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Facile synthesis of novel indolo[3,2-*b*]carbazole derivatives and a chromogenic-sensing 5,12-dihydroindolo[3,2-*b*]carbazole†

Rong Gu, Koen Robeyns, Luc Van Meervelt, Suzanne Toppet and Wim Dehaen*

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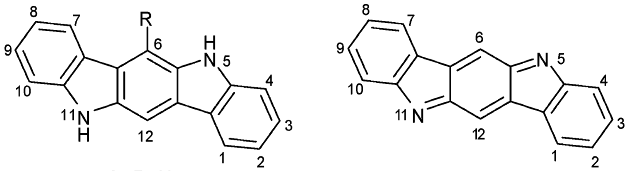
Novel indolo[3,2-*b*]carbazole derivatives and a chromogenic-sensing 5,12-dihydroindolo[3,2-*b*]carbazole have been synthesized starting from tetra-*tert*-butylated 6,12-diaryl-5,11-dihydroindolo[3,2-*b*]carbazoles, which were prepared *via* an efficient *tert*-butylation of 6,12-diaryl-5,11-dihydroindolo-[3,2-*b*]carbazoles.

5,11-Dihydroindolo[3,2-*b*]carbazole (ICZ) **1a** (Fig. 1) is formed in acidic medium as a condensation product of indole-3-carbinol, which originates from cruciferous vegetables. It has been reported that the ICZ is a natural agonist of the TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) receptor (Ah receptor)[1] and 6-formylindolo[3,2-*b*]carbazole **1b** has indeed an extremely strong affinity to the Ah receptor, binding 5–8 times as strong to the receptor as TCDD itself.[2] Since the last decade, the electrical and optical properties of ICZs have been widely studied. 5,11-Dihydroindolo[3,2-*b*]carbazoles and polyindolo[3,2-*b*]carbazoles can be used as active materials for organic light-emitting diodes,[3] organic field-effect transistors,[4] organic thin-film transistors[5] and photovoltaic cells.[6] Two-step redox processes of ICZ have been studied and the first indolo[3,2-*b*]carbazole derivative **2** was prepared by the oxidation of 5,11-dihydroindolo[3,2-*b*]carbazole **1a** with PbO_2 or DDQ.[7] Until now, only one such indolo[3,2-*b*]carbazole derivative has been reported, mainly because of poor solubility in organic solvents and lack of chemical stability.



1a R=H
1b R=CHO

2

Fig. 1

In this communication, we disclose a facile method to prepare indolo[3,2-*b*]carbazole derivatives in good yields based on *tert*-butylated ICZs which show an increased solubility in organic solvents. Moreover, a novel 5,12-dihydroindolo[3,2-*b*]carbazole was synthesized for the first time and this ICZ derivative can act as a selective colorimetric sensor either for F^- or Brønsted acids in aprotic solvents.

In our previous work,[8] we reported a three-stage one pot approach to synthesize 6-monosubstituted ICZs which have better solubility in organic solvents. Thus, we tried to prepare indolo[3,2-*b*]carbazoles starting from 6-pentyl-5,11-dihydroindolo[3,2-*b*]-carbazole **3a**. In 2000, Yudina *et al.* showed that 5,11-dihydroindolo[3,2-*b*]carbazole can be oxidized to indolo[3,2-*b*]carbazole **2** with DDQ in a large volume of ethyl acetate (30 mg ICZ in 200 mL ethyl acetate).[7b] Under the same conditions, we treated 6-pentyl-5,11-dihydroindolo[3,2-*b*]carbazole **3a** with 2 equivalents DDQ in ethyl acetate under reflux. After 5 hours, much longer than the described reaction time, we did not observe the corresponding indolo[3,2-*b*]carbazole formed, and only the starting materials were present in the reaction solution. As reported by Horner *et al.* in 1982, the deprotonated 5,11-dihydro ICZs are a two-step redox system, in which the three oxidation levels are separated by the redox potentials E_1 and E_2 (Fig. 2).[9] Apparently, SEM state is the intermediate for the preparation of indolo[3,2-*b*]carbazoles, which is the OX state in the redox process. Moreover, the final OX state has partial biradical character, which may lead to decomposition *via* coupling reactions. We have previously observed such C–C and C–N coupling reactions on treating ICZ derivatives with oxidants.[10] It has been reported that a stable radical compound was successfully prepared from 1,3,6,8-tetra-*tert*-butyl-9*H*-carbazole.[11] Thus, the *tert*-butyl group can stabilize the indolo[3,2-*b*]carbazoles. Furthermore, *tert*-butyl groups can improve the solubility of ICZs in organic solvents. We have applied the same method to increase the yield of Ullmann coupling reactions with 3,6-di-*tert*-butylcarbazole.[12]

