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Two-Step Synthesis of Substituted 3-Aminoindazoles from 2-Bromobenzonitriles

Valerie Lefebvre, Thomas Cailly, Frederic Fabis,* and Sylvain Rault

Centre d'Etudes et de Recherche sur le Médicament de Normandie, UPRES EA 4258, INC3M FR-CNRS 3038, UFR des Sciences Pharmaceutiques, Université de Caen Basse-Normandie, boulevard Becquerel 14032 Caen Cedex, France

frederic.fabis@unicaen.fr

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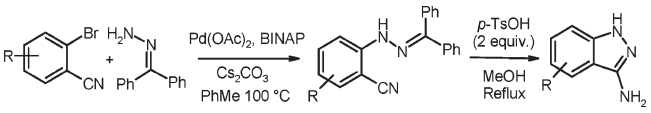

A general two-step synthesis of substituted 3-aminoindazoles from 2-bromobenzonitriles involving a palladium-catalyzed arylation of benzophenone hydrazone followed by an acidic deprotection/cyclization sequence is described. This procedure offers a general and efficient alternative to the typical S_NAr reaction of hydrazine with *o*-fluorobenzonitriles.

The 3-aminoindazole scaffold is found in a great number of compounds displaying a wide range of biological activities including kinase inhibitors,[1] MCH receptor 1 antagonists,[2] HIV protease inhibitors,[3] factor XIa inhibitors[4] and CB1 receptor inhibitors.[5] Moreover, the 3-aminoindazoles have been shown to be able to mimic the adenine nucleus of ATP for the design of ATP-competitive receptor tyrosine kinase inhibitors with potent antitumor activities.[1d]

Due to their potential as valuable templates for medicinal chemistry, considerable effort has recently been devoted to the synthesis of substituted indazoles.[6] In this context, the synthesis of 3-aminoindazoles has attracted much attention. Their synthesis typically involved an aromatic nucleophilic substitution between hydrazine and *o*-substituted benzonitriles. The leaving group used for the reaction to succeed is mainly fluorine[1,7] but also more rarely chlorine[8] or a nitro group.[9] 3-Aminoindazoles substituted on the amino group were prepared as well by reaction of hydrazine with *N*-substituted fluoroarylthioamides.[10] The main drawback of these methods is the low yields and harsh conditions when *o*-fluorobenzonitriles are deactivated by an electron-donating group. Some alternative methods have been described such as the Buchwald−Hartwig amination of 3-haloindazoles[2,5] or the Pd-catalyzed intramolecular cyclization of tosylhydrazines;[11] however, these latter methods need the preparation of the required starting material in several steps.

Transition-metal-catalyzed C−N bond formation has become in the past decades one of the most valuable tools for the synthesis of arylamines.[12,13] Arylation of hydrazine derivatives can be performed as well using either copper[14]

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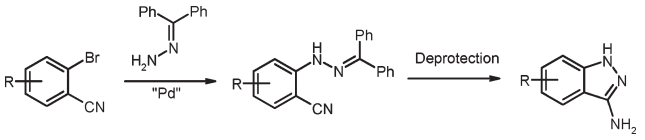
SCHEME 1. Two-Step Procedure for the Synthesis of Substituted 3-Aminoindazoles



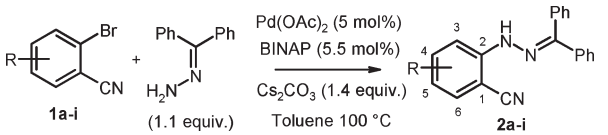
or palladium[15] catalysts. This methodology has permitted a more general access to diverse aryl- or heteroarylhydrazine derivatives avoiding the use of conventional methods such as reduction of diazonium salts or S_NAr reactions using hydrazine derivatives. Interestingly, the *N*-arylation of benzophenone hydrazone and subsequent deprotection of the arylhydrazone intermediate in the presence of enolizable ketones or *β*-dicarbonyl derivatives, afforded respectively substituted indoles[15a,c] and *N*-arylpyrazoles.[16] The intramolecular *N*-arylation of hydrazones has recently been described as well for the synthesis of 3-arylindazoles.[17]

We thought that a two-step sequence involving the *N*-arylation of benzophenone hydrazone with *o*-halobenzonitriles followed by the deprotection of the hydrazone intermediate would afford 3-aminoindazoles, thus circumventing the limitations of the S_NAr reaction (Scheme 1).

