Synthesis of 3-Amino-substituted *N*-Alkylindazoles via Palladium(II)-catalyzed Intramolecular N-Arylation of Tosylhydrazines

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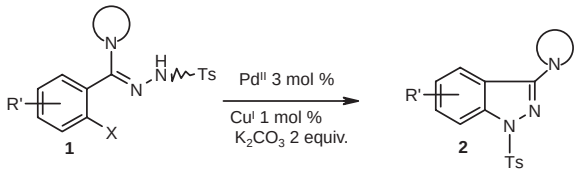
An efficient synthesis of 3-amino-substituted *N*-alkyl indazoles is described. Reaction of readily available *o*-halo aryl hydrazines with palladium(II) acetate and cupper(I) iodide in the presence of a base afforded the corresponding 3-substituted *N*-tosylindazoles in excellent yields. These products were further functionalized after detosylation with Na–Hg, followed by alkylation to afford 3-amino-substituted *N*-alkylindazoles.

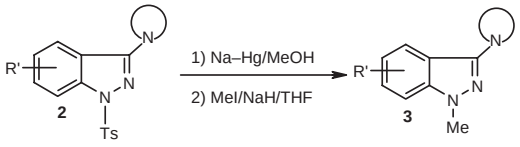
The indazole ring is an important pharmacophore in medicinal chemistry due to its association with various potent biologically active molecules.[1] In fact, compounds containing the indazole skeleton are known to show a variety of biological properties, such as high binding affinity for estrogen receptor,[2] inhibition of protein kinases like C-β, 5-HT_2, $5HT_3$ receptor antagonism,[3] HIV protease inhibition,[4] anti-inflammatory,[5] and as anti-tumor agents.[6] Thus, the search for an efficient synthesis of the indazole ring system has been a longstanding goal. Several methods for the synthesis of indazoles have been reported in literature. They include intramolecular amination of *N*-aryl-*N*′-(*o*-halobenzyl)hydrazines,[7] hydrazones of 2-halobenzaldehydes, and 2-haloacetophenones.[8] However, these methods have limited success in the case of synthesis of 3-amino-substituted *N*-alkyl indazoles.

The palladium-catalyzed aromatic carbon–nitrogen bond forming reactions by the cross coupling of aryl halides and amines has recently had an upsurge as a useful synthetic tool; various *N*-aryl amines can be prepared by this protocol.[9] Whereas, by intramolecular N-arylation ca affords a variety of nitrogen heterocycles.[7,8] In this connection, some synthetic routes have been reported for the synthesis of indazoles. Herein, we report an efficient synthesis of 3-amino-substituted *N*-alkylindazoles via palladium(II)-catalyzed intramolecular N-arylation of tosylhydrazines.

In this report (Schemes 1 and 2), we have described an efficient method for the synthesis of 3-amino-substituted *N*-alkylindazoles via palladium(II) acetate-catalyzed intramolecular N-arylation of tosylhydrazines. The amino-substituted intermediate **1** was readily prepared from the corresponding tosylhydrazone[10] and which on intramolecular N-arylation with palladium(II) acetate (3 mol %) and cupper(I) iodide (1 mol %) in the presence of 2 equiv. of K_2CO_3 at 60 °C in 1,4-dioxane yielded the corresponding 3-amino-substituted *N*-tosylindazoles **2** in 95% (Scheme 1, Table 2, Entry 1). In order to optimize the reaction conditions, we varied the amount of palladium(II) acetate and cupper(I) iodide. In the absence of cupper(I) iodide, more amount of palladium(II) acetate was needed and the formation of product was low (Table 1, Entries 1–4). However, using 1 mol % of cupper(I) iodide gave interesting results (Table 1, Entry 9). We believe that cupper(I) iodide forms complex



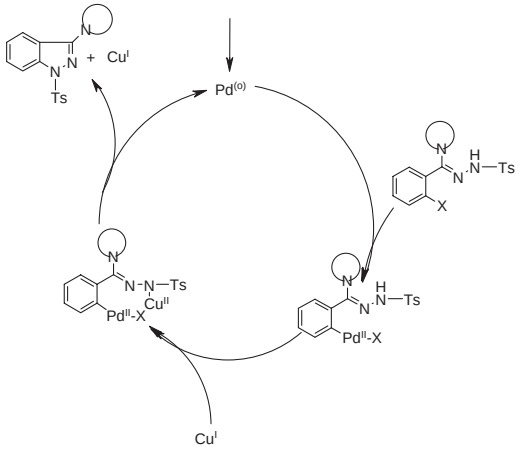
Scheme 1.



Scheme 2.

Table 1. Optimization of reaction conditions on the intramolecular N-arylation of *N*-(*o*-chlorophenyl)morpholinomethylidene-*N*′-tosylhydrazine **1** in 1,4-dioxane at 60 °C

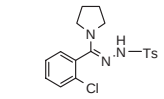
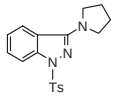
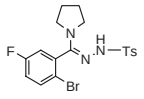
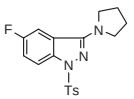
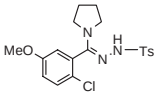
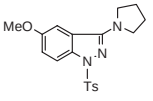
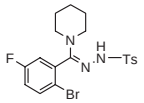
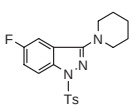
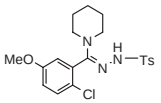
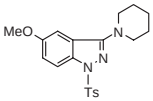
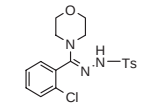
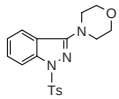
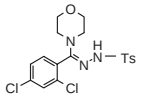
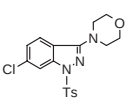
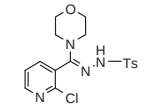
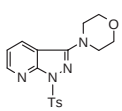
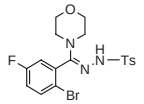
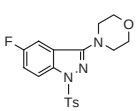
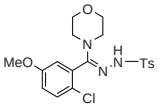
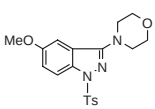
Entry	Pd^{II} (mol %)	Cu^{I} (mol %)	Time/h	Yield/%
1	20	—	6	75
2	15	—	6	70
3	10	—	6	50
4	5	—	6	50
5	1	20	2	96
6	2	10	2	96
7	3	5	1	95
8	3	3	1	95
9	3	1	1	95