First we studied the *tert*-butylation of 6-pentyl-5,11-dihydroindolo[3,2-*b*]carbazole **3a**. $AlCl_3$ or $ZnCl_2$ were used as a Lewis acid and chloroform or nitromethane were used as solvents for Friedel–Crafts *tert*-butylation. It turned out that $ZnCl_2$ and chloroform were the best combination for the *tert*-butylation. The reaction of compound **3a** with excess $ZnCl_2$ and *tert*-butyl

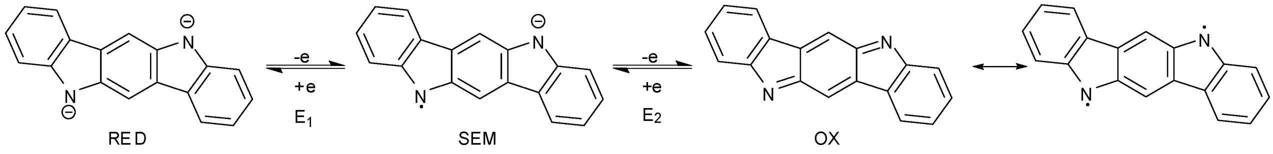
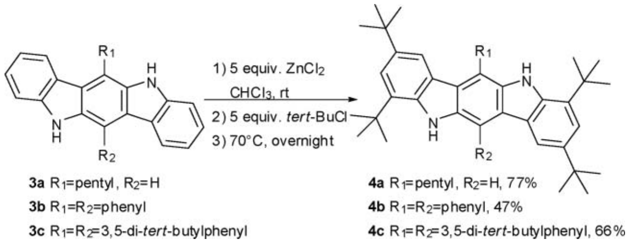


Fig. 2 Two-step redox process of deprotonated ICZs.

Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001, Leuven, Belgium. E-mail: wim.dehaen@chem.kuleuven.be; Fax: +32(16)327990;; Tel: +32(16)327439

† Electronic supplementary information (ESI) available: Details for the synthesis and characterization of compounds and X-ray crystallography of compound **4a** and **5b**. See DOI: 10.1039/b807255h

chloride (5 equivalents) mainly afforded the tetra-*tert*-butylated 6-pentyl ICZ **4a** in 77% yield (Scheme 1). Even when we treated 6-pentyl ICZ with large excesses (10 equivalents) of $ZnCl_2$ and *tert*-butyl chloride, we only obtained the tetra-substituted ICZ with a trace amount of tri- and di-substituted ICZ and none of the penta-substituted or more complex ICZs. From the X-ray crystallography of compound **4a**, we can confirm that the *tert*-butyl groups were indeed at the 2,4,8,10-positions of the ICZ ring (Fig. 3).‡



Scheme 1 *tert*-Butylation of ICZs.

