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Highly efficient synthesis of 5-benzyl-3-aminoindazoles

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ABSTRACT

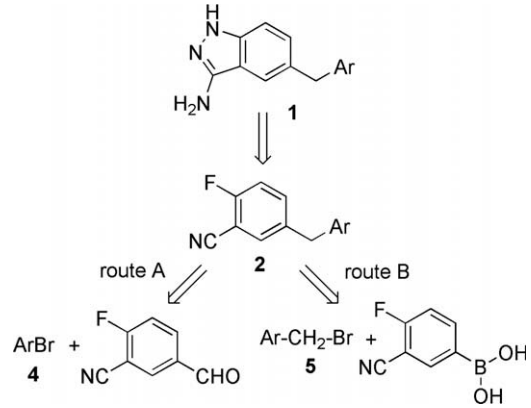
A rapid and efficient procedure for the preparation of 5-benzyl-3-aminoindazoles **1** is reported. Key intermediates are fluoro-cyano diarylmethanes **2** which have been obtained by two different synthetic approaches. Benefits of these methods result from the use of commercially available starting materials and practical experimental conditions that allow easy scale-up.

The indazole ring system represents the core skeleton of an important class of heterocyclic compounds possessing a broad range of biological activities.[1] For this reason the development of a wide array of synthetic approaches for their preparation has been reported in the literature.[2] In particular, 3-aminoindazole derivatives have attracted great interest due to their activity against a number of pharmacological targets, including kinases,[3] central nervous system,[4] and inflammatory pathway.[5]

In the course of a drug discovery program, aimed at finding new low molecular weight kinase inhibitors,[6] we had to devise an efficient synthesis of 5-benzyl-3-aminoindazoles **1** to be further elaborated at the amino moiety. We needed to prepare a series of such compounds and were particularly interested in fluorinated 5-benzyl derivatives. Methods for the preparation of 3-aminoindazoles typically involve the reaction of a 2-haloaryl nitrile with hydrazine[7] thus, according to our purpose, we required an efficient and practical synthesis of unsymmetrical diarylmethanes **2**, which are important building blocks in organic synthesis.[8]

To obtain the key intermediates **2**, we pursued two possible alternative routes: (A) reduction of diarylcarbinols, in turn obtained by addition of Grignard reagents to 3-cyano-4-fluorobenzaldehyde; (B) palladium-catalyzed cross-coupling reaction of benzylbromides with 3-cyano-4-fluorophenylboronic acid (Scheme 1). To possibly extend the scope of this approach, a number of papers recently reported the use of benzylic carbonates and phosphates in cross-coupling reactions with aryl and heteroarylboronic acids.[9]

According to route A,[10] bromoarenes **4** were treated with magnesium to generate the corresponding Grignard reagents that were then allowed to react with 3-fluoro-4-cyanobenzaldehyde to provide diarylcarbinols **3** in excellent yields.[11] Temperature control seems to be a critical parameter, as keeping the reaction temperature between −5° and 0 °C prevents the oxidation to the corresponding ketones.[12] Initial attempts to reduce these diarylcarbinols to the desired diarylmethanes **2** via reaction with triethylsilane under a variety of conditions were unsuccessful. Remarkably, good results were obtained by using iodotrimethylsilane, generated in situ from chlorotrimethylsilane and sodium iodide in dry acetonitrile.[13] Although substrates are electron-deficient benzylic alcohols, this reagent provided high yields of deoxygenated products leaving a reduction-sensitive functional group such as the nitrile unaffected.[14] Noteworthy, this reaction sequence has been successfully



Scheme 1. Retrosynthetic approaches to 5-benzyl-3-aminoindazoles.

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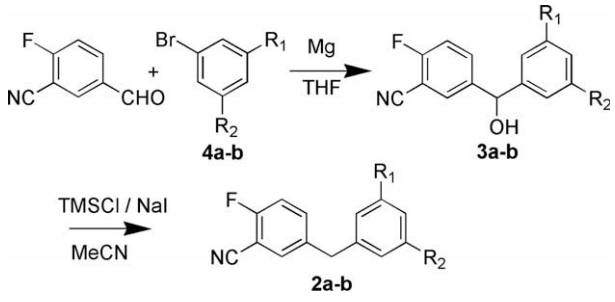
scaled up and applied to 50 g of starting material; no chromatographic purifications are needed to obtain key intermediates **2a–b** (Table 1).

