A Short, Multigram Synthesis of 1,8-Diaminocarbazole

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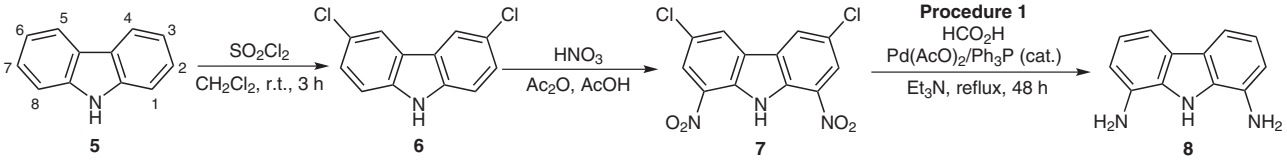
Received 21 June 2010; revised 7 July 2010

PSP No 193

Abstract: A one-pot, multigram, and chromatography-free procedure has been developed for the preparation of 1,8-diamino-9*H*-carbazole, a versatile synthon for the synthesis of anion receptors and conducting polymers. The synthesis consists of a one-pot, palladium-catalyzed reduction of nitro groups and hydrodechlorination of 3,6-dichloro-1,8-dinitrocarbazole, which in turn can be easily produced on a large scale from inexpensive carbazole.

Key words: heterocycles, amines, palladium catalysis, dechlorination, anion receptors



Scheme 1

Polyaromatic systems containing fused pyrrole rings, such as indoles, carbazoles, and indolocarbazoles, are very attractive scaffolds for the construction of anion receptors.[1] They bind anions with their strongly hydrogen bond donating NH groups and have interesting optical and fluorescent properties, which may be used for anion sensing. Moreover, if appropriately functionalized, they may serve as rigid platforms for the attachment of other recognition sites. In this context amino functionalization is particularly versatile, because amino groups can be easily transformed into many other powerful hydrogen bond donors such as amides, thioamides, sulfonamides, ureas, thioureas, guanidines, etc.

The above considerations drew our attention to 1,8-diaminocarbazole as an attractive building block for the construction of anion receptors. It has an interesting array of two NH_2 groups flanking the central carbazole NH moiety, which can be easily elaborated into the binding pocket of a receptor. Unfortunately however, the unsubstituted 1,8-diaminocarbazole has not been easily accessible thus far due to the strong preference of carbazole to undergo electrophilic substitution at positions 3 and 6. For example, direct nitration of carbazole under various conditions gave only 3,6-dinitro- and 1,6-dinitrocarbazole and no trace of the desired 1,8-dinitrocarbazole.[2] Thus, the only literature preparation of 1,8-diaminocarbazole is multistep and impractical.[3]

However, if positions 3 and 6 of the carbazole are blocked by chlorine atoms, nitration smoothly gives 3,6-dichloro-1,8-dinitrocarbazole, which can be easily reduced to 1,8-diamino-3,6-dichlorocarbazole.[4,5] Using this approach we synthesized and studied the first carbazole-based receptors **1** and **2** (Figure 1).[5] These simple compounds, containing two amide groups attached to the carbazole skeleton that form a tridentate binding site, showed remarkably strong and selective anion binding in the very competitive dimethyl sulfoxide–0.5% water medium. More recently, Kim and co-workers described urea derivatives of 1,8-diamino-3,6-dichlorocarbazole as chromogenic and fluorogenic anion sensors (Figure 1).[6]

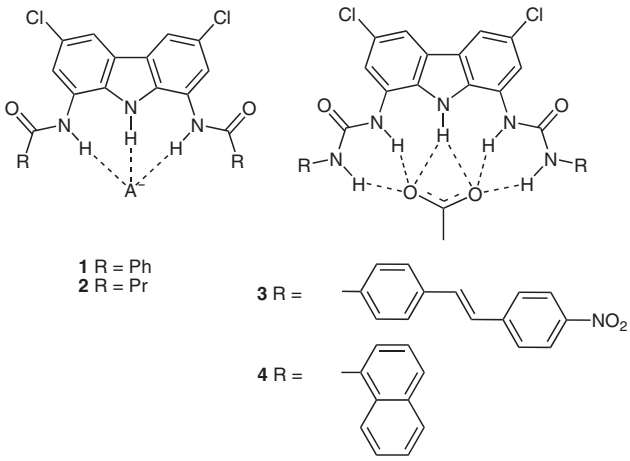


Figure 1

Although chlorine substituents are perhaps beneficial for anion binding, their removal opens new reactivity pathways, leading to exciting opportunities. We have recently shown that the unsubstituted 1,8-diamino-9*H*-carbazole

