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New synthesis of unsymmetrically-substituted 2,5-diarylpyrroles from homopropargyl sulfonamides†

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Unsymmetrically-substituted 2,5-diarylpyrroles were prepared by 5-*endo-dig* cyclization with consecutive deprotection of homopropargyl sulfonamides. Stepwise elaboration of an aldehyde allows the introduction of a variety of functional aryl moieties at the pyrrole ring.

Heterocyclic compounds are of great importance since they are widely distributed in nature and have shown great potential as components in the design of macromolecules.[1] The introduction of heteroatoms such as nitrogen into macromolecular systems introduces particular physical and chemical properties compared to the carbon-only systems.[2] Pyrrole rings are especially well known as π-conjugated aromatic heterocyclic moieties and have been used extensively as building blocks of a broad range of macrocycles including porphyrins,[3] corroles,[4] and calixpyrroles.[5] In addition, pyrrole groups have been demonstrated to be indispensable to the functions of naturally occurring and synthetic prodigiosin and tambjamine derivatives (Fig. 1), which are known to possess substantial antimalarial, immunosuppressive and anticancer potencies due to their H^+/Cl^- binding and transmembrane transport properties.[6] Preorganization of a polarized hydrogen-bond about the pyrrole ring, forming a central binding pocket, is of great importance for the operation of macrocycles and transmembrane transporter systems.

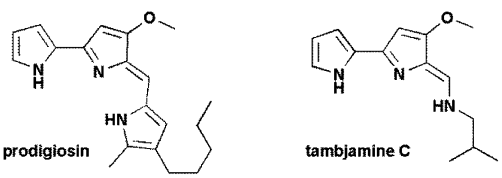

Fig. 1 Natural compounds prodigiosin and tambjamine C.

Prior to this work, we had envisioned synthesis of a variety of anion receptors based on an oligomeric aryl-pyrrole framework. Thus, we set out to explore the potential synthetic methodologies towards pyrroles bearing aryl groups only at the 2,5-positions. Maintaining the 3,4-positions substituent-free allows for the preparation of systems with lower molecular weights (<500 Da), which is one of the requirements stipulated by the Lipinski rules for pharmaceuticals, supposed to increase membrane permeability in biological systems.[7] Various routes for the synthesis of multi-substituted pyrrole moieties have been investigated.[8] There also exist methods for the preparation of 2,5-diarylpyrrole derivatives usually containing an additional electrophilic substituent other than a hydrogen atom at the 3 or 4 positions.[9] Other known methods involve azides,[10a] boronic acid/esters,[10b] toxic stannyl compounds,[11] or unstable intermediates requiring glovebox conditions are available.[12] Other useful methods involve 1,4-butanediones[13] but these are less flexible for syntheses of unsymmetrical derivatives.

A recent development in indole synthesis describes the tetra-*n*-butylammonium fluoride (TBAF)-promoted cyclization of 1-acetyl-2-tosylaminophenyl derivatives leading to unprotected indole compounds.[14] There are three aspects to the function of TBAF in this reaction: the strongly basic character of the fluoride ion results in deprotonation of the sulfonamide with subsequent reaction of the nitrogen at the acetylene forming an *N*-tosylindole ring; nucleophilic fluoride ions lead directly to detosylation giving the 1*H*-indole moiety; finally, tetra-*n*-butylammonium counterions promote the solubility of the fluoride ion in the appropriate solvent. To investigate the potency of TBAF in the synthesis of 2,5-diarylpyrroles a series of homopropargyl sulfonamides was prepared (Scheme 1). Acid-catalyzed condensation reaction on *p*-methoxybenzaldehyde (**1**) with *p*-toluenesulfonamide yielded the corresponding

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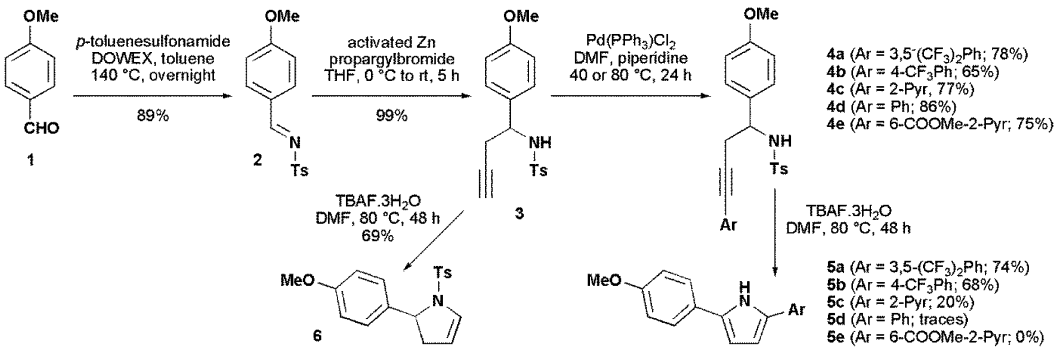
† Electronic supplementary information (ESI) available: Experimental procedures and data for all novel compounds, and CIF file for **5c**. CCDC 962821. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ra46579a



Scheme 1 Synthesis of homopropargyl sulfonamides **4a–e**, 2,5-diarylpyrroles **5a–c** and 2-pyrroline **6**.

