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Synthesis of 3-Substituted Indazoles from Arynes and *N*-Tosylhydrazones

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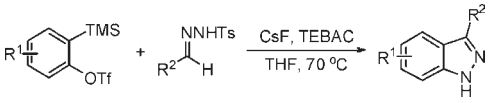
ABSTRACT

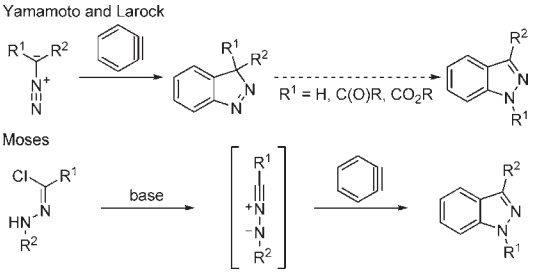


Readily available, stable, and inexpensive *N*-tosylhydrazones react with arynes under mild reaction conditions to afford 3-substituted indazoles in moderate to good yields. The reaction appears to involve a dipolar cycloaddition of *in situ* generated diazo compounds and arynes.

The indazole unit constitutes a key structural moiety in pharmaceutically relevant structures that exhibits a broad range of bioactivities.[1,2] Synthesis of the indazole system has therefore attracted much attention from the synthetic organic chemistry community.[1b,3] Recently, new and effective routes for the synthesis of indazoles utilizing aryne [3 + 2] dipolar cycloaddition reactions have been developed. We[2,4] and Yamamoto[5] reported the dipolar cycloaddition of arynes with diazo compounds to be an effective route to indazoles, and Moses disclosed the [3 + 2] dipolar cycloaddition of arynes with *in situ* generated nitrile imides (Scheme 1).[6]

Despite the success of these synthetic approaches, both methods have their drawbacks. Moses' method is limited to *N*-aryl nitrile imides and therefore can only be used to prepare 1,3-diarylindazoles. Yamamoto's and our previous methods are limited to stable and isolable diazo compounds, which typically contain electron-withdrawing groups. Since simple monosubstituted diazo compounds are unstable and difficult to handle, the simplest 3-substituted indazoles remain ironically largely inaccessible through aryne cycloaddition chemistry. Thus, the aryne approach to indazoles needs further refinement. Herein, we wish to report a formal aryne [3 + 2] annulation route to simple 3-substituted indazoles using stable, readily available, and inexpensive *N*-tosylhydrazones as starting materials.

Scheme 1. Aryne Approaches to Indazoles



N-Tosylhydrazones have been recognized as precursors to diazo compounds under basic conditions in many transformations,[7–9] including [3 + 2] dipolar cycloaddition reactions.[10] Although strong bases, such as LiO^{t}Bu[11]

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(1) For excellent reviews of the bioactivity and synthesis of indazoles, see: (a) Cerecetto, H.; Gerpe, A.; González, M.; Arán, V. J.; de Ocáriz, C. O. *Mini-Rev. Med. Chem.* **2005**, *5*, 869. (b) Stadlbauer, W. *Science of Synthesis*, Vol. 12; Georg Thieme: Stuttgart, 2002; pp 227–324.

(2) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219 and references therein.

(3) (a) Counceller, C. M.; Eichman, C. C.; Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2008**, *10*, 1021. (b) Huang, L.-J.; Shih, M.-L.; Chen, H.-S.; Pan, S.-L.; Teng, C.-M.; Lee, F.-Y.; Kuo, S.-C. *Bioorg. Med. Chem.* **2006**, *14*, 528. (c) Bartsch, R. A.; Yang, I. W. *J. Heterocycl. Chem.* **1984**, *21*, 1063. (d) Kovach, E. G.; Barnes, D. E. *J. Am. Chem. Soc.* **1954**, *76*, 1176. (e) Inamoto, K.; Katsuno, M.; Takashi, Y.; Arai, Y.; Hiroya, K.; Sakamoto, T. *Tetrahedron* **2007**, *63*, 2695.