For the arylation of benzophenone hydrazone with 2-bromobenzonitrile **1a**, we tested different palladium catalysts and ligands usually used in this reaction and found that the combination of $Pd(OAc)_2$ (5 mol %) and BINAP (5.5 mol %) in toluene at 100 °C with cesium carbonate as base gave the arylhydrazone **2a** in 99% yield (Table 1). It should be noted that the use of cesium carbonate in place of NaO-*t*-Bu conventionally used in this reaction avoids the Wolff–Kischner-type reduction of benzophenone hydrazone.[15c] We then applied these conditions to diversely substituted 2-bromobenzonitriles **1b**–**i**. All the corresponding arylhydrazones **2b**–**i** were obtained in 80–99% yield (Table 1). The main advantage of this methodology over the S_NAr reaction with hydrazine is the possibility to use benzonitriles substituted with either strong electron-donating or strong electron-withdrawing groups (**2e** and **2f**). Moreover, fluorobromobenzonitriles **1g**–**i** led to fluoroarylhydrazones **2g**–**i** without nucleophilic displacement of the fluorine atom.

The deprotection of stable benzophenone hydrazones generally requires heating with strong acids such as concentrated HCl in ethyl alcohol. The formation of insoluble hydrazine hydrochloride derivatives allows the reaction to go to completion.[15f] Using *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) in place of HCl gives only modest results due to the equilibrated nature of the reaction and the formation of aniline byproduct.[15a,b] We thought that the presence of the carbonitrile group *ortho* to the hydrazone would assist the deprotection by the irreversible formation of the aminoindazole nucleus. Thus, by refluxing the arylhydrazones **2a**–**i** with 2 equiv of *p*-TsOH·H_2O in methanol, we were pleased to isolate the corresponding 3-aminoindazoles **3a**–**i** in 73–90% yields (Table 2).[18] As in the arylation step, the nature of the substituent did not influence the cyclization step.

TABLE 1. Arylation of Benzophenone Hydrazone with Substituted 2-Bromobenzonitriles



entry	R	yield[a] (%)
2a	H	99
2b	3-Me	80
2c	4-Me	86
2d	5-Me	84
2e	5-MeO	92
2f	5-NO_2	86
2g	4-F	87
2h	5-F	91
2i	6-F	87

[a]Isolated yield.

Due to the nucleophilic nature of the *N*-1 and 3-amino group, the *N*-alkylation of 3-aminoindazoles with alkyl halides results in the competitive formation of the *N*-1-alkyl- and 3-alkylamino derivatives.[19] Therefore, the synthesis of selectively *N*-1-alkylated 3-aminoindazoles generally requires the protection of the 3-amino group before the alkylation of the indazole nitrogen atom.[1c,8] Moreover, the direct access to *N*-1 substituted 3-aminoindazoles by the S_NAr reaction is limited by the low availability of *N*-substituted hydrazines and by the possible competitive nucleophilic displacement of the leaving group by the two nitrogen atoms. The *N*-alkylation of the hydrazone intermediate followed by the deprotection/cyclization step would provide selectively *N*-1-substituted-3-aminoindazoles. As an example, hydrazone **2a** was easily benzylated, and after a typical extraction workup, the crude mixture was directly engaged in the deprotection step affording free 3-amino-1-benzylindazole **4** in 80% overall yield (Scheme 2).

In summary, we have developed a new general route to substituted 3-aminoindazoles in two steps from substituted 2-bromobenzonitriles using a simple and scalable procedure. Moreover, the *N*-alkylation of the hydrazone intermediates allows the selective formation of *N*-1-substituted-3-aminoindazoles, thus avoiding a protection–deprotection sequence needed for the selective alkylation of 3-aminoindazoles.

Experimental Section

General Procedure for the Synthesis of Hydrazones 2a–i. A Schlenk tube was charged with benzophenone hydrazone

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(18) The benzophenone released during the deprotection step was easily removed by flash chromatography, see the Supporting Information.

