ORGANIC LETTERS

2011
Vol. 13, No. 14
3667–3669

The Benzyne Fischer-Indole Reaction

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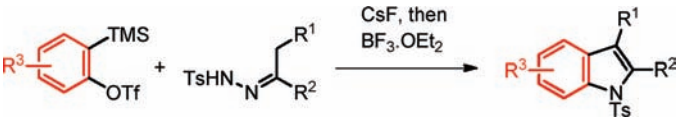
Received May 25, 2011

ABSTRACT

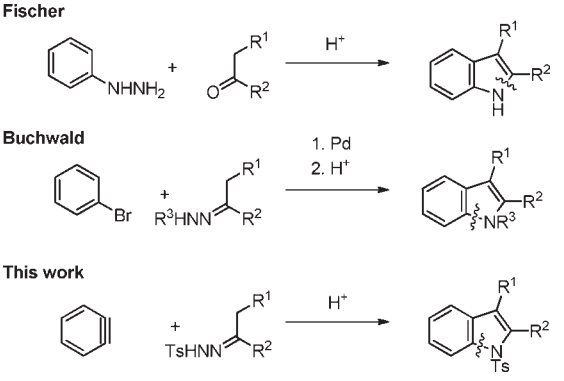


A new approach to the Fischer-indole synthesis is reported that uses the reactive intermediate benzyne. The addition of *N*-tosyl hydrazones to arynes, generated through fluoride activation of 2-(trimethylsilyl)phenyl triflate precursors, leads to efficient *N*-arylation. Addition of a Lewis acid to the same reaction pot then affords *N*-tosylindole products *via* Fischer cyclization.

The Fischer-indole synthesis, discovered in 1883,[1,2] remains one of the most powerful and versatile routes to the indole heterocycle. Initial observations concerned the acid-catalyzed rearrangement of enolizable arylhydrazones to give indoles (Fischer cyclization). It quickly became standard to form these arylhydrazones *in situ*, and aryl hydrazines and enolizable aldehydes or ketones are now considered the starting materials for a Fisher-indole synthesis (Scheme 1).

The fundamental importance of indoles in the fine chemical industry has made the Fischer synthesis one of the most studied of all organic reactions, with a large number of modifications being reported over the past century.[3] A prominent development in recent times was Buchwald's introduction of Pd-catalyzed *N*-arylation to access the key *N*-arylhydrazone intermediate, which then undergoes a conventional Fischer cyclization on treatment with acid (Scheme 1).[4] By disconnecting across the aniline C–N bond, the Buchwald approach harnesses a different and complementary set of building blocks, inexpensive aryl halides which are far less toxic and more readily available than the aryl hydrazines required in the classic Fischer.

Scheme 1. Selected Fischer-Indole Syntheses[5]



We were interested in developing an indole synthesis that uses the same C–N bond disconnection but employs the reactive intermediate benzyne as the arene source in the reaction. The reaction would represent both a transition-metal-free variant of Buchwald's approach and a novel way of capturing the benzyne

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(1) (a) Fischer, E.; Jourdan, F. *Chem. Ber.* **1883**, *16*, 2241. (b) Fischer, E.; Hess, O. *Chem. Ber.* **1884**, *17*, 559.

(2) Reviews: (a) Robinson, B. *The Fischer Indole Synthesis*; J. Wiley & Sons: New York, NY, 1982. (b) Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 609.

(3) Humphrey, G. R; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875.

(4) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251.

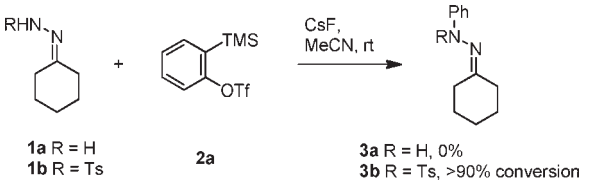
(5) The *N*-arylhydrazone in Buchwald's synthesis is usually formed via Pd-catalyzed *N*-arylation of benzophenone hydrazone followed by exchange with the requisite carbonyl component during the Fischer cyclization step.

10.1021/ol201413r
Published on Web 06/14/2011

intermediate for a synthesis of the fundamental indole heterocycle.

Nucleophilic addition to benzyne is a principal reaction mode in aryne chemistry.[6,7] Nitrogen-based nucleophiles, in particular, have been widely employed in a host of recently described transformations that exploit the strained aryne triple bond.[8] For the reaction at hand, we require the addition of a hydrazone to benzyne as the first step. This addition has not been widely reported in the literature,[9] so we began work with a simple study of this *N*-arylation reaction. Using benzyne precursor **2a**, our initial attempts at arylating unprotected hydrazones led to low yields of unstable products that were difficult to purify (Scheme 2). Better results were obtained with hydrazones **1** containing electron-withdrawing groups on the amino nitrogen atom, with the tosylhydrazone **1b** being the best substrate.