(4) Wu, C.; Fang, Y.; Larock, R. C.; Shi, F. *Org. Lett.* **2010**, *12*, 2234.

(5) Jin, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3323.

(6) Spiteri, C.; Keeling, S.; Moses, J. E. *Org. Lett.* **2010**, *12*, 3368.

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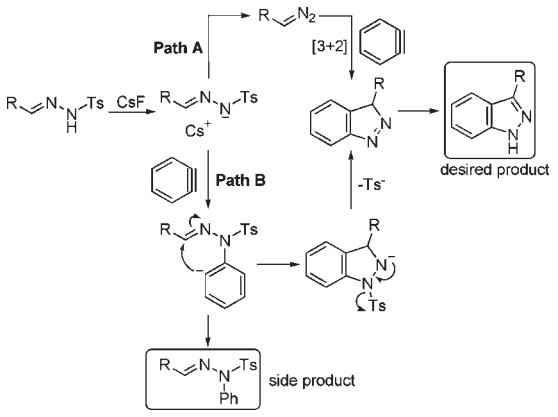
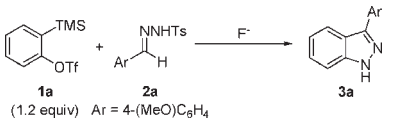
Scheme 2. Reaction of *N*-Tosylhydrazones with Arynes: Different Mechanisms Leading to the Same Indazoles



and Cs_2CO_3,[12] are often used, the fluoride used for the *in situ* generation of arynes from *o*-(trimethylsilyl)aryl triflates should be sufficiently basic to generate diazo compounds from *N*-tosylhydrazones *in situ* (Scheme 2, path A).[13] From a mechanistic point of view, even if this *in situ* generation of diazo compounds does not occur for whatever reasons, the formal [3 + 2] annulation of arynes through the conjugate bases of the *N*-tosylhydrazones (Scheme 2, path B) looks equally promising.

Thus, we examined the reaction of anisaldehyde *N*-tosylhydrazone (**2a**) with the benzyne precursor **1a** under various reaction conditions (Table 1). Three equivalents of fluoride were employed in this reaction to provide sufficient base for generation of the tosylhydrazone anion. Upon initial screening (entries 1–4), we found that CsF was the best fluoride source, and THF and acetonitrile were both suitable solvents. However, we noticed that the reaction quickly formed large amounts of a precipitate, likely the Cs salt of the conjugate base of **2a**, that inhibited efficient stirring of the reaction. Although heating the reaction mixture to increase the solubility led to a higher yield in acetonitrile (compare entries 1 and 2), it failed to improve the yield in ethereal solvents (entries 4–7). Under these reaction conditions, the reaction afforded a complex

Table 1. Reaction Optimization[a]



1a (1.2 equiv) **2a** Ar = 4-(MeO)C_6H_4 **3a**

entry	F^-	TEBAC (mol %)	solvent	*t* (°C)	time (h)	yield (%)[b]
1	CsF	0	MeCN	50	16	45
2	CsF	0	MeCN	80	6	51
3	TBAF	0	THF	rt	24	0
4	CsF	0	THF	70	24	38[c]
5	CsF	0	DME	85	10	37
6	CsF	0	dioxane	105	10	0
7	CsF	0	THF	90	24	38
8	CsF	10	MeCN	80	6	50
9	CsF	10	THF	70	24	61
10	CsF	10	THF	90	24	58
11[d]	CsF	10	THF	70	24	77
12[d]	**CsF**	**25**	**THF**	**70**	**24**	**87**

[a] All reactions were carried out on 0.4 mmol of **2a** in 5 mL of solvent. TEBAC = $[Et_3NBn]Cl$. [b] Isolated yield. [c] Incomplete conversion; 59% of **2a** recovered. [d] 10 mL of solvent were used.

