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Efficient and chromatography-free methodology for the modular synthesis of oligo-(1H-pyrazol-4-yl)-arenes with controllable size, shape and steric bulk

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Keywords: Pyrazoles, Oligo-(1*H*-pyrazol-4-yl)-arenes, Pyrazolate metal-organic frameworks, Suzuki coupling, Boronate pinacol esters

Abstract

A novel methodology to synthesise oligo-(1*H*-pyrazol-4-yl)-arenes with controllable size, shape and steric bulk from 1-trityl-1*H*-pyrazol-4-ylboronate pinacol esters. This straightforward and efficient procedure can be applied to a variety of brominated aromatic precursors in a manner which leaves the pyrazole NH intact for further modification or coordination to metal ions. This will enable the synthesis of novel bioactive molecules and molecular material precursors, all achievable without any purification techniques beyond standard extraction and trituration.

Introduction

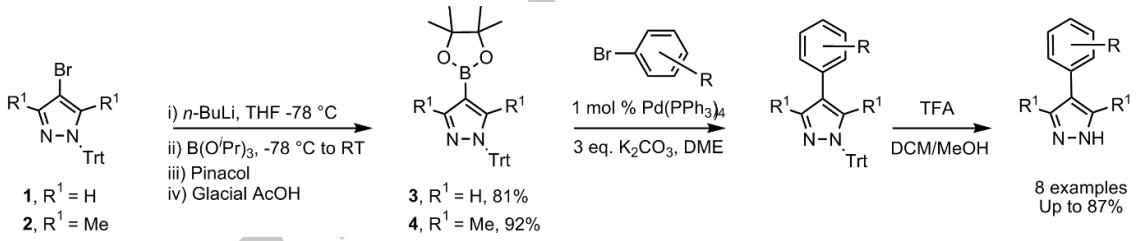
Pyrazoles are an important class of molecules due to their inherent bioactivity,[1,2] leading to their integration into pharmaceuticals,[3] and agrochemicals.[4] Pyrazoles have also attracted the interest of inorganic/supramolecular chemists as they possess diverse coordination modes,[5] making them ideal tectons for generating molecular materials.[6,7] The typical route to synthesise pyrazoles is via the condensation of hydrazines with 1,3-dielectrophiles[7–9] such as dicarbonyls, ynones, enones and β-ketoesters. However, this methodology has limited regioselective control and relies upon the integration of desired functional groups into the building blocks. This extends the number of synthetic steps and can require the use of toxic/hazardous reagents.

Recently pyrazoles have been utilised as ligands to construct metal-organic frameworks (MOFs) as their hydrolytically stable coordination bonds lead to materials with enhanced chemical and thermal stability.[10,11] The ligands most commonly utilised in MOFs are derived from 1*H*-pyrazole or 3,5-dimethyl-1*H*-pyrazole, linked through the 4-position with phenylene spacers of fixed stereochemical geometry.[11–13] Within these materials, pyrazole is deprotonated to yield the pyrazolate anion which bridges between two metal centres, with each N atom coordinating to a distinct metal ion. Materials are also formed from ligands bearing carboxylic acids either directly at the 4-position or with a *para*-phenyl spacer. The common route to synthesise oligo-(1*H*-pyrazol-4-yl)-arenes is to attach a oligo-1,3-dielectrophile to an arene via the Vilsmeier-Haack-Arnold formylation reaction, isolating the oligo-

1,3-electrophile as a bis- or tris-perchlorate salt. This potentially explosive intermediate is then condensed with hydrazine to yield the final pyrazole ligand.[10] Typical yields are between 34%[10] and 41%.[12]