Scheme 3. Plausible mechanism.

with nitrogen of tosylhydrazine and facilitates the reaction (Scheme 3). Encouraged by these findings we have carried out the reaction using 3 mol % of palladium(II) acetate and

Table 2. Synthesis of 3-substituted *N*-tosylindazoles via intramolecular N-arylation of tosylhydrazines

Entry	Substrate	Product[a]	Time/h	Yield[b]/%
1			1	95
2			2	95
3			2	93
4			3	92
5			2	93
6			1	95
7			2	95
8			2	94
9			1	96
10			2	94

[a]Products were characterized by ^{1}H NMR and EIMS spectral data. [b]Isolated yields after column chromatography.

1 mol % of cupper(I) iodide to synthesize various 3-amino-substituted *N*-tosylindazoles with excellent yields (Table 2).

The 3-amino-*N*-tosylindazoles **2** on reaction with 5 equiv. of Na–Hg in methanol at room temperature gave the corresponding detosylated product; which on further treatment with MeI in the presence of 1 equiv. of NaH in THF at room temperature afforded the 3-amino-substituted *N*-alkylindazoles **3** in good yields.

In conclusion, we have described an efficient method for 3-amino-substituted *N*-alkylindazoles via intramolecular N-arylation of tosylhydrazines.

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References and Notes

1 a) H. Cerecetto, A. Gerpe, M. Gonzalez, V. J. Aran, C. O. de Ocariz, *Mini-Rev. Med. Chem.* **2005**, *5*, 869. b) R. C. Elderfield, in *Heterocyclic Compounds*, ed. by R. C. Elderfield, Wiley, New York, NY, **1957**, Vol. 5, p. 162.
2 a) R. J. Steffan, E. Matelan, M. A. Ashwell, W. J. Moore, W. R. Solvibile, E. Trybulski, C. C. Chadwick, S. Chippari, T. Kenney, A. Eckert, L. Borges-Marcucci, J. C. Keith, Z. Xu, L. Mosyak, D. C. Harnish, *J. Med. Chem.* **2004**, *47*, 6435. b) M. D. Angelis, F. Stossi, K. A. Carlson, B. S. Katzenellenbogen, J. A. Katzenellenbozen, *J. Med. Chem.* **2005**, *48*, 1132.
3 H.-C. Zhang, C. K. Derian, D. F. Mc Comsey, K. B. White, H. Ye, L. R. Hecker, J. Li, M. F. Addo, D. Croll, A. J. Ekardt, C. E. Smith, Q. Li, M.-W. Cheung, B. R. Conway, S. Emanuel, K. T. Demarest, P. Andrade-Gorden, B. P. Damiano, B. E. Maryanoff, *J. Med. Chem.* **2005**, *48*, 1725.
4 a) P. Fludzinski, D. A. Evrard, W. E. Bloomquist, W. B. Lacefield, W. Pfeifer, N. D. Jones, J. B. Deeter, M. L. Cohen, *J. Med. Chem.* **1987**, *30*, 1535. b) H. Harada, T. Morie, Y. Hirokaw, S. Kato, *Tetrahedron: Asymmetry* **1997**, *8*, 2367.
5 a) W. Han, J. C. Pelletier, C. N. Hodge, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3615. b) M. Patel, J. D. Rodgers, R. J. McHugh, Jr., B. L. Johnson, B. C. Cordova, R. M. Klaba, L. T. Bacheler, S. Erickson-Viitanen, S. S. Ko, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3217.
6 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, J. L. Shillis, *J. Med. Chem.* **1988**, *31*, 1527.
7 a) K. Inamoto, M. Katsuno, T. Yoshino, I. Suzuki, K. Hiroya, T. Sakamoto, *Chem. Lett.* **2004**, *33*, 1026. b) T. J. Watson, T. A. Ayers, N. Shah, D. Wenstrup, M. Webster, D. Freund, S. Horgan, J. P. Carey, *Org. Process Res. Dev.* **2003**, *7*, 521. c) J. J. Song, N. K. Yee, *Tetrahedron Lett.* **2001**, *42*, 2937. d) J. J. Song, N. K. Yee, *Org. Lett.* **2000**, *2*, 519. e) J. Elgero, in *Comprehensive Heterocyclic Chemistry*, ed. by A. R. Kartritzky, C. W. Rees, Pergamon, New York, **1984**, Vol. 5, p. 167.
8 a) C. Pabba, H.-J. Wang, S. R. Mulligan, Z.-J. Chen, T. M. Srark, B. T. Gregg, *Tetrahedron Lett.* **2005**, *46*, 7553. b) A. Y. Lebedev, A. S. Khartulyari, A. Z. Voskoboynikov, *J. Org. Chem.* **2005**, *70*, 596.
9 J. F. Hartwig, *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.
10 Supporting Information describing typical experimental procedures and spectral data for selective compounds are available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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