# Synthesis of 7-Pentafluorophenyl-1*H*-indole: An Anion Receptor for Anion–π Interactions

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*Received: 07.05.2014; Accepted after revision: 10.06.2014*

Dedicated to Professor Yu Liu on the occasion of his 60th birthday

**Abstract:** 7-Pentafluorophenyl-1*H*-indole has the potential to be a key compound for the investigation of anion–π interactions in solution. Unfortunately, it was not possible to obtain it by aryl–aryl coupling reaction. Finally, it has been prepared by Bartoli indole synthesis. The key compound as well as analogues were submitted to preliminary studies of anion binding. Single crystals of two key receptors were obtained.

**Key words:** Bartoli indole synthesis, receptors, halides, indoles, molecular recognition

Cation–π interactions have been investigated and applied in various fields for several decades.[1] However, until the beginning of this millennium, corresponding anion–π interactions were sparely investigated. In 2002, several groups[2,3] started thorough investigations of anion–π interactions through quantum chemical calculations and crystallographic studies. Potential roles in chemical and biological systems[4,5] made anion–π interactions an interesting field of investigation.[6,7] For example. Johnson et al.[6] and Wang et al.[8] have studied anion–π interactions in both solution and/or solid state. Reedijk and Gamez,[9] Matile and Schalley,[10] Ballester,[11] Dunbar and Chifotides[7] and coworkers have focused on exploring anion–π interactions and their applications in crystal engineering and other fields. Most recently, Ballester and coworkers thermodynamically characterized anion–π interactions and validated their thermodynamics using extended calix[4]pyrroles.[12] Since 2008 we have been performing detailed studies on the interaction of anions with fluorophenyl moieties in the solid state as well as in solution.[13] However, the role of anion–π interactions in solution are not well and fully understood.[5] In particular, anion–π interactions are easily hidden within a concert of various noncovalent interactions such as hydrogen bonding, lone-pair π and/or π–π interactions. Therefore, the design and preparation of elaborately preorganized anion receptors for exploring and further elucidating anion–π interactions in solution is required. As a recent impressive example, 3,6-di-*tert*-butyl-1,8-bis(pentafluorophenyl)carbazole (**1**) was described to show anion–π interactions in solution (Figure 1).[14] In analogy to this, we identified 7-pentafluorophenyl-1*H*-indole (**2**) and its nonfluorinated analogue **3** to be ideal candidates for the investigation of anion–π interactions. The preparation and characterization of **2** and **3** and of the related amides **4**–**6** including preliminary anion binding studies are described.