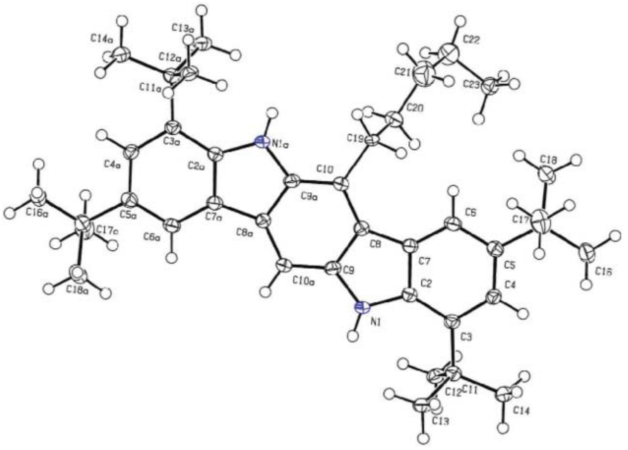
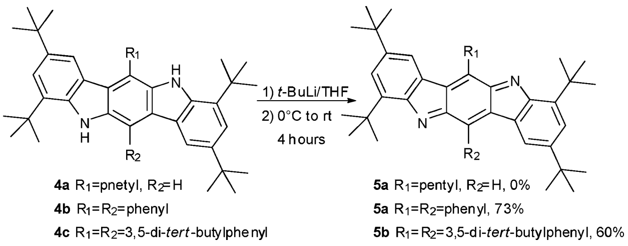


Fig. 3 ORTEP representation of **4a** with thermal displacement ellipsoids shown at the 50% probability level.‡

Recently, we have reported a two-step method to prepare 6,12-diaryl-5,11-dihydroindolo[3,2-*b*]carbazoles **3b–c** in moderate yields.[13] These symmetrical molecules are slightly soluble in chloroform. However, the *tert*-butylation leading to ICZs **4b–c** was successfully accomplished in good yields (47–66%). Compounds **4b–c** were only slightly soluble in polar solvents, such as ethyl acetate or methanol. This allowed an easy purification of the compounds **4b–c**, simply by dispersing the crude product in ethyl acetate or methanol and then filtering the pure products. On the other hand, these *tert*-butylated 6,12-diaryl ICZs have good solubility in less polar organic solvents such as chloroform and dichloromethane. Therefore, 2,4,8,10-tetra-*tert*-butyl-6,12-diaryl-5,11-dihydroindolo[3,2-*b*]carbazoles are good candidates for our preparation of indolo[3,2-*b*]carbazole derivatives.

When we treated compound **4b** with 2 equivalents of DDQ in dry THF at room temperature or 70 °C, we found that only part of the starting material converted to the oxidized product **5b**. When compound **4b** was deprotonated with 2 equivalents of *t*-BuOK in dry THF at 0 °C and then oxidized with 2 equivalents of DDQ at room temperature or 70 °C, the same result was observed as the reaction with DDQ. Interestingly, we found the oxidation reagent DDQ is not necessary for the preparation of indolo[3,2-*b*]carbazoles. When we treated compound **4b** only with 4 equivalents of *t*-BuOK at −40 °C, most of the 5,11-dihydro ICZ was oxidized to the indolo[3,2-*b*]carbazole after 4 hours (monitored by TLC) and we isolated compound **5b** in 50% yield. Keeping the reaction going for a longer time did not help the conversion of all of the starting material to the desired product. Later we found that *t*-BuLi was a more efficient base for the preparation of the oxidized ICZs **5b–c**. We treated compound **4b** with 4 equivalents of *t*-BuLi in dry THF at 0 °C and then the reaction solution was stirred at room temperature for 4 hours to afford 2,4,8,10-tetra-*tert*-butyl-6,12-diphenyl-indolo[3,2-*b*]carbazole **5b** in 73% yield (Scheme 2). From the structure determination of compound **5b** (Fig. 4), the bond lengths confirmed the formation of the 1,4-quinonediimine structure. There was no stable analogue of **5** formed when we treated compound **4a** and 6,12-diphenyl-5,11-dihydroindolo[3,2-*b*]carbazole **3b**, which are insufficiently shielded for coupling reactions, with the same method.



Scheme 2 Synthesis of indolo[3,2-*b*]carbazole derivatives.

