17833; found: 326.17801.