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Rapid Access to 3-Aminoindazoles from Tertiary Amides

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Supporting Information

ABSTRACT: A two-step synthesis of structurally diverse 3-aminoindazoles from readily available starting materials was developed. This sequence includes a one-pot synthesis of aminohydrazones through chemoselective Tf_2O-mediated activation of tertiary amides and subsequent addition of nucleophilic hydrazides. These precursors then participate in an intramolecular ligand-free Pd-catalyzed C−H amination reaction. The azaheterocycles synthesized via this approach were further diversified through subsequent deprotection/functionalization reactions.

The ubiquity of bioactive nitrogen-containing heterocycles in recently approved drugs continues to inspire organic chemists to develop modular synthetic methodologies for preparing members of this large family.[1] For example, recent increasing interest in the indazole scaffold stems in part from the natural rarity of this bicyclic motif and also to its ability to successfully act as an active bioisostere of indole in various drug designs.[2−4] In this context, the 3-aminoindazole scaffold has found particularly broad applications in medicinal chemistry.[5] Pharmaceutical leads incorporating this privileged heterocycle display a wide range of biological responses, including antipsoriasis (**I**),[5a] anti-inflammatory (**II**),[5c] and anticancer (**III**)[5a,b] activities (Figure 1). Considering their expanded

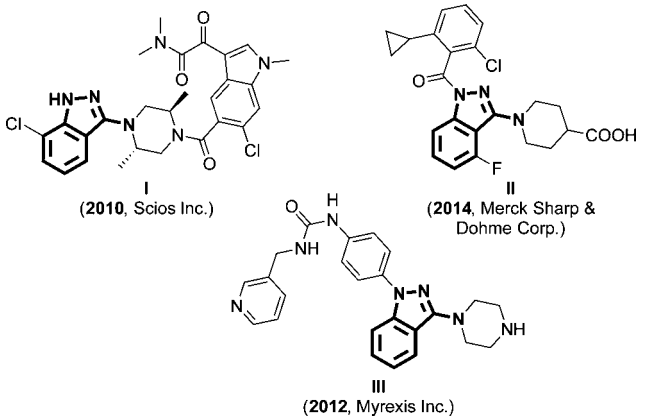
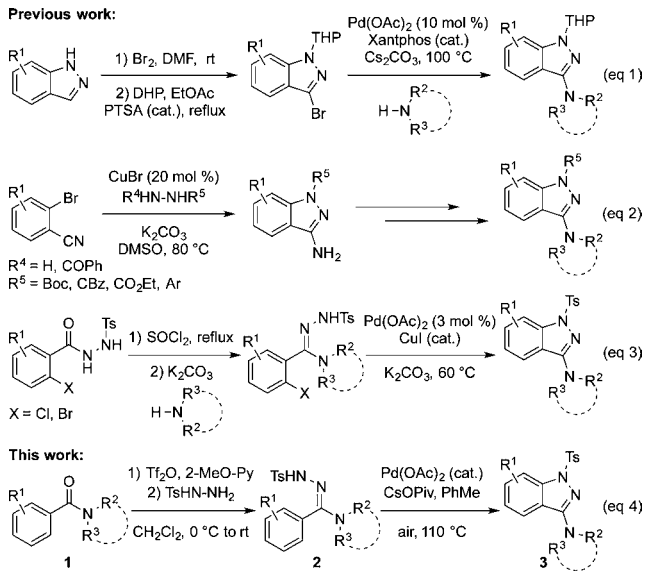


Figure 1. Bioactive pharmaceutical leads bearing substituted 3-aminoindazoles.

incorporation into important therapeutic leads, intensive efforts have been dedicated toward finding general synthetic operations for the assembly and functionalization of 3-aminoindazoles.[6]

With this goal in mind, various metal-catalyzed amination strategies toward 3-aminoindazole were recently disclosed. For example, a 3-step amination protocol based on a preformed indazole subunit was optimized to facilitate a Buchwald−Hartwig cross-coupling between secondary amines and the 3-bromoindazoles (Scheme 1, eq 1).[7] With the advantage of being

Scheme 1. Synthetic Strategies toward Substituted 3-Aminoindazoles



operationally simple, the efficacy of this pathway suffers from three main drawbacks: the preparation of the initial free base indazole, a limited functional group tolerance, and a narrow scope. A different approach to 3-aminoindazoles involves a sequential intermolecular C−N bond forming step via either aromatic nucleophilic substitution or metal-catalyzed cross-coupling of 2-halobenzonitriles with hydrazides, followed by a condensation reaction (Scheme 1, eq 2).[8] However, these