An alternative methodology to generate 4-aryl-1*H*-pyrazoles is via Suzuki coupling.[14] This has previously been utilised to synthesise the pyrazolecarboxylic acid ligands, 4-(1*H*-pyrazol-4-yl)benzoic acid[15] and 5-(1*H*-pyrazol-4-yl)isophthalic acid.[16] Within these syntheses, the pyrazole NH groups were protected using ethylvinylether and trityl chloride respectively, both of which can be readily cleaved under acidic conditions. To date Suzuki coupling has not been utilised to synthesise extended oligo-(1*H*-pyrazol-4-yl)-arenes. Sonogashira coupling has been used to synthesise a series of extended bis-(1-Boc-1*H*-pyrazol-4-yl)-1,2-alkynes (Boc = tert-butyloxycarbonyl).[15] However, the major drawback of this methodology is that the Boc group cannot be removed by conventional methods and must be removed under solvothermal conditions. There are currently no examples of Suzuki or Sonogashira coupling to yield oligo-(1*H*-pyrazol-4-yl)-arenes based upon 3,5-dimethyl-1*H*-pyrazole. These synthetic difficulties restrict the availability of pyrazole ligands, hindering the research of novel pyrazolate derived molecular materials.

We therefore decided to develop an efficient modular Suzuki coupling methodology for the facile attachment of 1*H*-pyrazole and 3,5-dimethyl-1*H*-pyrazole to arenes via the 4-position (Scheme 1). This will permit the synthesis of a vast library of oligo-(1*H*-pyrazol-4-yl)-arenes, aiding the advancement of pyrazolate MOFs, other pyrazole derived molecular materials, and natural products/agrochemicals containing 4-aryl-1*H*-pyrazole or 4-aryl-3,5-dimethyl-1*H*-pyrazole.



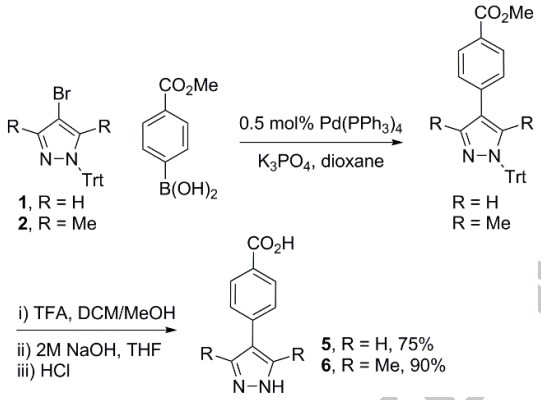
Scheme 1. Our methodology for the synthesis of oligo-(1*H*-pyrazol-4-yl)-arenes from 4-bromo-1-trityl-1*H*-pyrazoles via 1-trityl-1*H*-pyrazol-4-ylboronate pinacol esters.

Herein, we describe the development of a facile and high yielding modular synthesis of 4-(1*H*-pyrazol-4-yl)benzoic acids and oligo-(1*H*-pyrazol-4-yl)-4-arenes from 4-bromo-1-trityl-1*H*-pyrazoles and 1-trityl-1*H*-pyrazol-4-ylboronate pinacol esters respectively. This methodology can be achieved using either 1*H*-pyrazole or 3,5-dimethyl-1*H*-pyrazole precursors, permitting steric control over the pyrazolate-coordinating moiety. Furthermore the synthesis can be completed without the use of column chromatography, with isolation possible through standard aqueous/organic extraction and trituration. The effectiveness of this protocol is demonstrated by the synthesis of the novel oligo-(1*H*-pyrazol-4-yl)-4-arenes; 1,3,5-tri(3,5-dimethyl-1*H*-pyrazol-4-yl)benzene (H_3BTdmPz), 1,3,5-tris[4-phenyl(1*H*-pyrazol-4-yl)]benzene (H_3BTBPz) and 1,3,5-tris[4-phenyl-(3,5-dimethyl-1*H*-pyrazol-4-yl)]benzene (H_3BTBdmPz).

Our initial strategy focused upon the synthesis of 1*H*-pyrazole and 3,5-dimethyl-1*H*-pyrazole derivatives of 4-(1*H*-pyrazol-4-yl)benzoic acid. This was achieved from the Suzuki coupling of trityl

protected 4-bromopyrazoles with (4-(methoxycarbonyl)-phenyl)boronic acid based upon previous methodologies,[14,17] but with minor adjustment. This facile route gives yields in excess of 95% for both 4-bromo-1*H*-pyrazole and 4-bromo-3,5-dimethyl-1*H*-pyrazole precursors. The formation of the corresponding 4-(1*H*-pyrazol-4-yl)benzoic acid species is then completed by Suzuki coupling using catalytic $Pd(PPh_3)_4$ in 1,4-dioxane with $K_3PO_4 \cdot 2H_2O$. Complete reaction can be achieved with as little as 0.5 mol% catalyst loading, demonstrating the high activity of these species without the need for expensive or customised Pd ligands. This is in contrast to previous reports of Suzuki coupling with 4-bromo-1-trityl-1*H*-pyrazole, where up to 10 mol% loading was required for successful reaction.[14–17]

