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Synthesis of 1-aryl-1*H*-indazoles via the palladium-catalyzed cyclization of *N*-aryl-*N*′-(*o*-bromobenzyl)hydrazines and [*N*-aryl-*N*′-(*o*-bromobenzyl)-hydrazinato-*N*′]-triphenylphosphonium bromides

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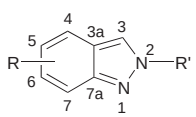
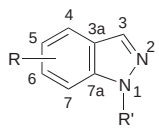
Abstract—1-Aryl-1*H*-indazoles were synthesized by the palladium-catalyzed intramolecular amination [$Pd(OAc)_2$/dppf/*t*BuONa (150 mol%)/toluene/90°C] of the corresponding *N*-aryl-*N*′-(*o*-bromobenzyl)hydrazines. It was further demonstrated that cyclization of [*N*-aryl-*N*′-(*o*-bromobenzyl)-hydrazinato-*N*′]-triphenylphosphonium bromides under the conditions of [$Pd(OAc)_2$/dppf/*t*BuONa (250 mol%)/dioxane/90°C] also led to the formation of the corresponding 1-aryl-1*H*-indazoles. These methods were applied to a group of representative substrates to give indazole products in moderate to very good yields.

The indazole subunit (Fig. 1) is a frequently found motif in drug substances with important biological activities such as anti-inflammatory,[1] anti-tumor[2] and anti-HIV activities.[3] Despite the importance of indazoles in pharmaceutical development, the invention of efficient and general methodologies for the synthesis of *N*-substituted indazoles has met with limited success. The existing methods often require the use of harsh reaction conditions or special equipment, which significantly limited their applications.[4] We recently reported a novel synthesis of 2-aryl-2*H*-indazoles from the corresponding *N*-aryl-*N*-(*o*-bromobenzyl)hydrazines via the palladium-catalyzed intramolecular C–N bond formation followed by spontaneous aromatization.[5] It represents the first general method by which 2-aryl-2*H*-indazoles are constructed through the creation of the N(1)–C(7a) bond. In this letter, we wish to describe a complementary method for the synthesis of 1-aryl-1*H*-indazoles which involves the palladium-catalyzed cyclization of *N*-aryl-*N*′-(*o*-bromobenzyl)-hydrazines as well as [*N*-aryl-*N*′-(*o*-bromobenzyl)-hydrazinato-*N*′]-triphenylphosphonium bromides.

Based on our experience with 2-aryl-2*H*-indazoles, the initial efforts to synthesize 1-aryl-1*H*-indazoles focused on the preparation of *N*-aryl-*N*′-(*o*-bromobenzyl)hydrazines (e.g. **3**, Scheme 1) and their subsequent cyclizations. Compound **3** was synthesized in two steps



2-R'-2*H*-indazoles



1-R'-1*H*-indazoles

R' = aryl, alkyl

Figure 1.

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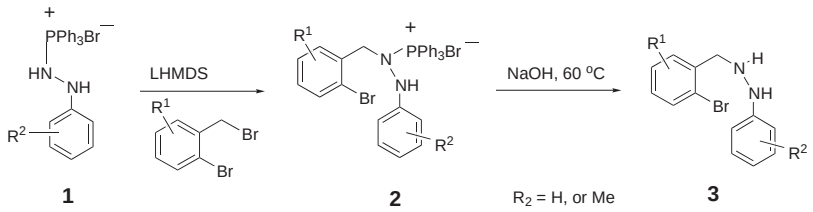
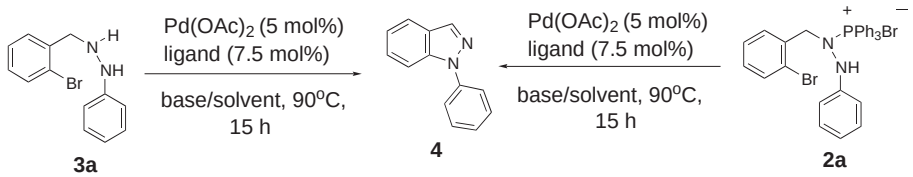


Scheme 1.

Table 1. Optimization of solvent, ligand, and base in palladium-catalyzed intramolecular amination



Entry	Substrate	Solvent	Ligand	Base (mol%)	Yield (%)
1	**3a**	Toluene	dppf	*t*BuONa (150)	81[b]
2	**2a**	Toluene	dppf	*t*BuONa (250)	8[a]
3	**2a**	Dioxane	dppf	*t*BuONa (250)	53[b]
4	**2a**	Dioxane	dppf	Cs_2CO_3 (250)	0[a]
5	**2a**	Dioxane	(*R*)-BINAP	*t*BuONa (250)	38[a]
6	**2a**	Dioxane	No ligand	*t*BuONa (250)	0[a]

[a] Yields were determined by ^{1}H NMR of the crude products using 2-methoxynaphthalene as an internal standard.
[b] Isolated yield by chromatography.