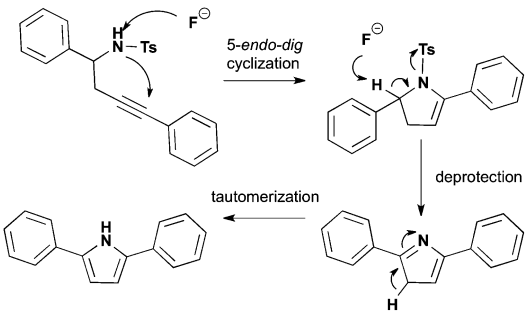
N-tosylimine **2** in 89% yield. Subsequently, Barbier reaction of the *N*-tosylimine **2** with excess propargylzinc bromide yielded homopropargyl sulfonamide **3** in quantitative yield. Sonogashira reactions of the terminal acetylene of sulfonamide **3** with various aryl halides gave sulfonamide derivatives **4a–e** in excellent yields (65–86%; Scheme 1).

Treating CF_3-substituted propargyl sulfonamides **4a** and **4b** with an excess of TBAF·$3H_2O$ (5 equiv.) in DMF at 80 °C for 48 h resulted in the formation of 2,5-diarylpyrroles **5a** and **5b** in excellent yields (74% and 68%, respectively; Scheme 1). The ease with which the CF_3-substituted aryl groups can be introduced onto the pyrrole ring is very useful for tuning the lipophilicity and acidity of molecular receptors. In addition, formation of the pyrrole ring starting from a benzaldehyde allows for the smooth introduction of an electron rich arylgroup without the formation of instable intermediates, making this methodology suitable for various applications.

Under the same reaction conditions (TBAF·$3H_2O$, DMF, 80 °C, 48 h) only 20% yield of pyrrole **5c** was derived from sulfonamide **4c** while for **4d** only trace amounts of pyrrole **5d** were obtained, leaving most of the starting material **4d** intact (Scheme 1). A potential explanation for this lies in the lower electron withdrawing character of pyridinyl and phenyl groups relative to CF_3-substituted phenyl groups. This results in a weaker induced δ^+ charge on the acetylene moiety making nitrogen atom insertion at the sp-hybridized carbon atom more difficult. Even at higher temperatures (stirring at 160 °C) no noteworthy changes were observed and again 18% and trace amounts of pyrrole **5c** and **5d**, respectively, were obtained.

Reaction of a more electron deficient pyridinyl derivative **4e**, containing a methyl ester in the 6-position, resulted solely in the hydrolysis of the ester function without any cyclization. Interestingly, upon exposure of the aryl-free sulfonamide **3** to these cyclization/deprotection reaction conditions (TBAF·$3H_2O$, DMF, 80 °C, 48 h) the reaction terminated upon completion of the 5-*endo-dig* cyclization without deprotection occurring resulting in the *N*-tosyl protected 2-pyrroline **6** in excellent yield (69%; Scheme 1).

When the cyclization/deprotection reaction on a sulfonamide was neutralized after 24 h a mixture of *N*-tosyl-2-pyrroline and 1*H*-pyrrole was obtained. Therefore, the reaction sequence can be considered to commence with an initial 5-*endo-dig*

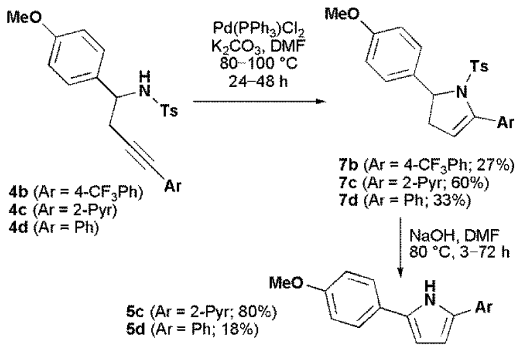


Scheme 2 Proposed reaction sequence from sulfonamide to pyrrole.

cyclization upon deprotonation of the *N*-tosylamide, followed by deprotection through elimination of sulfinic acid, and finally tautomerization leads to formation of the pyrrole ring (Scheme 2).