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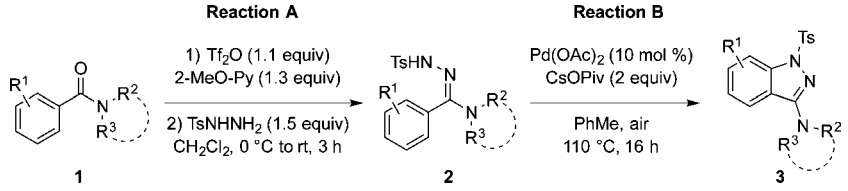
Table 1. Synthesis of Substituted 3-Aminoindazoles



entry	1, amide	2, hydrazonamide	3, 3-aminoindazole	R	2, yield (%)[a]	3, yield (%)[b]
1	**1a**	**2a**	**3a**	H	90	65
2	**1b**	**2b**	**3b**	Me	69	70
3	**1c**	**2c**	**3c**	F	79	55
4	**1d**	**2d**	**3d**	Cl	83	27
5	**1e**	**2e**	**3e**	CO_2Me	65	51
6	**1f**	**2f**	**3f**	2-thiophenyl	67	62
7	**1g**	**2g**	**3g**	OMe	74	15
8	**1h**	**2h**	**3h**	H	71	67
9	**1i**	**2i**	**3i**	CF_3	73	35
10	**1j**	**2j**	**3j**	COMe	56[c]	38
11	**1k**	**2k**	**3k**	CN	78	54
12	**1l**	**2l**	**3l**		68	41
13	**1m**	**2m**	**3m**		76	44
14	**1n**	**2n**	**3n**		82	59
15	**1o**	**2o**	**3o**		44	30[e]
16	**1p**	**2p**	**3p**		0	-
17	**1a**	**2q**	**3q**		70[d]	44
18	**1a**	**2r**	**3r**		84[d]	15
19	**1s**	**2s**	**3s**		86	27
20	**1t**	**2t**	**3t**		86	0

[a]Isolated yields on 0.56 mmol scale. [b]Isolated yields on 0.28 mmol scale. [c]1.1 equiv of $TsNHNH_2$ was used. [d]1.3 equiv of hydrazide was used. [e]A 4:1 mixture of regioisomers was observed (major isomer illustrated in Table 1).

reactions are intrinsically limited to costly starting materials and require further synthetic functionalization of free primary amine products, for which limited examples have been reported in the literature.[9] A more convergent and combinatorial approach toward *N*′,*N*′-disubstituted 3-aminoindazoles proceeds via intramolecular Pd-catalyzed cross-coupling of *ortho*-halogenated *N*-tosylamidrazones (Scheme 1, eq 3).[10] Unfortunately, the latter is likewise limited to prefunctionalized and noncommercially available tosylated hydrazides and involves tedious synthetic operations, including difficult purifications for each intermediate.[11] Thus far, most approaches suffer from lengthy syntheses of specific aromatic halides, which limit the synthetic availability of substituted 3-aminoindazoles.[12]

Our group has a long-standing interest in triflic-anhydride-mediated activation and derivatization of amides[13] as well as in metal-catalyzed C−H functionalization reactions.[14] We sought

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to unite both of these chemical processes in a step-economic and operationally simple procedure that is amenable to preparing substituted 3-aminoindazoles **3**, starting from readily available shelf-stable building blocks (Scheme 1, eq 4). Our envisioned strategy consisted of a novel intramolecular Pd-catalyzed C−H amination reaction with tosylhydrazonamides **2**, which are themselves derived from synthetic valuable and readily available tertiary amides[15,16] **1** and hydrazides.

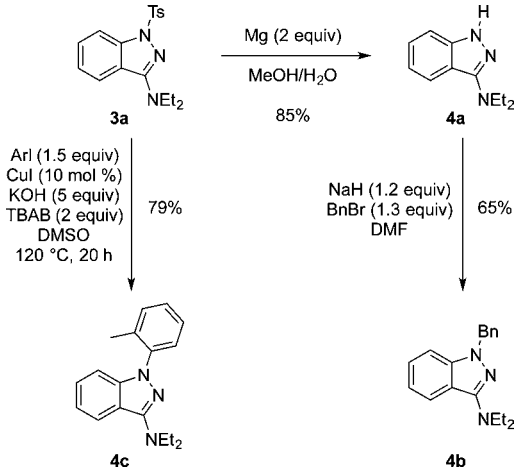
Initially, we carefully refined each of the parameters associated with the amide activation step, as well as for the *in situ* nucleophilic addition of the *N*-tosylhydrazide nucleophile.[17] Following other well-established chemoselective Tf_2O activation protocols,[18] an evaluation of various base additives was pursued for the activation of **1a** in the presence of 1.1 equiv of Tf_2O in CH_2Cl_2 at low temperatures. This tuning turned out to be essential, as the incorporation of 2-methoxypyridine (2-MeO-Py), a mild base additive, was mandatory for achieving an appreciable yield (90%) of **2a** (Table 1, Reaction A).[13b,19] As a proof of concept, stable tosylhydrazonamide **2a** was submitted to different transition-metal-catalyzed C−H amination conditions in the presence of external oxidizing agents.[17] Inspired by extensive developments in oxidative C−H functionalizations,[20] we were delighted to find that the desired C−N bond forming reaction was achieved when the reaction was run under an atmosphere of air in the presence of catalytic $Pd(OAc)_2$ and two equivalents of CsOPiv in refluxing toluene (Reaction B). Unfortunately, the use of other oxidizing reagents and/or catalytic amounts of ligand was detrimental to the reaction conversion.[17]