mixture containing the desired product **3a**, the product of *N*-arylation of the hydrazone (the "side product" shown in Scheme 2), and phenyl *p*-toluenesulfinate from the reaction of Ts^- with benzyne. We next examined the effect of adding a phase transfer catalyst[14] to help dissolve the conjugate base of **2a**. Indeed, although the addition of 10 mol % of TEBAC ($[Et_3NBn]^+Cl^-$) failed to improve the yield in acetonitrile, it significantly increased the yield of **3a** in THF (compare entries 4 and 9, and 7 and 10). Further dilution brought the yield up to 77% (entry 11), and increasing the TEBAC to 25 mol % resulted in an 87% yield of **3a**.[15] *To our pleasant surprise, further N-arylation of* ***3a*** *was minimal under these reaction conditions, as opposed to the previous diazo route*.[2]

Having the optimal conditions in hand, we examined the scope and limitations of this method. Different arynes were tested first (Table 2, entries 1 and 2). The symmetrical

(7) Creary, X. *Org. Synth.* **1986**, *64*, 207.

(8) For a comprehensive review of processes generating diazo compounds from *N*-tosylhydrazones, see: Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem.* **2005**, 1479.

(9) For the related Bamford–Stevens–Shapiro reaction, see: (a) Nickon, A.; Zurer, P. S. J. *J. Org. Chem.* **1981**, *46*, 4685. (b) Casanova, J.; Waegell, B. *Bull. Soc. Chim. Fr.* **1975**, 922. (c) Nickon, A.; Bronfenbrenner, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 2022.

(10) (a) Taber, D. F.; Guo, P. *J. Org. Chem.* **2008**, *73*, 9479. (b) Wu, L.; Shi, M. *J. Org. Chem.* **2010**, *75*, 2296.

(11) (a) Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2010**, *132*, 13590. (b) Xiao, Q.; Ma, J.; Yang, Y.; Zhang, Y.; Wang, J. *Org. Lett.* **2009**, *11*, 4732. (c) Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 5587. (d) Zhao, X.; Lu, K.; Zhang, Y.; Wang, J. *Chem. Commun.* **2010**, *46*, 1724. (e) Zhao, X.; Wu, G.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 3296.

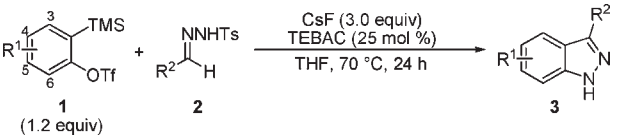
(12) (a) Xiao, Q.; Xia, Y.; Li, H.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1114. (b) Zhou, L.; Shi, Y.; Xiao, Q.; Liu, Y.; Ye, F.; Zhang, Y.; Wang, J. *Org. Lett.* **2011**, *13*, 968.

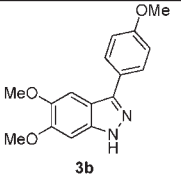
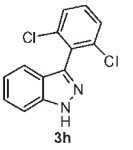
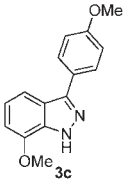
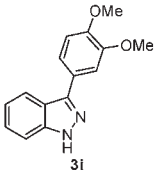
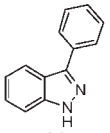
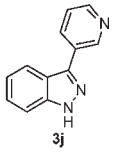
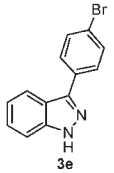
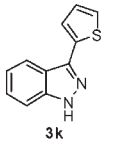
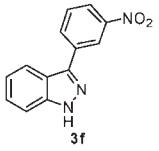
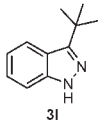
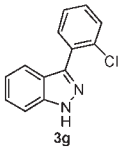
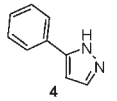
(13) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Nat. Chem.* **2009**, *1*, 494.