To extend the scope of applicable aryl groups the introduction of a transition metal catalyst to promote the 5-*endo-dig* cyclization was investigated. Catalytic amounts of various transition metal salts including $AuCl_3$, AgOAc, $AgNO_3$, and Ag_2CO_3 have been reported to promote 5-*endo-dig* cyclization of terminal alkyne homopropargyl sulfonamides.[8c,d,15] Unfortunately, upon reaction of aryl substituted sulfonamide **4a** with Au or Ag salts no cyclization occurred and mostly the starting material was recovered. Furthermore, the palladium-catalyzed intramolecular hydroamination of *o*-alkynylaniline and homopropargyl amide derivatives has proven extremely useful for the synthesis of indoles and multisubstituted pyrrole rings.[8b,16] Here, activation of the carbon–carbon triple bond towards nucleophilic attack by π-coordination to a Pd species leads to an increase in the electrophilicity of the triple bond, and is followed by 5-*endo-dig* cyclization with migratory insertion and consecutive elimination of the Pd species.

When sulfonamide **4c** was subjected to the earlier established reaction conditions (TBAF·$3H_2O$, DMF, 80 °C, 48 h) with the addition of a catalytic amount of $Pd(PPh_3)_2Cl_2$ (10 mol%) no significant improvement of the reaction outcome was observed (23%). Therefore, we set out to investigate the use of a palladium catalyst to induce 2,5-diaryl-2-pyrroline formation. Homopropargyl sulfonamide **4c** was stirred with $Pd(PPh_3)_2Cl_2$ as catalyst and K_2CO_3 (5 equiv.) as a base in DMF at 80 °C for



Scheme 3 Synthesis of 2,5-diarylpyrrolines **7b–d** and 2,5-diarylpyrroles **5c** and **d**.

24 h leading to a 60% yield of *N*-tosyl-2-pyrroline **7c** (Scheme 3). Consecutive addition of an excess of NaOH (20 equiv.; 80 °C, 3 h) resulted in the deprotected pyrrole **5c** in 48% overall yield (2 steps; Scheme 3). From this outcome the yield for the deprotection of the pyrroline **7c** can be deduced to be 80%. Interestingly, while for **4b** the TBAF-assisted cyclization/deprotection reaction gave an excellent conversion to pyrrole **5b**, the palladium-assisted cyclization afforded *N*-tosylpyrroline **7b** in a modest 27%. Under the same conditions phenyl derivative **4d** resulted in only traces of pyrroline **7d**. Fortunately, increasing the temperature (100 °C) and extending the reaction time (48 h) resulted in an improved conversion to the *N*-tosyl-2-pyrroline **7d** (33%). Further elevation of the temperature (120 °C) and extension of the reaction time (72 h) did not further improve the reaction outcome (30%). Deprotection of **7d** by reaction with an excess of NaOH in wet DMF at 80 °C for 72 h finally yielded pyrrole **5d** in a modest 18% yield (77% of the starting material **7d** was recovered).

Single crystals of **5c** suitable for X-ray diffraction were grown by vapour diffusion of hexane into a $CHCl_3$ solution of **5c** stored under a nitrogen atmosphere and shielded from light (Fig. 2). The structure appears almost completely planar with the aryl groups maintained at an angle of approximately 137°. Nitrogen atoms of both pyrrole and pyridine rings are oriented to the same side, presumably due to a weak N–H–N hydrogen bonding interaction.‡

In conclusion, we present new approaches towards unsymmetrical-substituted 2,5-diarylpyrroles by 5-*endo-dig* cyclization and simultaneous deprotection of readily available homopropargyl sulfonamides. A straightforward methodology utilizing TBAF is very promising for the development of rather electron deficient derivatives while, alternatively, palladium-assisted cyclization with a consecutive deprotection step opens up the route to pyrrolopyridine derivatives. Currently, we are applying these synthetic techniques in the development of the relatively unexplored molecular receptors consisting of carefully arranged pyrrole rings forming a highly preorganized hydrogen-bonding pocket with potentially interesting supramolecular properties. Further investigation of the effect of substituents is required for a more profound understanding of the reaction involved here and will establish these new approaches towards 2,5-diarylpyrroles and *N*-tosyl-2,5-diaryl-2-pyrrolines allowing for the 2,5-diarylpyrrole sequence to be explored more intensively.

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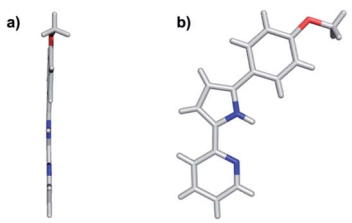

Fig. 2 Crystal structure of **5c**: (a) edge view, (b) plan view.

Notes and references

‡ X-ray data for **5c**: Rigaku Varimax Saturn; $T = 100(2)$ K. monoclinic, space group $P21$, $a = 5.6181(4)$ Å, $b = 21.2320(19)$ Å, $c = 10.8628(9)$ Å, $\alpha = 90°$, $\beta = 98.103(2)°$, $\gamma = 90°$, $V = 1282.82(18)$ Å^3, $Z = 4$, $\rho_{calc} = 1.291$ g cm^{-3}, $\mu = 0.082$ mm^{-1}. 3938 reflections, 3256 independent. Final w$R_2 = 0.1152$, $R_1 = 0.0414$ and $R_{int} = 0.0335$. GoF = 1.031.

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