Deprotection of the trityl and ester groups is achieved sequentially without the need for subsequent purification. Removal of the ester groups after trityl deprotection permits the extraction of all by-products into the organic phase, leaving sodium 4-(1*H*-pyrazol-4-yl)benzoate salts within the aqueous medium which can be trivially protonated to yield the corresponding acids in excellent yields (Scheme 2).

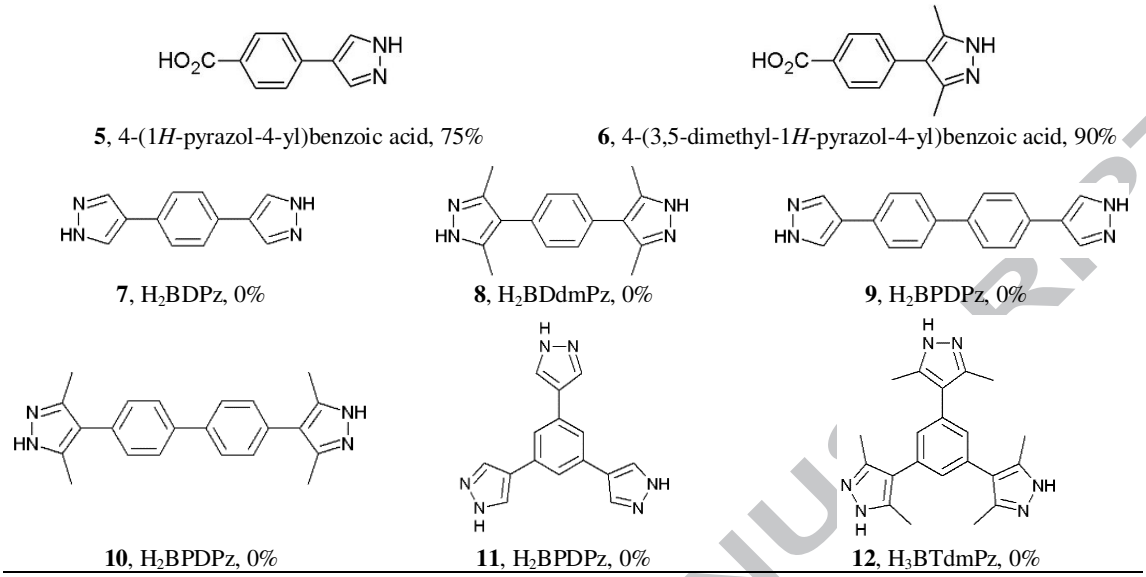


Scheme 2. Synthesis of 4-(1*H*-pyrazol-4-yl)benzoic acids from 1-trityl-1*H*-4-bromopyrazoles and subsequent deprotection using TFA in CH_2Cl_2/MeOH. Quoted yields for **5** and **6** are for the combined coupling and deprotection steps.

Although phenylboronic acids containing various functional groups have shown high conversion to the Suzuki coupled products,[14] it was found that this chemistry does not extend to aryl species containing more than one boronic acid group. Substrates attempted to employ under Suzuki coupling conditions with 4-bromo-1-trityl-1*H*-pyrazole (**1**) and 4-bromo-3,5-dimethyl-1-trityl-1*H*-pyrazole (**2**) include 1,4-benzenediboronic acid, 4,4′-biphenyldiboronic acid and 1,3,5-tris-(4-phenylboronic acid)benzene (Table 1).[18] However, little or no reaction was observed with either **1** or **2**, even with increased catalyst loading. In order to circumvent this issue an alternative strategy was employed, coupling 1-trityl-1*H*-pyrazol-4-ylboronate pinacol esters to polybrominated arenes. The wide scope of this innovative strategy allows for modular construction of new compounds based upon the brominated arene precursor.