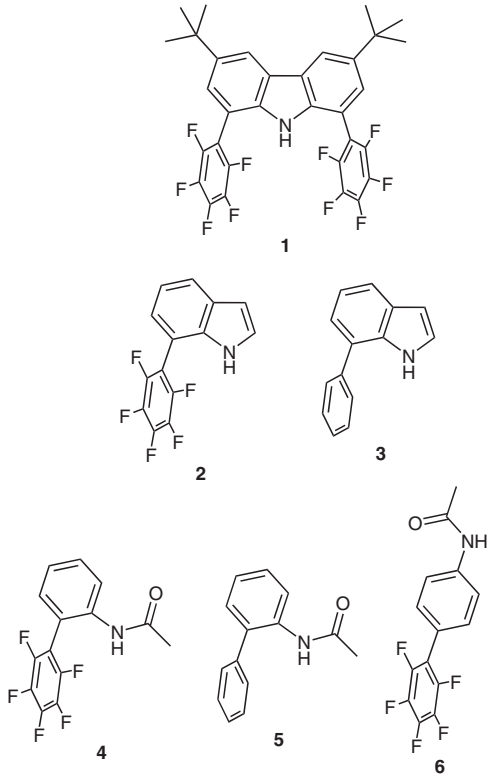


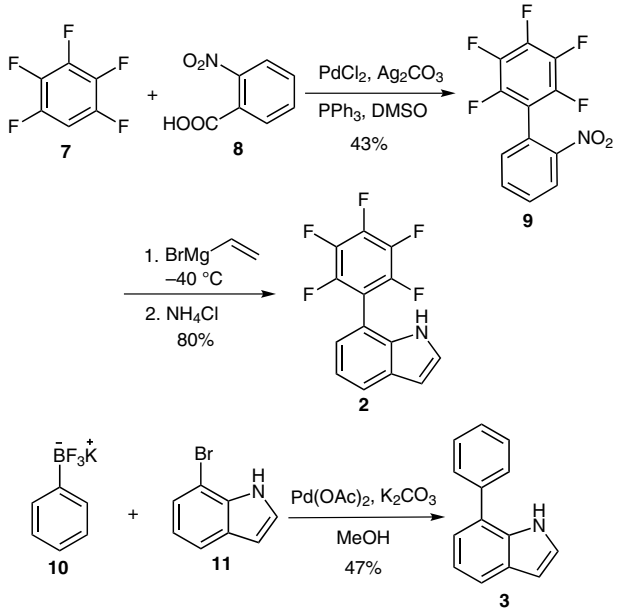

**Figure 1** The already described carbazole anion receptor **1** as described by Meyer, and the indoles **2**, **3**, and amide derivatives **4**–**6** described in this study

Preparation of the perfluorophenylindole **2** was attempted by copper/palladium[6] or just copper-mediated Ullmann coupling,[15] which failed as well as palladium-catalyzed Suzuki–Miyaura coupling using pentafluorophenylboronic acid or potassium pentafluorophenyltrifluoroborates and 7-bromo-1*H*-indole.[16] Palladium-catalyzed Suzuki–Miyaura coupling of 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-1*H*-indole[17] and reaction of hexafluorobenzene with 7-bromo-1*H*-indole[18] were also not

*SYNLETT* 2014, 25, 2075–2077
Advanced online publication: 16.07.2014
DOI: 10.1055/s-0034-1378449; Art ID: st-2014-b0394-l

successful. Thus, the direct coupling of indole and pentafluorophenyl fragments seemed to be no appropriate way for the preparation of **2**.

As an alternative the build-up of the indole skelton bearing the pentafluorophenyl group was applied following the Bartoli indole synthesis.[19] The palladium-catalyzed coupling of pentafluorobenzene (**7**) with 2-nitrobenzoic acid (**8**) afforded pentafluorophenyl-2′-nitro-1,1′-biphenyl (**9**) in 43% yield. Subsequently, **9** was reacted with vinylmagnesium bromide at –40 °C to yield the indole **2** in 80% yield (Scheme 1).[20]



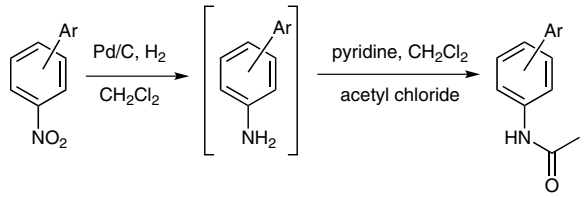

**Scheme 1** Preparation of indoles **2** and **3**

In contrast to the fluorinated derivative, 7-phenyl-1*H*-indole (**3**) was easily obtained in 47% by Suzuki–Miyaura coupling as described before.[16] The difference in the availability of the fluorinated or nonfluorinated compounds **2** and **3** by cross-coupling reaction can be assigned to the 'electronic character' (electron-deficient vs. electron-rich) of the aromatic coupling partner.

The acetamides **4**–**6** were prepared by reduction of the nitro group of the corresponding biaryls[15] **12**–**14** and subsequent reaction of the obtained amines **15** and **16** with acetyl chloride in the presence of pyridine in dichloromethane (yield over two steps: 83% **4**, 79% **5**, 83% **6**; Scheme 2).

The compounds **2**–**6** were characterized by mass spectrometry, elemental analysis, $^1$H NMR, $^{13}$C NMR, $^{19}$F NMR, and IR spectroscopy. The single-crystal structures of fluorinated receptors **2** and **4** were characterized by single-crystal X-ray crystallography.

The key compound **2** shows characteristic signals by $^1$H NMR in $CD_3CN$ at δ = 9.32 (br s, 1 H), 7.77 (dd, $J$ = 2.4, 6.4 Hz, 1 H), 7.31 (m, 1 H), 7.20 (m, 2 H), 6.60 (dd, $J$ = 2.0, 3.2 Hz, 1 H). By $^{19}$F NMR ($CD_3CN$) corresponding




**12** Ar = 2-$C_6F_5$ **15** **4** 83%
**13** Ar = 2-$C_6H_5$ **16** **5** 79%
**14** Ar = 4-$C_6F_5$ **17** **6** 83%

**Scheme 2** Preparation of the acetamides **4**–**6**

resonances are observed at δ = –142.01 (m, 2 F), –158.24 (m, 1 F), –164.51 (m, 2 F).

