Efficient Synthesis of 3-Substituted Indazoles Using Pd-Catalyzed Intramolecular Amination Reaction of *N*-Tosylhydrazones

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The efficient method for the preparation of 3-substituted indazoles was developed using the palladium catalyzed intramolecular amination reaction of 2-bromophenyl hydrazone derivatives. Good functional group compatibility was observed under mild reaction conditions and various 3-substituted indazoles were obtained in moderate to excellent yield.

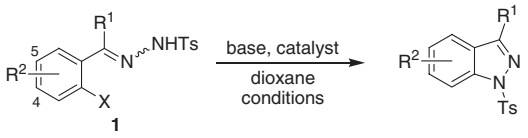
The development of methods for the efficient construction of aromatic heterocycles still attracts much attention due to their numerous presence in natural products, their potent biological activities, and specific material properties. Despite being not abundant in nature, indazole derivatives are considered as important pharmacophores that have a broad range of biological activities.[1] Song et al. have reported the *N*-arylindazole synthesis via the palladium-catalyzed amination reaction using hydrazine derivatives as starting materials.[2] However, gained indazoles are not manifold and the yields are moderate. More recently, Cho et al. have demonstrated that the reaction of arylhydrazines and 2-bromobenzaldehydes gave the *N*-arylindazoles in the presence of a palladium catalyst and a base.[3] Though this one-pot indazole synthesis is a novel method, the reaction conditions are somewhat harsh so the substituents compatible during the reaction seem to be limited. Meanwhile, as compared with the preparation of *N*-substituted indazoles, the synthesis of 3-substituted indazoles is much rarer.[4,5] To overcome this restriction, we employed the palladium-catalyzed intramolecular amination reaction[6] of hydrazone derivatives (**1**) for the synthesis of 3-substituted indazoles.[7]

During the course of the optimization of the reaction conditions, it was found that the use of dioxane as a solvent and Cs_2CO_3 or NaO^{t}Bu as a base allowed the cyclization to proceed efficiently under mild conditions (even at room temperature in some cases).[8]

For example, 3-*tert*-butoxycarbonyl-*N*-tosylindazole was obtained in 81% yield from the corresponding hydrazone **1a** in the presence of $Pd_2(dba)_3$ and P(2-Tol)$_3$ along with Cs_2CO_3 (Table 1, Entry 1). The reaction proceeded smoothly at room temperature and the desired indazole produced exclusively. The reaction of hydrazone **1b** possessing amide moiety also afforded the cyclized product in 72% yield without forming any side reaction products (Table 1, Entry 2).

We next investigated the synthesis of 3-arylindazoles with various substituents. As shown in Table 1, bidentate dppp or dppf served as an excellent ligand for this reaction. 3-Phenyl-*N*-tosylindazole was obtained in 83% yield from hydrazone **1c** (Table 1, Entry 3). Furthermore, substituents on the arene such as -NO_2, -OMe, and -Me were tolerated in this reaction, and a variety of 3-arylindazoles were obtained in moderate to high yield (Table 1, Entries 4–7). In addition, aryl nonaflate (ArONf = $ArOSO_2(CF_2)_3CF_3$)[9] was also employed as a substrate for this process. The reaction of hydrazone **1h** rapidly proceeded at room temperature and gave the cyclized product in 96% yield (Table 1, Entry 8).

Table 1. Pd-catalyzed amination for indazoles synthesis



1

1a : R^1 = $CO_2{}^t$Bu, R^2 = H, X = Br
1b : R^1 = $CONEt_2$, R^2 = H, X = Br
1c : R^1 = Ph, R^2 = H, X = Br
1d : R_1 = Ph, R^2 = 4-NO_2, X = Br
1e : R^1 = Ph, R^2 = 5-OMe, X = Br
1f : R^1 = Ph, R^2 = 4-Me, X = Br
1g : R^1 = (4-OMe)C_6H_4, R^2 = H, X = Br
1h : R^1 = Ph, R^2 = H, X = ONf