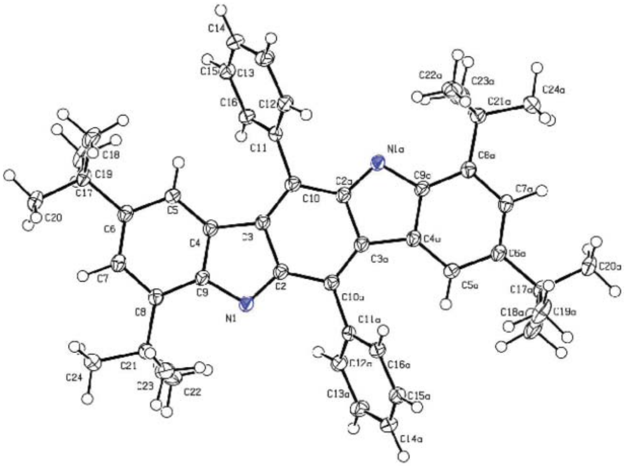
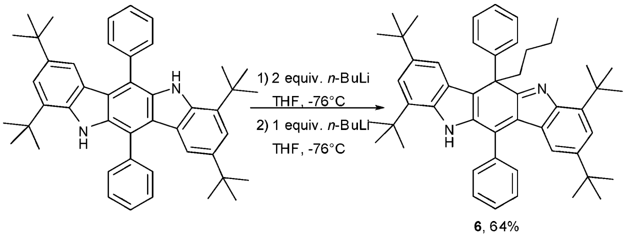


Fig. 4 ORTEP representation of **5b** with thermal displacement ellipsoids shown at the 50% probability level.‡

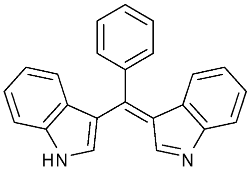
After we used *n*-BuLi as a base during the optimization of the reaction condition of the synthesis of compound **5b**, we isolated an orange compound with MS (ESI) *m*/*z* 689 ([M + H]$^+$). The structure of this compound was assigned as a novel 5,12-dihydroindolo[3,2-*b*]carbazole based on 1D and 2D NMR spectra. The reasonable mechanism was that the deprotonated ICZ was oxidized by oxygen to indolo[3,2-*b*]carbazole, and then the Michael addition of *n*-BuLi to the formed indolo[3,2-*b*]carbazole occurred. To test our hypothesis, we treated compound

5b with 1 equivalent of *n*-BuLi in the dark. The 5,12-dihydro ICZ was formed after 4 hours at room temperature. In our optimized reaction conditions, we first treated compound **4b** with 2 equivalents of *n*-BuLi at −76 °C in the dark for 20 minutes, then 1 equivalent of *n*-BuLi was added at the same temperature. After 20 minutes, the reaction was stopped by the addition of H_2O. Thus, we prepared 5,12-dihydroindolo[3,2-*b*]carbazole **6** in 64% yield (Scheme 3).



Scheme 3 Synthesis of 5,12-dihydro ICZ.

It has been demonstrated that 3,3′-bis(indolyl)methene **7** (Fig. 5) can act as a selective colorimetric sensor either for F^- in aprotic solvent or for HSO_4^- and weak acidic species in a water-containing medium.[14] The 5,12-dihydro ICZ **6**, which contains a 2,3-bis(indolyl)methene moiety with an acidic H-bond donor –NH and a basic H-bond acceptor nitrogen, has some similarity with compound **7**.



7

Fig. 5 3,3′-Bis(indolyl)methene **7**.

In the aprotic solvent, acetonitrile, we observed a significant color change of compound **6** from yellow to blue after the addition of 25 equivalents of F^-. A similar, but more remarkable spectral change was observed upon the addition of a Brønsted acid, such as acetic acid and trifluoroacetic acid. There was no noticeable color change on addition of AcO^- and HSO_4^- anions (Fig. 6). A dramatic color change was caused by the deprotonation/protonation of indolyl moieties. The band at 480 nm of the starting solution was red-shifted to 554 nm in the presence of F^- and to 595 nm on addition of acetic acid or trifluoroacetic acid, while the intensity of the red-shifted band remarkably increased in the presence of the stronger Brønsted acid, CF_3COOH. The titration of compound **6** with trifluoroacetic acid showed three isosbestic points at 297 nm, 343 nm and 517 nm and in the presence of 10 equivalents of CF_3COOH, the band at 595 nm almost reached the maximum (Fig. 7).