Results of the crystal-structure analyses of **2** and **4** are shown in Figure 2. In both structures the NH units are well orientated in order to interact with an anion flanked by the pentafluorophenyl moiety. Due to the bicyclic ring system of the indole **2**, this conformation cannot change in solution which due to the flexibility of the acetamide is possible in **4**.

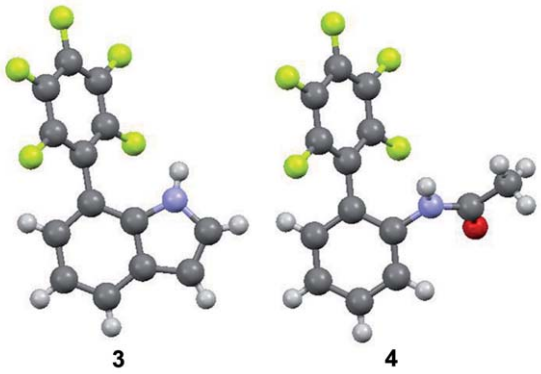



**Figure 2** Molecular structures of **2** and **4** as observed in the crystal. Black: C, grey: H, green: F, blue: N, red: O.[21]

The compounds **2**–**6** were used for anion binding studies with tetrabutylammonium chloride in acetonitrile. The nonfluorinated derivatives **3** and **5** did not show specific binding of the anion. Addition of the chloride salt to the compounds in acetonitrile-$d_3$ resulted in a more or less linear shifting of the resonance of the NH protons. No convergence could be observed.

For **2** and **4** a 1:1 interaction can be shown by Job plots and association constants of 46 $M^{-1}$ (**2**) or 52 $M^{-1}$ (**4**) are determined by $^1$H NMR titrations ($^{19}$F NMR: 50 $M^{-1}$ for **2** and 55 $M^{-1}$ for **4**). Most probably the electron-deficient aromatic units of **2** and **4** allow the binding of the halide to the NH by utilization of attractive anion–π interactions. In addition, enhanced acidity of the indolyl NH due to the influence of the electron-deficient $C_6F_5$ group may lead to the stronger binding. Perhaps both effects contribute to the increased anion binding affinity. In compounds **3** and **5** this interaction is repulsive and no specific binding occurs.



The '*para*'-acetamide **6** behaves in a different fashion as anion binder. Relatively 'high' chloride binding constants of 92 $M^{-1}$ (following NH) or 128 $M^{-1}$ (following $CH_{ortho}$) are determined. Based on the strong effect of anion addition on the resonances of the protons *ortho* to the acetamide of **6**, participation of this proton as extra complexation site is expected.[6] The 2D NOESY cross-peak intensities between N–H and its *ortho* proton increase with the addition of chloride anions. This indicates a coplanar conformation of the amide, and the aryl ring which is enforced by anion binding as shown in Figure 3. There is no indication that similar binding occurs with receptors **2** or **4**.

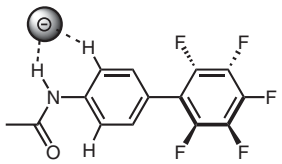



**Figure 3** Proposed receptor **6**–chloride interaction

In this report we presented a facile synthesis for 7-pentafluorophenyl-1*H*-indole (**2**). This key compound could not be obtained by metal-catalyzed aryl–aryl coupling reaction but finally was built up by classical Bartoli indole synthesis. Comparison of **2** with the nonfluorinated **3** as well as **4** and **5** in chloride binding studies shows the ability of the fluorinated receptors **2** and **4** to interact with anions in a specific manner. For the nonfluorinated derivatives no specific interaction is observed. This can be assigned to attraction between the anion and the electron-deficient pentafluorophenyl groups in **2** and **4** and repulsion in case of **3** and **5**. For compound **6** chelated binding of the anion by NH and an *ortho* aryl proton is observed by NMR spectroscopy.

## Acknowledgment

Z.-H. Sun and F. Pan are thankful to the China Scholarship Council for scholarship assistance. K.R. thanks the Academy of Finland for financial support (project no. 263256 and 265328).

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(21) CCDC 1001536 (**2**) and 955438 (**4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



 