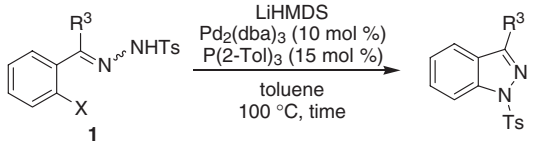
Entry	Hydrazone[a]	Base/Catalyst[b,c]	Conditions	Yield/%
1	**1a**	Cs_2CO_3/A	rt, 3 h	81
2	**1b**	NaO^{t}Bu/B	50 °C, 12 h	72
3	**1c**	Cs_2CO_3/C	50 °C, 17 h	83
4	**1d**	Cs_2CO_3/B	50 °C, 12 h	74
5	**1e**	NaO^{t}Bu/C	50 °C, 2 h	56
6	**1f**	NaO^{t}Bu/B	50 °C, 15 h	66
7	**1g**	NaO^{t}Bu/B	rt, 8 h	94
8	**1h**	Cs_2CO_3/B	rt, 2 h	96

[a] Single isomer was used, which was a major product in hydrazone synthesis.
[b] A; $Pd_2(dba)_3$, P(2-Tol)$_3$, B; $Pd(OAc)_2$, dppf, C; $Pd(OAc)_2$, dppp.
[c] palladium; 10 mol %, phospine ligand; 15 mol %.

Although employing the combination such as Cs_2CO_3 or NaO^{t}Bu/dioxane provided mild cyclization of several hydrazones, not all types of substrates reacted effectively. When the hydrazones possessing alkyl group as R^3 in Table 2 were subjected to the reaction under the conditions above, 3-alkylindazoles produced in up to only 52% yield. However, a survey of other reaction conditions indicated that the use of LiHMDS, $Pd_2(dba)_3$, and P(2-Tol)$_3$ in toluene could remarkably promote the cyclization and the expected products were obtained in high yield, albeit at relatively higher temperature (Table 2, Entries 1–4). It is noteworthy that aryl chloride **1k** also successfully reacted under this reaction condition to give 2-ethyl-*N*-tosylindazole in 62% yield (Table 2, Entry 4).

In conclusion, efficient construction of 3-substituted indazole derivatives was accomplished using the palladium-catalyzed intramolecular amination reaction. The procedures introduced here are practically useful and good functional group-compatibility was observed under mild reaction conditions; base-sensitive substituents such as ester and amide remained intact during the reaction. In addition, we have confirmed that the

Table 2. 3-Alkylindazoles synthesis



1i : R^3 = Me, X = Br **1k** : R^3 = Et, X = Cl
1j : R^3 = Et, X = Br

Entry	Hydrazone	Time/h	Yield/%
1	**1i** (E)	4	68
2	**1i** (Z)	1	91
3	**1j** (Z)	3	84
4	**1k** (Z)	15	62

detosylation of the indazoles effectively proceeded to give the deprotected indazoles (Scheme 1). It may offer the possibility of the further functionalization of 3-substituted indazoles by the subsequent transformation such as *N*-arylation and *N*-alkylation. Continuous studies to extend the scope of the substrates and to apply this method for natural product synthesis are underway.

conditions : for R^4 = $CO_2{}^tBu$; TBAF, THF, 50 °C, 24 h : **>99%**
for R^4 = Me ; Mg, MeOH, rt, 1.5 h : **87%**

Scheme 1. Detosylation of indazoles.

References and Notes

1 a) P. Fludzinski, D. A. Evrard, W. E. Bloomquist, W. B. Lacefield, W. Pfeifer, N. D. Jones, J. B. Deeter, and M. L. Cohen, *J. Med. Chem.*, **30**, 1535 (1987). b) H. D. H. Showalter, M. M. Angelo, E. M. Berman, G. D. Kanter, D. F. Ortwine, S. G. Ross-kesten, A. D. Sercel, W. R. Turner, L. M. Werbel, D. F. Worth, E. F. Elslager, W. R. Leopald, and J. L. Shillis, *J. Med. Chem.*, **31**, 1527 (1988). c) J. D. Rodgers, B. L. Johnson, H. Wang, S. Erickson-Viitanen, R. M. Klabe, L. Bacheler, B. C. Cordova, G. N. Lam, and C.-H. Chang, *Bioorg. Med. Chem. Lett.*, **8**, 715 (1998).