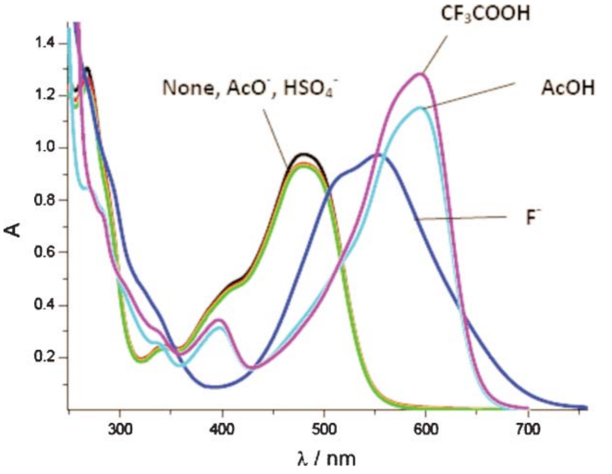


Fig. 6 UV–Vis spectra of compound **6** in MeCN (5.0×10^{-5}M) after the addition of 25 equivalents of various anions and Brønsted acids (none, AcO^-, HSO_4^-, F^-, AcOH, CF_3COOH).

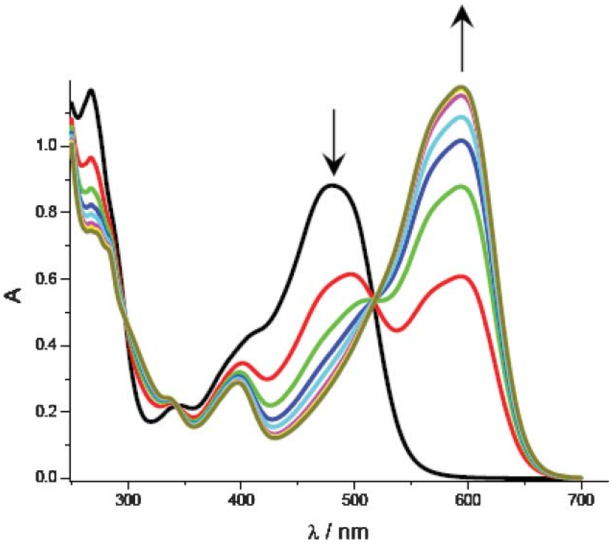


Fig. 7 UV–Vis spectra of compound **6** (5.0×10^{-5}M) in MeCN after the addition of 1, 2, 3, 4, 6, 8, 10 equivalents of CF_3COOH.

In summary, the Friedel–Crafts *tert*-butylation of 6-pentyl and 6,12-diaryl-5,11-dihydroindolo[3,2-*b*]carbazoles has been accomplished by using $ZnCl_2$ as a Lewis acid and chloroform as a solvent in moderate to good yields. Novel indolo[3,2-*b*]carbazole derivatives **5b–c** have been successfully synthesized based on the *tert*-butylated 6,12-diaryl ICZs. Meanwhile, a 5,12-dihydroindolo[3,2-*b*]carbazole derivative **6** was prepared for the first time, which can act as a selective chemosensor in aprotic solvents, either for F^- or Brønsted acids.

Acknowledgements

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Notes and references

‡ CCDC reference numbers 686527 and 686528. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b807255h

1 (*a*) M. Gillner, J. Bergman, C. Cambillau, B. Fernstrom and J. A. Gustafsson, *Mol. Pharmacol.*, 1985, **28**, 357; (*b*) U. Rannug, E. Agurell, A. Rannug and H. Cederberg, *Environ. Mol. Mutagen.*, 1992, **20**, 289; (*c*) M. Gillner, J. Bergman, C. Cambillau, M. Alexandersson, B. Fernstrom and J. A. Gustafsson, *Mol. Pharmacol.*, 1993, **44**, 336; (*d*) H.