(14) *In situ* generation of diazo compounds from *N*-tosylhydrazones is often performed in the presence of phase transfer catalysts; see: (a) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381. (b) Aggarwal, V. K.; Fulton, J. R.; Sheldon, C. G.; de Vicente, J. *J. Am. Chem. Soc.* **2003**, *125*, 6034. (c) Aggarwal, V. K.; Patel, M.; Studley, J. *Chem. Commun.* **2002**, 1514. (d) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J. L.; Winn, C. L. *J. Am. Chem. Soc.* **2003**, *125*, 10926. (e) Zhang, Z.; Liu, Y.; Ling, L.; Li, Y.; Dong, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 4330.

(15) Typical procedure (entry 12, Table 1): to an oven-dried 25 mL round-bottom flask equipped with a stir bar were added 122 mg of **2a** (0.4 mmol), followed by 143 mg of **1a** (0.48 mmol). THF (10 mL) was added, followed by 23 mg of TEBAC (0.1 mmol) and 182 mg of CsF (1.2 mmol). The reaction mixture was stirred at 70 °C for 24 h, cooled to room temperature, poured into brine, and extracted with EtOAc. The combined extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (petroleum ether/EtOAc = 2:1) to afford 78 mg of **3a** (87%) as a white solid.

Table 2. Reaction Scope[a]



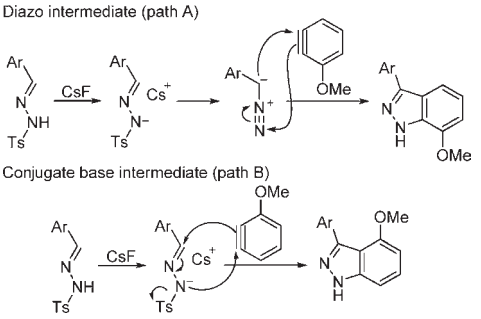
entry	1, R^1	2, R^2	product 3	yield %[b]	entry	1, R^1	2, R^2	product 3	yield %[b]
1	**1b** 4,5-$(MeO)_2$	**2a** 4-$(MeO)C_6H_4$	 **3b**	56	7	**1a** H	**2f** 2,6-$Cl_2C_6H_4$	 **3h**	75
2	**1c** 3-MeO	**2a** 4-$(MeO)C_6H_4$	 **3c**	60[c]	8	**1a** H	**2g** 3,4-$(MeO)_2C_6H_4$	 **3i**	84
3	**1a** H	**2b** Ph	 **3d**	82	9	**1a** H	**2h** 3-pyridyl	 **3j**	68
4	**1a** H	**2c** 4-BrC_6H_4	 **3e**	85	10	**1a** H	**2i** 2-thiophenyl	 **3k**	36
5	**1a** H	**2d** 3-$(O_2N)C_6H_4$	 **3f**	55	11	**1a** H	**2j** *t*-Bu	 **3l**	33
6	**1a** H	**2e** 2-ClC_6H_4	 **3g**	77	12	**1a** H	**2k** PhCH=CH	 **4**	99

[a] All reactions were carried out on approximately 0.4 mmol of hydrazone in 10 mL of solvent. [b] Isolated yield. [c] 4.8:1 Regioselectivity, combined yield. The major isomer was assigned by an NOESY experiment (see the Supporting Information).

dimethoxybenzyne afforded the desired indazole in a moderate 56% yield (entry 1). The unsymmetrical monomethoxybenzyne gave a 4.8:1 mixture of regioisomers in a 60% combined yield (entry 2). The latter example is particularly worth mentioning, as it provides valuable information on the reaction mechanism. It is already known[16] that reactions involving 3-methoxybenzyne can be highly regioselective with nucleophilic attack at the *meta*-position (with respect to OMe) being more favorable for both electronic and steric reasons. Therefore, if the reaction goes through the diazo intermediate (path A in Scheme 2), one would expect formation of the 7-methoxy regioisomer (Scheme 3), as was reported in our previous publication.[2] On the contrary, if the reaction proceeds through the conjugate base of the *N*-tosylhydrazone (path B in Scheme 2), one might expect formation of the 4-methoxy regioisomer (Scheme 3).[17] As a matter of fact, the reaction shown in entry 2, Table 2, afforded the 7-methoxy isomer as the major product[18] in an ~4.8:1 ratio. This appears to be strong evidence for possible involvement of the diazo intermediate, although the other route cannot be ruled out.

