

Polyhalogenoheterocyclic compounds

Part 54: [1] Suzuki reactions of 2,4,6-tribromo-3,5-difluoropyridine

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In commemoration of the centenary of the birth of Professor Ivan Ludvigovich Knunyants.

Abstract

Palladium catalysed Suzuki cross-coupling reactions between 2,4,6-tribromo-3,5-difluoropyridine and a short series of aromatic boronic acid derivatives gave 4-bromo-3,5-difluoro-2,6-diphenylpyridine derivatives arising from displacement of bromine atoms attached to positions *ortho* to ring nitrogen or the corresponding triaryl systems depending on the reaction conditions. Consequently, the use of polybromofluoropyridine scaffolds for the synthesis of polyfunctional heteroaromatic derivatives is expanded further.

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1. Introduction

Polybromofluoropyridine derivatives are, potentially, very valuable scaffolds for the synthesis of multifunctional pyridine derivatives [2,3] because not only are nucleophilic substitution reactions possible, involving either replacement of fluorine or bromine depending upon the nature of the nucleophile, but also, for example, palladium catalysed processes involving activation of a carbon–bromine bond [1,2]. We have developed effective methodology for the synthesis of various polybromofluoroheteroaromatic systems [2] and are exploring the use of these novel scaffolds for a variety of synthetic applications in both the medicinal chemistry and materials arenas. A surprisingly high proportion of commercially important pharmaceutical and plant protection products are based upon a small heterocyclic ring core scaffold [4–7] and, consequently, efficient methodology for the synthesis of polyfunctional heterocyclic systems is an important research goal [8,9].

The palladium catalysed Suzuki cross-coupling reaction is a versatile method for the synthesis of biaryl and hetero-aryl derivatives [10] and the wide range of commercially available boronic acids, the relatively low toxicity of the by-products formed and the possibility to work under aqueous conditions has been widely exploited in all aspects of synthetic organic chemistry.

In this paper, we describe representative Suzuki cross-coupling reactions between a short series of aromatic boronic acid derivatives and 2,4,6-tribromo-3,5-difluoropyridine **1** and demonstrate how this readily accessible system can be used as a building block for the synthesis of polyfunctional fluoroarylpyridine derivatives.

2. Results and discussion

Electron rich arene boronic acids are prone to deboronation under the reaction conditions [Pd(PPh₃)₄, Cs₂CO₃/H₂O, toluene] first reported by Suzuki for the synthesis of biaryl derivatives but, subsequently, Gronowitz demonstrated that such deboronations can be suppressed by using glycol dimethyl ether (DME) as the solvent. Consequently, we have used refined Gronowitz conditions [11,12] [Pd(PPh₃)₄,

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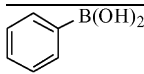
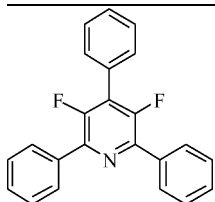
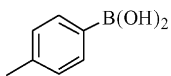
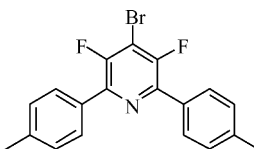
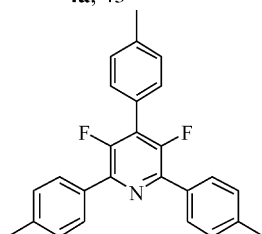
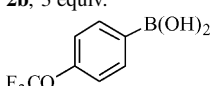
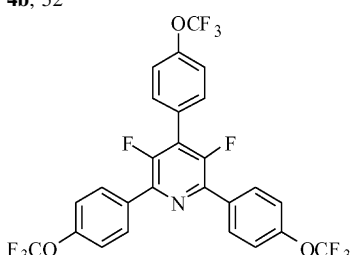
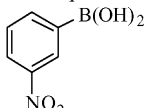
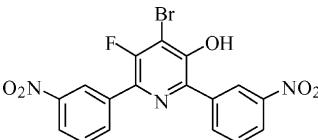
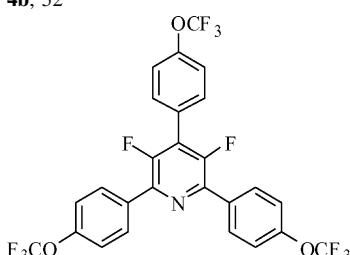
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Ba(OH)₂/H₂O, DME] for Suzuki coupling reactions between a short range of boronic acids **2** and 2,4,6-tribromo-3,5-difluoropyridine **1** and the results are collated in Table 1. Using one equivalent of boronic acid generally afforded a mixture of diphenyl **3** and triphenylated **4** pyridine derivatives with complete conversion of the starting material whereas an excess of boronic acid led to good yields of the corresponding triphenyldifluoropyridine systems **4**. All products were isolated and fully characterised and, in addition, the diphenyl derivative **3b** was characterised by X-ray crystallography

(Fig. 1). The phenyl group at C(6) is almost coplanar to the pyridine ring (dihedral angle 8.8°) whilst the phenyl group at C(2) is disordered equally between two orientations (A and B), which are inclined to the pyridine ring by similar, opposite angles (29.4° and 26.8°). Molecules related by the *b* translation form a π–π stack with an interplanar separation of ca. 3.6 Å and have the same orientation of the disordered ring, whereas molecules related by the inversion—*x*1–*y*–*z*, must have different orientations (i.e. A versus B), to avoid impossibly short intermolecular contacts.

Table 1
Suzuki reactions of 2,4,6-tribromo-3,5-difluoropyridine

Boronic acid 2	3 , Yield %	4 , Yield%
 2a , 3 equiv.	–	 4a , 43
 2b , 1.2 equiv.	 3b , 32	 4b , 21
 2c , 0.8 equiv.	–	 4c , 52
 2d , 1.2 equiv.	 3d , 54%	 4c , 8

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