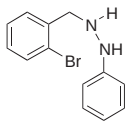
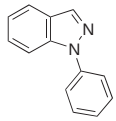
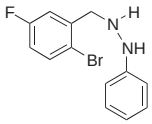
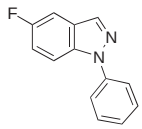
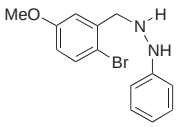
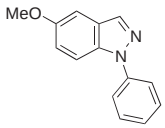
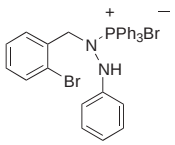
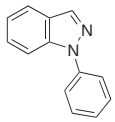
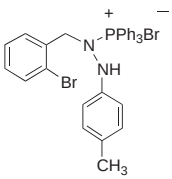
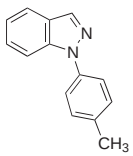
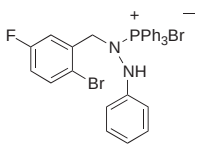
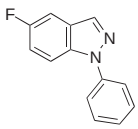
(one pot) analogously to a literature procedure,[6] as shown in Scheme 1. Intermediate **2** can also be isolated and deprotected in a separate step to give **3**.

When *N*-phenyl-*N*′-(*o*-bromobenzyl)hydrazine (**3a**, Table 1) was subjected to the conditions of [$Pd(OAc)_2$/dppf/*t*BuONa (150 mol%)/toluene/90°C, method A], the cyclization and the spontaneous aromatization occurred smoothly to furnish 1-phenyl-1*H*-indazole (**4**) in 81% isolated yield (Table 1, entry 1). Unlike the synthesis of 2-aryl-2*H*-indazoles, very little debromonated by-product was observed. During the course of this study, we also noticed that in some cases the *N*-aryl-*N*′-(*o*-bromobenzyl)hydrazines are unstable upon long-term storage. Therefore we investigated the use of **2** as the reaction substrate, since this compound proved to be stable under ambient conditions.

Results from the investigation of different cyclization conditions for **2a** are summarized in Table 1 (entries 2–6). The 1-phenyl-1*H*-indazole was obtained in moderate yield from compound **2a** using the conditions of [$Pd(OAc)_2$/dppf/*t*BuONa (250 mol%)/dioxane/90°C, method B]. The use of toluene as the solvent afforded the product in only 8% yield due to the insolubility of the starting material in toluene. It is also worth noting that 250 mol% of the base was necessary for the desired product to be formed. Presumably the extra equivalent of the base is consumed to deprotect the triphenylphosphine. Cesium carbonate was found to be ineffective in promoting the reaction. As was the case for the synthesis of 2-aryl-2*H*-indazoles, the use of (*R*)-BINAP as the supporting ligand[7] resulted in a decrease in the yield. Finally, it was shown that the cyclization did not proceed without the presence of the ligand. Using the above-described methods (A or B),[8] a group of representative substrates were cyclized to furnish indazole products in moderate to very good yields, and the results are presented in Table 2.[9]

In summary, we have developed a new method for the facile synthesis of 1-aryl-1*H*-indazoles from *N*-aryl-*N*′-(*o*-bromobenzyl)hydrazines via the palladium-catalyzed C–N bond formation followed by the spontaneous aromatization. It was further demonstrated that [*N*-aryl-*N*′-(*o*-bromobenzyl)-hydrazinato-*N*′]-triphenylphosphonium bromides also underwent cyclizations under suitable conditions to afford 1-aryl-1*H*-indazoles. The present approach offers several advantages, including mild reaction conditions and ease of operation. Applications of this methodology to the synthesis of novel biologically active compounds are under investigation in these laboratories and will be reported in due course.

Table 2. Indazole synthesis via a palladium-catalyzed intramolecular C–N bond formation

entry	substrate[a]	product	method	yield[b]
1			A	81%
2			A	90%
3			A	87%
4			B	58%
5			B	40%
6			B	63%

[a]All substrates were prepared according to the modified literature procedure.

[b] Isolated yields by chromatography.

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8. Method A: To a solution of the *N*-phenyl-*N′*-(*o*-bromobenzyl)hydrazine (84 mg, 0.3 mmol) in anhydrous toluene (2.0 mL) in a pressure tube were added $Pd(OAc)_2$ (3.5 mg, 0.015 mmol), dppf (13 mg, 0.0225 mmol) and *t*BuONa (43 mg, 0.45 mmol). Then the pressure tube was filled with Ar and closed. The reaction was heated at 90°C for 15 h and

filtered through a pad of silica gel (50% ether/hexanes). After the removal of the volatiles, the residue was purified by flash chromatography on silica (5–10% ether/hexanes) to provide the desired product as white crystals (48 mg, 81%). For Method B the starting material was [*N*-phenyl-*N*′-(*o*-bromobenzyl)-hydrazinato-*N*′]-triphenylphosphonium bromide, the solvent was dioxane and *t*BuONa was used in 250 mol%.