Liu, M. Wormke, S. H. Safe and L. F. Bjeldanes, *J. Natl. Cancer Inst.*, 1994, **86**, 1758.

2 J. Tholander and J. Bergman, *Tetrahedron*, 1999, **55**, 6243.

3 (*a*) H. X. Hu, S. Xie, Z. Popovic, B. Ong and A. M. Hor, *J. Am. Chem. Soc.*, 1999, **121**, 5097; (*b*) H. P. Zhao, X. T. Tao, P. Wang, Y. Ren, J. X. Yang, Y. X. Yuan, C. X. Yuan, H. J. Liu and D. C. Zhou, *Org. Electron.*, 2007, **8**, 673; (*c*) H. P. Zhao, X. T. Tao, F. Z. Wang, Y. Ren, X. Q. Sun, J. X. Yang, Y. X. Yan, D. C. Zou, X. Zhao and M. H. Jiang, *Chem. Phys. Lett.*, 2007, **439**, 132.

4 S. Wakim, J. Bouchard, M. Simard, N. Drolet, Y. Tao and M. Leclerc, *Chem. Mater.*, 2004, **16**, 4386.

5 (*a*) Y. L. Wu, Y. N. Li, S. Gardner and B. S. Ong, *J. Am. Chem. Soc.*, 2005, **127**, 614; (*b*) Y. N. Li, Y. L. Wu, S. Gardner and B. S. Ong, *Adv. Mater.*, 2005, **17**, 849; (*c*) Y. N. Li, Y. L. Wu and B. S. Ong, *Macromolecules*, 2006, **39**, 6521.

6 (*a*) N. Blouin, A. Michaud, S. Wakim, P. L. T. Boudreault, M. Leclerc, B. Vercelli, S. Zecchin and G. Zotti, *Macromol. Chem. Phys.*, 2006, **207**, 166; (*b*) N. Blouin, M. Leclerc, B. Vercelli, S. Zecchin and G. Zotti, *Macromol. Chem. Phys.*, 2006, **207**, 175.

7 (*a*) S. Hünig and H. C. Steinmetzer, *Justus Liebigs Ann. Chem.*, 1976, 1090; (*b*) L. N. Yudina, M. N. Preobrazhenskaya and A. M. Korolev, *Chem. Heterocycl. Compd.*, 2000, **36**, 1112.

8 (*a*) R. Gu, A. Hameurlaine and W. Dehaen, *Synlett*, 2006, **10**, 1535; (*b*) R. Gu, A. Hameurlaine and W. Dehaen, *J. Org. Chem.*, 2007, **72**, 7207.

9 M. Horner, S. Hünig and H. Pütter, *Electrochim. Acta*, 1982, **27**, 205.

10 R. Gu, K. Van Hecke, L. Van Meervelt, S. Toppet and W. Dehaen, *Org. Biomol. Chem.*, 2006, **4**, 3785.

11 F. A. Neugebauer, H. Fischer, S. Bamberger and H. O. Smith, *Chem. Ber.*, 1972, **105**, 2694.

12 (*a*) A. Hameurlaine and W. Dehaen, *Tetrahedron Lett.*, 2003, **44**, 957; (*b*) N. D. McClenaghan, R. Passalacqua, F. Loiseau, S. Campagna, B. Verheyde, A. Hameurlaine and W. Dehaen, *J. Am. Chem. Soc.*, 2003, **125**, 5356; (*c*) F. Loiseau, S. Campagna, A. Hameurlaine and W. Dehaen, *J. Am. Chem. Soc.*, 2005, **127**, 11352.

13 R. Gu, K. Ahmad and W. Dehaen, unpublished results.

14 X. M. He, S. Z. Hu, K. Liu, Y. Guo, J. Xu and S. J. Shao, *Org. Lett.*, 2006, **8**, 333.