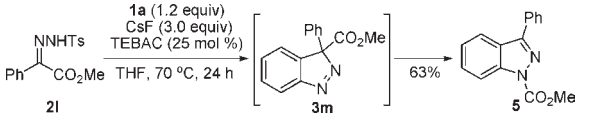
(16) (a) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 1180. (b) Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1224.

Scheme 3. Possible Reaction Mechanisms of an Unsymmetrical Benzyne



With regard to the scope of the *N*-tosylhydrazones, those derived from aromatic aldehydes give the best yields (entries 3−8). The scope includes electron-poor (entries 4−7), electron-rich (entries 1, 2, and 8), and sterically hindered (entries 6 and 7) aryl *N*-tosylhydrazones. Those derived from heteroaromatic aldehydes, such as pyridine-3-carbaldehyde (**2h**) and thiophene-2-carbaldehyde (**2i**), also afforded the expected indazole products (entries 9 and 10). However, the 36% yield for the latter reaction was less than satisfactory (entry 10). Unfortunately, *N*-tosylhydrazones derived from aliphatic aldehydes were not suitable substrates. Only pivalaldehyde *N*-tosylhydrazone (**2j**) gave a 33% yield of the desired product **3l** (entry 11). All other aliphatic substrates tested failed to provide the anticipated indazoles. Observed side products included simple *N*-arylation of the hydrazone and phenyl *p*-toluenesulfinate. Notably, compared with *N*-tosylhydrazones derived from other aliphatic aldehydes, **2j** has the greatest steric bulk adjacent to the imine carbon and, therefore, should in theory disfavor path B (Scheme 2). Therefore, its success might provide additional support for the postulated involvement of the diazo intermediate at least for this particular substrate, as the steric bulk may be beneficial to the stability of the diazo intermediate. It is also worth noting that hydrazone **2k** derived from cinnamaldehyde did not react with benzyne under the reaction conditions but simply cyclized to form 5-phenyl-1*H*-pyrazole.[19] Hydrazone **2l** with an ester group was also tested (Scheme 4). This substrate should initially afford the adduct **3m**, which is already known[2] to undergo an acyl migration to form a more stable isomer **5**. Indeed, this rearrangement proceeded smoothly and the desired product **5** could be isolated in a 63% yield. It should be pointed out that this ketone-derived hydrazone might be the only one that worked in our reaction, as *N*-tosylhydrazones derived from other ketones, either aromatic or aliphatic, cyclic or open chain, failed to give the desired indazoles. Thus, the current protocol is largely limited to *N*-tosylhydrazones derived from aromatic aldehydes.

Scheme 4. An Indazole from Additional Acyl Migration



In summary, we have developed a method for the preparation of 3-arylindazoles starting from arynes and readily available, bench stable, inexpensive *N*-tosylhydrazones. The reaction appears to involve *in situ* formation of a diazo compound and eliminates the problem of preparing and isolating such unstable and hazardous intermediates. Thus, it extends our previous aryne-diazo cycloaddition route to indazoles.

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Supporting Information Available. Experimental details and characterization of the final products, including full ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) From Hammond's postulate and a soft−hard acid−base argument, we consider the other resonance structure of the conjugate base, where the negative charge resides on the imine carbon, as a less important structure to participate in the reaction. A brief computational study of benzaldehyde *N*-mesylhydrazone as a simplified system on a B3LYP/6-31G(d) level reveals that the nitrogen carries a much more negative charge (−0.494 vs −0.065 for the carbon), and therefore the reaction with a highly reactive agent, such as benzyne, should occur more favorably at the nitrogen, rather than at the carbon.

(18) See the Supporting Information for the NOESY spectrum.

(19) Similiar reactions have been reported in the literature; see: Doyle, M. P.; Yan, M. *J. Org. Chem.* **2002**, *67*, 602. See also ref 12d.