SYNTHESIS 2010, No. 18, pp 3067–3069
Advanced online publication: 04.08.2010
DOI: 10.1055/s-0030-1258191; Art ID: P09710SS

(**8**) smoothly undergoes electropolymerization to give a conducting polymer with attractive properties.[7–9] Based on these results we hypothesize that some anion receptors derived from 1,8-diaminocarbazole **8** may form anion responsive conducting polymers. To explore these opportunities further, we needed an easy access to multigram quantities of the key precursor. Here we present a detailed procedure for a practical, one-pot, chromatography-free, and multigram synthesis of 1,8-diamino-9*H*-carbazole (**8**).

9*H*-Carbazole (**5**) is an inexpensive starting material, available industrially on a multi-ton scale, so the synthetic strategies based on its derivatization have a clear advantage over approaches involving the construction of the carbazole skeleton. Also, any practical, large-scale derivatization of carbazole **5** may be of industrial significance. Taking advantage of the versatile literature procedures for the selective chlorination of carbazole at positions 3 and 6 to give 3,6-dichlorocarbazole **6**, and subsequent nitration at positions 1 and 8 to give 3,6-dichloro-1,8-dinitrocarbazole **7**, we sought an effective dechlorination procedure for **7** to complete the protection–nitration–deprotection sequence (Scheme 1).

The best results were obtained using palladium-catalyzed reduction with triethylammonium formate developed by Cortese and Heck.[10] With simple chloronitroarenes the method allows removal of chlorine atoms without affecting the nitro group. However, in our case reduction of the nitro groups was faster than dechlorination, and 1,8-dinitrocarbazole could not be isolated. Instead, an excess of reagent transforms 3,6-dichloro-1,8-dinitrocarbazole **7** directly into the desired 1,8-diaminocarbazole **8** in a one-pot reaction. Palladium-on-carbon, originally proposed as the catalyst of choice for this transformation, did not work with our substrate. However, palladium(II) acetate/triphenylphosphine, also proposed by Cortese and Heck, gives the desired amine **8** in 70% yield on a 5-mmol scale after column chromatography or in 51% yield on a 50-mmol scale after crystallization. Thus, the status of the chlorine substituents changed from blocking groups to protective groups.

Although iodine and bromine substituents are both easier to introduce and easier to remove from carbazole, they were not considered as protecting groups because of their lability under nitration conditions.[11,12]

1,8-Diamino-9*H*-carbazole (**8**) is prone to aerial oxidation and decomposes in solution over a period of several hours to give a violet tar. Therefore, whenever possible and practical, deoxygenated solvents should be used for the synthesis and crystallizations to maximize yields and purity.

Preparative crystallization of 1,8-diaminocarbazole **8** from hot water–methanol mixture gives high-quality crystals suitable for X-ray analysis. The analysis revealed that the product crystallizes as a semihydrate $C_{12}H_{11}N_3 \cdot 0.5H_2O$. Interestingly, the 1,8-diaminocarbazole forms an unsymmetric dimer in the solid state, where the amino group of one molecule is bound within the binding pocket of the other molecule and vice versa (Figure 2). Pyrrolic NH groups form the shortest hydrogen bonds, 2.087 Å and 2.184 Å in length. The dimer is L-shaped with planes of the two carbazole moieties intersecting at almost exactly right angles (89.6°).

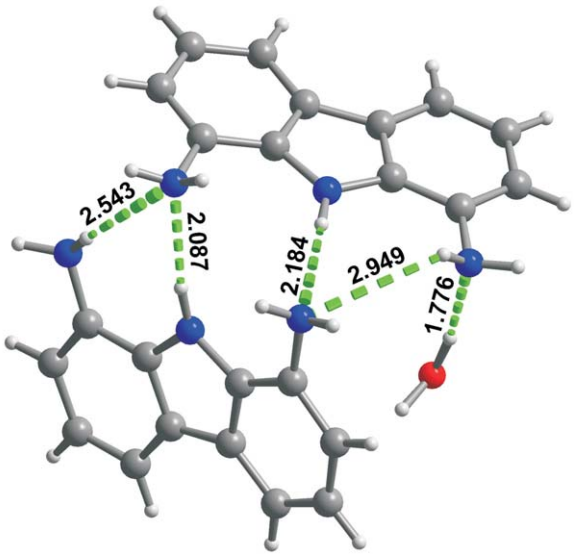


Figure 2 Crystal structure of the 1,8-diaminocarbazole semihydrate $C_{12}H_{11}N_3 \cdot 0.5H_2O$; distances are given in Å