2 a) J. J. Song and N. K. Yee, *Org. Lett.*, **2**, 519 (2000). b) J. J. Song and N. K. Yee, *Tetrahedron Lett.*, **42**, 2937 (2001).

3 C. S. Cho, D. K. Lim, N. H. Heo, T.-J. Kim, and S. C. Shim, *Chem. Commun.*, **2004**, 104.

4 a) A. Alberti, N. Bedogni, R. Leardini, D. Nanni, G. F. Pedulli, A. Tundo, and G. Zanardi, *J. Org. Chem.*, **57**, 607 (1992). b) C. Dell'Erba, M. Novi, G. Petrillo, and C. Tavani, *Tetrahedron*, **50**, 3529 (1994).

5 For cross-coupling reactions of 3-haloindazoles, see: a) V. Collot, P. Dallemagne, P. R. Bovy, and S. Rault, *Tetrahedron*, **55**, 6917 (1999). b) V. Collot, D. Varlet, and S. Rault, *Tetrahedron Lett.*, **41**, 4363 (2000). c) A. Arnautu, V. Copllot, J. C. Ros, C. Alayrac, B. Witulski, and S. Rault, *Tetrahedron Lett.*, **43**, 2695 (2002).

6 For reviews, see: a) J. P. Wolfe, S. Wagaw, J.-F. Marcoux, and S. L. Buchwald, *Acc. Chem. Res.*, **31**, 805 (1998). b) J. F. Hartwig, *Angew. Chem., Int. Ed.*, **37**, 2046 (1998). c) B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, **576**, 125 (1999).

7 General procedure for hydrazones syntheses was as follows: A mixture of ketone (1.0 mmol), NH_2NHTs (1.2–2.0 mmol), and AcOH or AcCl (cat.) in EtOH (5 mL) was heated under reflux for 4–24 h. The reaction mixture was treated with saturated aqueous $NaHCO_3$ (10 mL) followerd by extraction with AcOEt (20 mL × 3). The combined organic layer was washed with saturated aqueous NaCl (20 mL), and the organic layer was dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the residue was purified by SiO_2 column chromatography to give hydrazones **1a**–**1k** as single isomers or mixtures of *E*- and *Z*-isomers, which were separable by recrystallization or flush column chromatography. Not all of the geometries of hydrazones were determined. In the case of hydrazones **1b**, **1c**, **1d**, and **1e**, the major product was used for next cyclization. In the case of hydrazones **1i**–**1k**, geometries of both isomers were determined by ^{1}H HMR, ^{13}C NMR (steric effect), HMQC, and NOESY. **1a**; 65% (single isomer), **1b**; 96% (1.3:1), **1c**; 70% (5:1), **1d**; 36% (6:1), **1e**; 35% (6:1), **1f**; 80% (single isomer), **1g**; 99% (single isomer), **1h**; 73% (single isomer), **1i**; 81% (*E*:*Z* = 4:1), **1j**; 48% (*E*:*Z* = 1:8), **1k**; 99% (*E*:*Z* = 1:1).

8 General procedure for cyclizations was as follows: Under Ar atmosphere, a mixture of a hydrazone (1.0 mmol), a base (1.5 mmol), a palladium catalyst (10 mol %), a phosphine ligand (15 mol %) and a solvent (10 mL) was stirred. The reaction mixture was filtered through Celite and the solvent was removed under reduced pressure. The residue was purified by SiO_2 column chromatography to give the indazoles.

9 For Pd-catalyzed amination reaction of aryl nonaflates, see: K. W. Anderson, M. Mendez-Perez, J. Priego, and S. L. Buchwald, *J. Org. Chem.*, **68**, 9563 (2003).

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