9. Spectroscopic data for all new compounds: *N*-(2-Bromobenzyl)-*N*′-phenylhydrazine: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 (d, $J=7.64$ Hz, 1H), 7.32 (m, 2H), 7.25–7.15 (m, 3H), 6.94 (d, $J=8.60$ Hz, 2H), 6.81 (t, $J=7.24$ Hz, 1H), 4.99 (br s, 1H), 4.09 (s, 3H). *N*-(2-Bromo-5-fluorobenzyl)-*N*′-phenylhydrazine: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (dd, $J=5.21$, 8.73 Hz, 1H), 7.23 (dd, $J=7.43$, 8.41 Hz, 2H), 7.14 (dd, $J=3.08$, 9.00 Hz, 1H), 6.92 (m, 3H), 6.82 (t, $J=5.97$ Hz, 1H), 5.04 (s, 1H), 4.07 (s, 3H). *N*-(2-Bromo-5-methoxybenzyl)-*N*′-phenylhydrazine: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (d, $J=8.71$ Hz, 1H), 7.24 (m, 2H), 6.94 (m, 2H), 6.88 (d, $J=3.06$ Hz, 1H), 6.81 (t, $J=6.31$ Hz, 1H), 6.76 (dd, $J=3.65$, 6.70 Hz, 1H), 5.07 (s, 1H), 4.04 (s, 2H), 3.77 (s, 3H). [*N*-Phenyl-*N*′-(*o*-bromobenzyl)-hydrazinato-*N*′]-triphenylphosphonium bromide: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (s, 1H), 8.24 (d, $J=7.54$ Hz, 1H), 7.98 (m, 6H), 7.78 (t, $J=6.05$ Hz, 3H), 7.65 (m, 7H), 7.23 (d, $J=7.91$ Hz, 1H), 7.03 (t, $J=6.62$ Hz, 1H), 6.91 (t, $J=7.74$ Hz, 1H), 6.82 (m, 4H), 6.53 (t, $J=6.88$ Hz, 1H). [*N*-Phenyl-*N*′-(2-bromo-5-methoxybenzyl)-hydrazinato-*N*′]-triphenylphosphonium bromide: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.37 (s, 1H), 8.03 (dd, $J=7.24$, 8.58 Hz, 6H), 7.96 (d, $J=3.04$ Hz, 1H), 7.80 (m, 3H), 7.66 (m, 7H), 7.07 (d, $J=8.79$ Hz, 1H), 6.80 (m, 4H), 6.54 (m, 1H), 6.45 (dd, $J=3.07$, 8.78 Hz, 1H). [*N*-Phenyl-*N*′-(2-bromo-5-fluorobenzyl)-hydrazinato-*N*′]-triphenylphosphonium bromide: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.32 (s, 1H), 7.99 (dd, $J=7.21$, 8.51 Hz, 7H), 7.80 (t, $J=7.42$ Hz, 3H), 7.67 (m, 7H), 7.19 (dd, $J=5.13$, 8.77 Hz, 1H), 6.83 (m, 4H), 6.60 (m, 2H). [*N*-(*p*-Tolyl)-*N*′-(*o*-bromobenzyl)-hydrazinato-*N*′]-triphenylphosphonium bromide: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.87 (s, 1H), 8.09 (d, $J=7.56$ Hz, 1H), 7.97 (m, 6H), 7.78 (t, $J=7.20$ Hz, 3H), 7.65 (m, 6H), 7.24 (dd, $J=1.24$, 8.12 Hz, 1H), 7.03 (dt, $J=1.20$, 7.42 Hz, 1H), 6.93 (dt, $J=1.73$, 7.77 Hz, 1H), 6.65 (m, 4H), 2.06 (s, 3H). [*N*-(*p*-Tolyl)-hydrazinato-*N*′]-triphenylphosphonium bromide: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.61 (d, $J=24.1$ Hz, 1H), 7.88 (m, 6H), 7.76 (t, $J=7.58$ Hz, 3H), 7.63 (m, 6H), 6.89 (d, $J=8.00$ Hz, 2H), 6.73 (d, $J=8.44$ Hz, 2H), 6.48 (br s, 1H), 2.20 (s, 3H). 5-Fluoro-1-phenyl-1*H*-indazole: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (s, 1H), 7.70 (m, 3H), 7.55 (t, $J=7.61$ Hz, 2H), 7.40 (m, 2H), 7.21 (dt, $J=2.46$, 9.00 Hz, 1H). 5-Methoxy-1-phenyl-1*H*-indazole: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (s, 1H), 7.72 (d, $J=8.60$ Hz, 2H), 7.65 (d, $J=9.11$ Hz, 1H), 7.53 (t, $J=7.76$ Hz, 2H), 7.35 (t, $J=7.44$ Hz, 1H), 7.14 (d, $J=2.09$ Hz, 1H), 7.10 (dd, $J=2.42$, 9.15 Hz, 1H), 3.89 (s, 3H).