In summary, we have developed a short, multigram, and chromatography-free synthesis of 1,8-diamino-9*H*-carbazole (**8**), a versatile synthon for the construction of anion receptors, conducting polymers, and heterocycles. The synthetic sequence utilizes chlorination/hydrodechlorination to protect/deprotect the most reactive positions 3 and 6 of the carbazole skeleton and to direct nitration to positions 1 and 8. The key step, described here, consists of a one-pot reduction of the nitro groups and hydrodechlorination. Thus, 1,8-diamino-9*H*-carbazole (**8**) is now available in three steps from inexpensive carbazole **5** or in just two steps from commercially available 3,6-dichlorocarbazole **6**.

NMR spectra were measured on a Varian Gemini 200 (^{1}H: 200 MHz, ^{13}C: 50 MHz) with the solvent signals as internal standards. ESI mass spectra were obtained with a Mariner (ESI TOF) and API 365 (ESI 3Q) mass spectrometers with MeOH as the spray solvent. All reagents for the syntheses were obtained from Aldrich or Fluka and were used as purchased. TLC was carried out on Merck silica gel 60 F254 aluminum plates; column chromatography used Merck silica gel 60 (63–100 μm mesh).

1,8-Diamino-9*H*-carbazole (8)

A 250-mL round-bottomed, 3-neck flask equipped with a large magnetic stirrer bar was charged with 3,6-dichloro-1,8-dinitro-9*H*-carbazole[5] (**7**, 16.305 g, 50 mmol), $Pd(OAc)_2$ (225 mg, 1 mmol), Ph_3P (525 mg, 2 mmol), and Et_3N (100 mL). The flask was fitted with a condenser with a $CaCl_2$ tube, a gas inlet, and a septum. The mixture was purged with argon for 15 min. HCO_2H (previously purged with argon for 15 min, 20 mL, 0.53 mol) was slowly added with stirring. During the addition the mixture heated up and dark-

ened, and CO began to evolve (*CAUTION!* Toxic! Work under an efficient fumehood). The mixture was vigorously stirred under reflux until chlorinated intermediates had disappeared [TLC monitoring (silica gel, CH_2Cl_2–MeOH, 9:1): R_f = 0.34 (**7**), 0.30 (**8**), 0.22 (1,8-diamino-3-chloro-9*H*-carbazole)]; typically, the reaction took 24–48 h. After this time the mixture was cooled to r.t. and excess Et_3N was decanted. The black, oily residue was dissolved in MeOH, filtered through Celite, and evaporated to dryness. The residue was dissolved in boiling MeOH (~80 mL) and carefully precipitated with a 3-fold excess of boiling H_2O (preferably deoxygenated by bubbling argon through it). A black oil precipitated first, and stuck to the flask walls. After ~10 min the aqueous suspension was decanted from the black oil and left in a refrigerator overnight. The product crystallized as long, silvery, translucent needles that were separated from a very fine suspension of a violet tar by filtration through a rather course filter (for example sintered glass G-3) and washing with H_2O. The crystals were further washed with a minimal amount of MeOH to yield $C_{12}H_{11}N_3 \cdot 0.5H_2O$ (5.3 g, 51%). Alternatively, the product was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 97:3).

^{1}H NMR (200 MHz, DMSO-d_6): δ = 10.37 (s, 1 H, NH), 7.27 (dd, J_1 = 7.4 Hz, J_2 = 1.0 Hz, 2 H, H4, H5), 6.86 (t, J_1 = 7.4 Hz, 2 H, H3, H6), 6.63 (dd, J_1 = 7.4 Hz, J_2 = 1.0 Hz, 2 H, H2, H7), 4.99 (s, 4 H, NH_2).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 133.4 (C_q), 128.7 (C_q), 123.5 (C_q), 119.3 (CH), 109.2 (CH), 108.8 (CH).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}N_3$: 198.1026; found: 198.1036.

Anal. Calcd for $C_{12}H_{11}N_3 \cdot 0.5H_2O$: C, 69.88; H, 5.86; N, 20.37. Found: C, 70.29; H, 5.83; N, 20.02.