Aiming at a shorter synthesis still amenable to be scaled up, we then investigated the aforementioned route B, where the benzylic carbon atom of the diarylmethane moiety could be directly obtained in the right oxidation state, thus avoiding the reductive step. The use of benzylic halides is not so common in the Suzuki–Miyaura cross-coupling, maybe because their use involves both the activation of a sp^3-hybridized carbon atom, not so prone to the oxidative insertion of a transition metal, and the slow reductive elimination of the cross-coupled product from the catalyst. Notwithstanding these drawbacks, Duchêne reports about the successful regioselective cross-coupling of a benzylic bromide with respect to an arylic bromide, with aryl- and heteroaryl-boronic acids.[15,16] As 3-cyano-4-fluorophenylboronic acid is commercially available,[17] we synthesized compounds **2b–f** using benzyl bromides as electrophilic components of the Suzuki–Miyaura cross-coupling reaction in the presence of 2% $Pd(Ph_3P)_4$ complex as a catalyst and K_3PO_4 as a base. The reaction was carried out in fairly good yields on a 10 mmol scale by refluxing in toluene for some hours (1.5–8 h) (Table 2).[18]

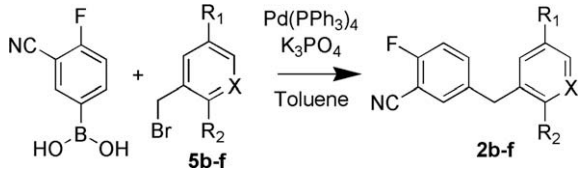
According to a comparative analysis between the two reported routes, method B results quite straightforward and allowed us to avoid the synthesis and the use of a Grignard reagent, highly undesirable in an industrial process. Furthermore, it fulfills the request of a green chemistry process. As for the costs, the two methods seemed to be comparable, but approach B is slightly better in yields, as shown by the synthesis of compound **2b**.

Table 1
Preparation of diarylmethanes **2a**–**b**



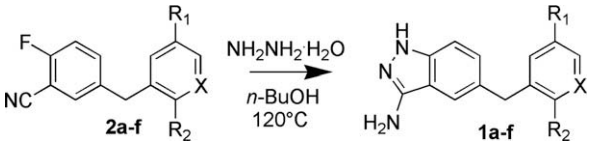
Entry	R_1	R_2	**3**, Yield (%)	**2**, Yield (%)
a	H	H	91	96
b	F	F	87	88

Table 2
Preparation of diarylmethanes **2b–f**



Entry	X	R_1	R_2	**2**, Yield (%)
b	CF	F	H	85
c	CH	F	F	66
d	CH	F	CH_3	75
e	CH	F	H	90
f	N	H	H	57

Table 3
Preparation of 5-benzyl-3aminoindazoles **1a–f**



Entry	X	R_1	R_2	**1**, Yield (%)
a	CH	H	H	77
b	CF	F	H	92
c	CH	F	F	88
d	CH	F	CH_3	88
e	CH	F	H	76
f	N	H	H	85

Having succeeded in developing a practical and efficient synthesis of diarylmethanes **2a–f**, these intermediates were treated with 5 equiv of hydrazine hydrate in *n*-butanol to provide target products **1a–f** (Table 3).[19] Interestingly, despite the presence of several regiochemically different fluorine atoms on various substrates (entries **2b–e**), reaction conditions allow a good yield conversion with a high degree of regioselectivity.

In conclusion we have presented simple and efficient synthetic procedures of coupling reactions developed to obtain 5-benzyl-substituted 3-aminoindazoles. Advantages of this method result from the use of easily available starting materials and practical experimental conditions. So obtained derivatives will be useful for the preparation of functionalized structurally more elaborated compounds.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.024.

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13. *General procedure for the preparation of diarylmethanes* ***2a–b***: Diarylcarbinols (1 equiv) and sodium iodide (10 equiv) were stirred in acetonitrile (4 mL/mmol carbinol) under nitrogen at 60 °C in oil bath. To the reaction mixture TMSCl (10 equiv) was gradually added over a period of 8 h. The mixture was diluted with EtOAc and washed with water, saturated aqueous sodium bicarbonate, 10% aqueous sodium thiosulfate, and brine. Trituration with ethyl ether afforded the title products in yields of 85–95%.
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17. From Small Molecules, Inc.
18. *General procedure for the preparation of diarylmethanes* ***2b–f***: 3-Cyano-4-fluorophenylboronic acid (1 equiv), powdered K_3PO_4 (2 equiv), and $Pd(PPh_3)_4$ (2% mol) were charged in an oven-dried flask under argon atmosphere. The flask was evacuated and back-filled with argon thrice. Toluene (3 mL/mmol boronic acid) and benzyl bromide (1 equiv) were added under good stirring. The reaction mixture was heated to 100 °C in half an hour and maintained at that temperature for 1.5-8 h. The dark mixture was taken up with diethyl ether, washed with saturated aqueous NH_4Cl and brine. The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was then purified by flash chromatography (*n*-hexane/EtOAc) to provide the desired diarylmethane in yields of 60–90%.
19. *General procedure for the preparation of 3-aminoindazoles* ***1a–f***: A mixture of 3-cyano-4-fluoro-diarylmethane (1 equiv) and hydrazine hydrate (5 equiv) in *n*-butanol (2.5 mL/mmol diarylmethane) was refluxed overnight. The reaction mixture was diluted with water/EtOAc and the organic phase was washed twice with brine, dried, and evaporated. The residue was purified by flash chromatography (CH_2Cl_2/EtOH) to provide the desired 3-aminoindazole in yields of 75–90%.