After establishing efficient reaction conditions for both the amide derivatization and intramolecular catalytic C−H amination reactions, the substrate scope was studied (Table 1). The overall process was shown to be effective in the presence of various amides, and it tolerates different substitution patterns on both the aryl and nitrogen substituents of the benzamide moiety (Table 1, entries 1−15). Cyclic and acyclic amines can be incorporated at the C-3 position of the desired indazole, with consistent yields for the preparation of the tosylhydrazonamides and a more variable efficiency for the C−H functionalization step. Indeed, varying the electronic properties at the para position of the aryl ring on the benzamide moiety marginally influenced Reaction A, while lower conversions were observed for the C−H amination step (Table 1, entries 1−14). With substrate **1o**, which contains a meta substituent on the aryl ring, the cyclization reaction produced a 4:1 mixture of regioisomers (Table 1, Reaction B, entry 15). However, an ortho substitution on the aryl ring was not tolerated in the amide derivatization step (Table 1, Reaction A, entry 16).

The commercially available tosylhydrazide nucleophile can also be replaced by other hydrazides with different electron-withdrawing protecting groups at the N-1 position (Table 1, entries 17 and 18). Remarkably, the transformation is also productive in the presence of amide **1s** bearing a benzothiophenyl group allowing for the formation of further diversified cores, such as 3-aminoindazole heterocycle **3s** (Table 1, entry 19). While Reaction A could be efficiently performed using secondary amide **1t**, the corresponding tosylhydrazonamide **2t** was not a suitable starting material for the C−H amination reaction (Table 1, entry 20).[17] Moreover, the KIE of the reaction was determined to be 0.92 from an intramolecular C−H/C−D functionalization competition employing substrate **2** bearing a deuterium atom at the ortho position of the aryl ring (R^1 = *o*-D).[17] This experiment suggests by simple means that C−H bond cleavage is not the rate-determining step.[21]

We were also eager to demonstrate that the *N*-Ts-3-aminoindazole moiety is a versatile stepping stone for subsequent functionalization reactions. To do so, we focused our attention on diversifying the *N*-1 position by applying useful synthetic transformations on **3a** as a benchmark (Scheme 2). For

Scheme 2. Diversification of *N*-Ts-3-Diethylaminoindazole 3a



example, the *N*-Ts protecting group was easily cleaved under reductive conditions to yield the free base 3-aminoindazole **4a** in 85% yield.[22] Alkylation of the free amine in the presence of BnBr affords 3-aminoindazole **4b** in 65% yield. Furthermore, a sequential one-pot deprotection−functionalization could be performed by applying a Cu-catalyzed Buchwald−Hartwig coupling to generate **4c** in 79% yield in the presence of *o*-Me substituted coupling partner.[22a]

In summary, we have developed a two-step process for the rapid conversion of readily available tertiary amides into valuable 3-aminoindazoles. The disclosed synthetic strategy includes a triflic-anhydride-mediated chemoselective derivatization, which furnishes tosylhydrazonamide intermediates poised for subsequent intramolecular palladium catalyzed C−H aminations. The optimized conditions allowed for the synthesis of substituted 3-aminoindazoles with broad substitution patterns including the complex 3-aminoindazobenzothiophene heterocycle. Moreover, the resulting azole product can take part in additional useful deprotection/functionalization reactions. These reactions provide rapid access to complex heterocyclic scaffolds, and consequently, our synthetic strategy should be valuable to both pharmaceutical and agrochemical industries, as it will significantly impact the step-economy in the synthesis of bioactive compounds.

■ ASSOCIATED CONTENT

Supporting Information

Optimization tables, experimental procedures, characterization data, and copies of NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00765.

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Notes

The authors declare no competing financial interest.

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