X-ray measurement: The above-described preparative crystallization gave high quality crystals suitable for X-ray diffraction. An X-ray measurement was performed at 100(2) K on an Oxford Diffraction Gemini κ-axis diffractometer with graphite-monochromated CuKα X-ray source. The crystal was positioned 55 mm from the CCD camera. 787 Frames were measured at 1° intervals with a counting time of 16 sec. Data reduction and analysis were carried out with the Kuma Diffraction programs. The data were corrected for Lorentz and polarization effects and multiscan absorption correction[13] was applied. The structure was solved by direct methods[14] and refined using SHELXL.[15] The refinement was based on F^2 for all reflections except for those with very negative F^2. The weighted *R* factor, *wR* and all goodness-of-fit *S* values are based on F^2. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms, except at carbons, were located from a difference maps and their positions refined isotropically. The other hydrogen atoms were placed in calculated positions and refined within riding model. The atomic scattering factors were taken from the international tables.[16] Crystal data for 1,8-diamine-9*H*-carbazole (**8**): 2 $C_{12}H_{11}N_3 \cdot H_2O$; *Mr* = 412.49, *T* = 100(2) K, orthorhombic, space group $P2_12_12_1$, *a* = 4.93510(10) Å, *b* = 12.1706(3) Å, *c* = 32.9493(5) Å, *V* = 1979.04(7) Å^3, *Z* = 4, *d* = 1.384 g cm^{-3}, μ = 0.711 mm^{-1}, *F*(000) = 872, θ range 4.52° to 67.19°, 10563 reflections collected, 2089 unique [R_{int} = 0.0314] which were used in all calculations, GOF = 1.055. The final R_1 and wR_2 (F^2) were 0.0321, 0.0758 (all data), 0.0297 and 0.0743 [$I > 2\sigma(I)$]. Largest diff. peak and hole: 0.186 and –0.166 eÅ^{-3}.[17]

Acknowledgment

We kindly acknowledge Dr Michał K. Cyrański (University of Warsaw) and Dr Izabela Madura (Warsaw University of Technology) for their help with X-ray analysis. Also, we gratefully acknowledge financial support from the Foundation for Polish Science and European Economic Area through Homing Programme.

References

(1) Gale, P. A. *Chem. Commun.* **2008**, 4525.
(2) Grotta, H. M.; Riggle, C. J.; Bearse, A. E. *J. Org. Chem.* **1964**, *29*, 2474.
(3) Takahashi, K.; Eguchi, H.; Shiwaku, S.; Hatta, T.; Kyoya, E.; Yonemitsu, T.; Mataka, S.; Tashiro, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1869.
(4) Mužik, F.; Allan, Z.; Poskočil, J. *Collect. Czech. Chem. Commun.* **1958**, *23*, 770.
(5) Chmielewski, M. J.; Charon, M.; Jurczak, J. *Org. Lett.* **2004**, *6*, 3501.
(6) Thangadurai, T. D.; Singh, N. J.; Hwang, I. C.; Lee, J. W.; Chandran, R. P.; Kim, K. S. *J. Org. Chem.* **2007**, *72*, 5461.
(7) Skompska, M.; Chmielewski, M. J.; Tarajko, A. *Electrochem. Commun.* **2007**, *9*, 540.
(8) Tarajko, A.; Cybulski, H.; Chmielewski, M. J.; Bukowska, J.; Skompska, M. *Electrochim. Acta* **2009**, *54*, 4743.
(9) Tarajko, A.; Michota-Kaminska, A.; Chmielewski, M. J.; Bukowska, J.; Skompska, M. *Electrochim. Acta* **2009**, *54*, 4751.
(10) Cortese, N. A.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3491.
(11) Allan, Z. J.; Mužik, F. *Collect. Czech. Chem. Commun.* **1957**, *22*, 64.
(12) Adimurthy, S.; Vaghela, S. S.; Vyas, P. V.; Bhatt, A. K.; Ramachandraiah, G.; Bedekar, A. V. *Tetrahedron Lett.* **2003**, *44*, 6393.
(13) CrysAlis RED, Oxford Diffraction Ltd., Version 1.171.28cycle4 beta (release 11-11-2005 CrysAlis171.NET) (compiled Nov 11 2005,15:50:43). Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
(14) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467.
(15) Sheldrick, G. M. SHELXL93, Program for the Refinement of Crystal Structures, University of Göttingen, Germany.
(16) *International Tables for Crystallography*, Vol. C; Wilson, A. J. C., Ed.; Kluwer: Dordrecht, **1992**.
(17) Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 770950. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].