Table 1. Attempts for generating 4-(1*H*-pyrazol-4-yl)benzoic acids, extended bis-1,4- and tris-1,3,5-aryl-1*H*-pyrazol-4-yls based upon pyrazole and 3,5-dimethylpyrazole using the approach outlined in

Scheme 2 from 1-trityl-1*H*-4-bromopyrazoles. Quoted yields are for the combined coupling and deprotection steps



5, 4-(1*H*-pyrazol-4-yl)benzoic acid, 75%

6, 4-(3,5-dimethyl-1*H*-pyrazol-4-yl)benzoic acid, 90%

7, H_2BDPz, 0%

8, H_2BDdmPz, 0%

9, H_2BPDPz, 0%

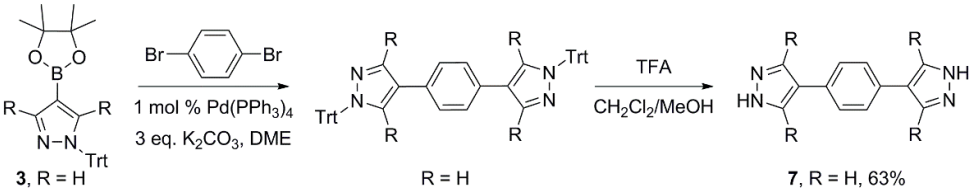
10, H_2BPDPz, 0%

11, H_2BPDPz, 0%

12, H_3BTdmPz, 0%

Pinacol esters were synthesised as previous reports suggest that pyrazol-4-ylboronic acids are not air-stable[19] while pinacol esters provide ease of workup.[20] Initially the formation of trityl protected analogues of 1-methyl-1*H*-pyrazol-4-ylboronic acid pinacol ester lithium ate complex were attempted based upon the method by Mullens,[19] as these compounds are reported to have high stability and Suzuki coupling activity. However we were unable to isolate these species from either **1** or **2**.

Successful formation of 1-trityl-1*H*-pyrazol-4-ylboronate pinacol ester (**3**) was achieved from a one-pot reaction in THF via lithium-halogen exchange, addition of triisopropyl borate and subsequent encapsulation of the boronic acid with pinacol to yield the final compound. The analogous reaction can also be completed with **2**, yielding 3,5-dimethyl-1-trityl-1*H*-pyrazol-4-ylboronate pinacol ester (**4**), permitting control over the steric bulk of the pyrazole subunit. Suzuki coupling of the 1-trityl-1*H*-pyrazol-4-ylboronate pinacol esters with polybrominated arenes is typically achieved using 1 mol% $Pd(PPh_3)_4$ in 1,2-dimethoxyethane (DME), with yields of up to 87% in 18 hours (Scheme 3 and Table 2). Removal of the trityl group is achieved using TFA in an analogous manner to the preparation of 1*H*-pyrazol-4-ylbenzoic acids described above (Scheme 3).



3, R = H
4, R = Me

R = H
R = Me

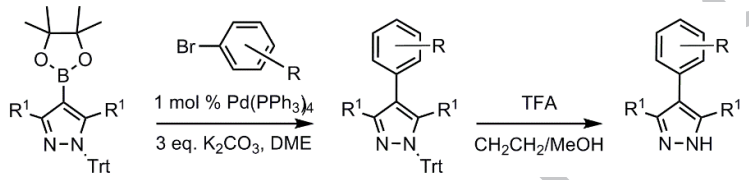
7, R = H, 63%
8, R = Me, 51%

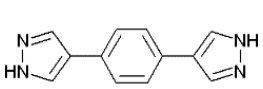
Scheme 3. Synthesis of 1,4-bis(1*H*-pyrazol-4-yl)benzenes from 1-trityl-1*H*-pyrazolyl-4-boronate pinacol esters and subsequent deprotection using TFA in CH_2Cl_2/MeOH. Quoted yields for **7** and **8** are for the combined coupling and deprotection steps.