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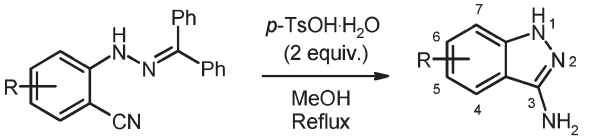
TABLE 2. Deprotection of Hydrazones and Subsequent Formation of 3-Aminoindazoles



2a-i **3a-i**

entry	R	yield[a] (%)
3a	H	86
3b	7-Me	86
3c	6-Me	85
3d	5-Me	84
3e	5-MeO	81
3f	5-NO_2	90
3g	6-F	73
3h	5-F	85
3i	4-F	81

[a]Isolated yield.

(1.1 equiv), palladium acetate (5 mol %), BINAP (5.5 mol %), and toluene (1.5 mL per mmol of bromobenzonitrile), evacuated, and backfilled with argon. The mixture was heated at 100 °C for 3 min, and after it was cooled to room temperature, bromobenzonitrile (1 equiv), cesium carbonate (1.4 equiv), and toluene (0.5 mL per mmol of bromobenzonitrile) were successively added. The Schlenk tube was then evacuated, backfilled with argon, and heated at 100 °C for 7 h. After cooling, the mixture was filtrated through a pad of Celite. Celite was washed with methylene chloride, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using cyclohexane/ethyl acetate 9:1.

2-[2-(Diphenylmethylene)hydrazino]benzonitrile (2a). According to general procedure: 7.9 g (99%) obtained as pale yellow crystals from 2-bromobenzonitrile **1a** (5 g, 27 mmol); mp = 97−99 °C (EtOH); IR (KBr) ν (cm^{-1}) 3323 (NH), 2213 (CN); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (s, 1H, NH), 7.73−6.83 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.2, 146.7, 137.5, 134.2, 132.1, 131.6, 130.0, 129.9, 128.9, 128.5, 128.1, 127.0, 119.3, 116.5, 113.5, 94.7; MS-ESI $[M + H]^+$ 298; HRMS-EI m/z $[M^+]$ calcd for $C_{20}H_{15}N_3$ 297.12659, found 297.12712.

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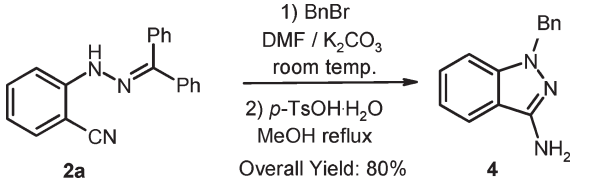
SCHEME 2. Selective Formation of 3-Amino-1-benzylindazole



2a **4**

General Procedure for the Synthesis of 3-Aminoindazoles 3a−i. Hydrazones **2a−i** (1 equiv) and *p*-toluenesulfonic acid monohydrate (2 equiv) were suspended in MeOH (2 mL/mmol of hydrazone), and the reaction mixture was refluxed overnight. The solution was diluted with a saturated solution of sodium carbonate (5 mL/mmol of hydrazone) and extracted with ethyl acetate (3×10 mL). The organic layer was then washed successively with brine (5 mL) and water (2 × 5 mL). After the layer was dried with anhydrous sodium sulfate, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using cyclohexane/EtOAc 9:1 to remove the benzophenone and then EtOAc 100% to afford the corresponding 3-aminoindazoles **3a−i**.

3-Amino-1*H*-indazole (3a). According to general procedure: 194 mg (86%) obtained as an off-white solid from **2a** (500 mg, 1.7 mmol); mp = 155−157 °C (lit.[20] mp 154−155 °C); IR (KBr) ν (cm^{-1}) 3449 (NH), 3316 (NH_2), 3192 (NH_2); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.34 (s, 1H, NH), 7.66 (d, 1H, J = 7.8 Hz), 7.20 (m, 2H), 6.87 (m, 1H), 5.21 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 149.2, 141.4, 126.0, 120.2, 117.3, 114.0, 109.3; HRMS-EI m/z $[M^+]$ calcd for $C_7H_7N_3$ 133.06399, found 133.06402.

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Supporting Information Available: Detailed experimental procedures and characterization data for the products included in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.