Using this methodology, a series of oligo-(1*H*-pyrazol-4-yl)-arenes with linear and trigonal geometries were synthesised based upon the 1*H*-pyrazole and 3,5-dimethyl-1*H*-pyrazole subunit (Table 2). We

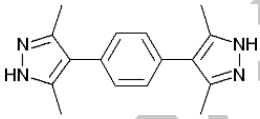
selected these geometries as they are the most common within MOF ligands. This includes pyrazoles which have been previously used as ligands to synthesise pyrazolate-derived MOFs (**7-11**), and novel compounds (**12-14**). Entries **13** and **14** are 1*H*-pyrazole/3,5-dimethyl-1*H*-pyrazole analogues of the carboxylic acid MOF ligand 1,3,5-tris(4-carboxyphenyl)benzene (H_3BTB). We envisage that both H_3BTBPz and H_3BTBdmPz could be utilised for the synthesis of novel pyrazolate MOFs with identical topologies to either MOF-177[21] or the mixed ligand material UMCM-1,[22] but with enhanced chemical stability known to be derived from metal-pyrazolate coordination.

Table 2. Substrates tested for the generation of extended linear bis-1,4- and trigonal tris-1,3,5- aryl-1*H*-pyrazol-4-yls based upon pyrazole and 3,5-dimethylpyrazole from 1-trityl-1*H*-pyrazol-4-ylboronate pinacol esters. Quoted yields are for coupling and subsequent deprotection.

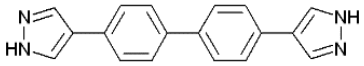




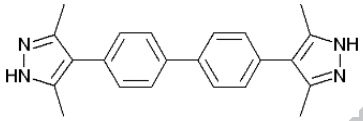
7, H_2BDPz, 63%



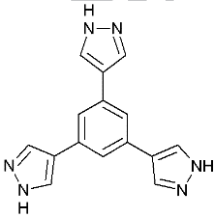
8, H_2BDdmPz, 87%



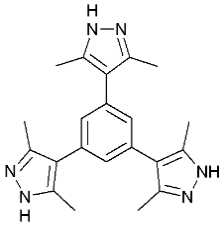
9, H_2BPDPz, 61%



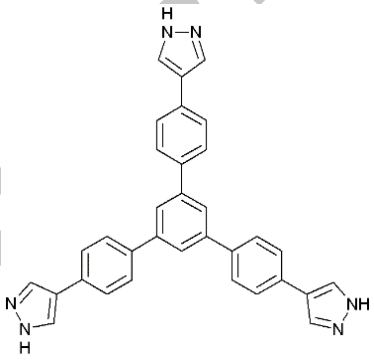
10, H_2BPDPz, 61%



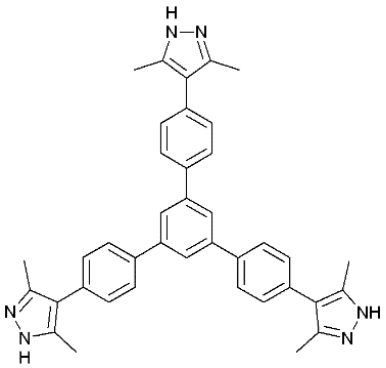
11, H_2BPDPz, 61%



12, H_3BTdmPz, 45%



13, H_3BTBPz 73%



14, H_3BTBdmPz, 69%

In summary, we report a Suzuki coupling methodology that permits the synthesis of a wide range of oligo-(1*H*-pyrazol-4-yl)-arenes with controlled size, geometry and steric bulk based upon the choice of brominated building block and pyrazol-4-ylboronate pinacol ester. This procedure will permit the advancement of pyrazole derived molecular materials, natural products, pharmaceuticals and agrochemicals containing 4-aryl-1*H*-pyrazole or 4-aryl-3,5-dimethyl-1*H*-pyrazole.

However, we envisage this methodology will have the greatest impact within the field of MOFs, as it permits facile synthesis of pyrazolate MOF ligands. This could be used to further study known materials, or it could be utilised to synthesise a wide range of new pyrazolate MOFs with control of porosity and functionality via the reticular approach currently used in carboxylate-MOF chemistry. The utilisation of pyrazole ligands for the synthesis of new MOFs is an important next step within the field where materials with increased stability is a priority, specifically for industrial application where long lifetimes of materials are essential.[23]

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures & NMR spectra) associated with this article can be found in the online version.

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Graphical abstract