Scheme 2. *N*-Arylation of Hydrazones with Benzyne



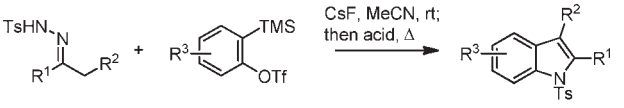
1a R = H
1b R = Ts

2a

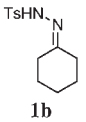
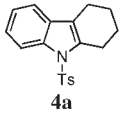
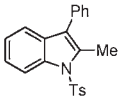
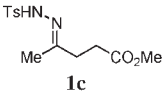
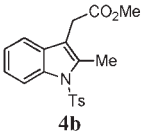
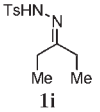
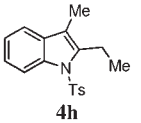
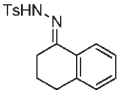
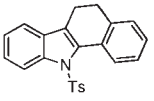
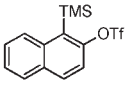
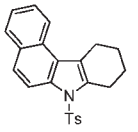
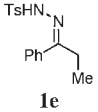
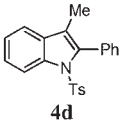
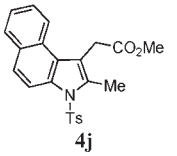
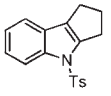
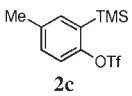
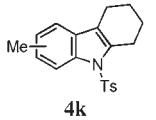
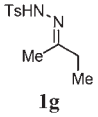
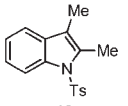
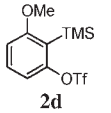
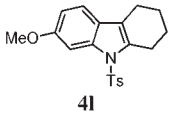
3a R = H, 0%
3b R = Ts, >90% conversion

The second step in the reaction, Fischer cyclization of *N*-tosylhydrazones **3**, has, to the best of our knowledge, not been reported in the literature.[10] In cases where *N*-protection is desired for further synthetic transformations, direct

Table 1. *N*-Arylation and Fischer Cyclization of *N*-Tosylhydrazones with Benzyne[a]



1 **2** **4**

entry	hydrazone	aryne precursor	product	yield (%)	entry	hydrazone	aryne precursor	product	yield (%)
1	 **1b**	**2a**	 **4a**	80	7	 **1h**	**2a**	 **4g**	63
2	 **1c**	**2a**	 **4b**	66	8	 **1i**	**2a**	 **4h**	68
3	 **1d**	**2a**	 **4c**	76	9	**1b**	 **2b**	 **4i**	51
4	 **1e**	**2a**	 **4d**	67	10	**1c**	**2b**	 **4j**	68
5	 **1f**	**2a**	 **4e**	54	11	**1b**	 **2c**	 **4k**	72
6	 **1g**	**2a**	 **4f**	69	12	**1b**	 **2d**	 **4l**	61

[a] Conditions: Hydrazone (1 equiv), aryne precursor (1.5 equiv), CsF (3 equiv), MeCN, rt, 12 h; then $BF_3 \cdot OEt_2$ (2 equiv), reflux, 5 h. Isolated yields after SiO_2 chromatography.

synthesis of *N*-tosyl indoles using Fischer cyclization would offer an efficient route to these compounds. We were pleased, therefore, to find that treatment of **3b** with either toluenesulfonic acid (TsOH) or $BF_3 \cdot OEt_2$ in refluxing acetonitrile gave a clean conversion to the desired *N*-tosyl indole **4a**. The use of acetonitrile as solvent in the Fischer cyclization, which is atypical, was deliberate as it suggested the possibility of integrating the two steps into a one pot procedure. Accordingly, we reacted hydrazone **1b** with a slight excess of benzyne precursor **2a** and excess CsF in acetonitrile at room temperature. Arylation was complete after 12 h, after which time we added $BF_3 \cdot OEt_2$ and raised the reaction temperature to reflux. Pleasingly, indole **4a** was isolated from the reaction in 80% yield (Table 1, entry 1).

An investigation into the scope of the reaction established the transformation to be general for a range of alkyl hydrazones. The Lewis acid $BF_3 \cdot OEt_2$ proved to be generally more effective than TsOH, and this was adopted as the standard treatment for the reaction. A range of ketone-derived hydrazones **1b**−**1i** proved effective in the reaction, affording good yields of *N*-tosylindoles **4a**−**4l**. The initial *N*-arylation was generally observed to be very clean; with erosion of the yield occurring in the Fischer cyclization. Cyclic (entries 1, 3, and 5), benzylic (entry 4), and alkyl hydrazones were all productive using benzyne as the arene source. Aldehyde-derived hydrazones were not good substrates for the arylation reaction.

The use of substituted arynes was also successful (entries 9−12) and enabled us to examine the question of regioselectivity. For naphthyne, both the initial arylation and the subsequent cyclization were highly selective, in line with literature precedent,[8] to afford the benzannulated indoles **4i** and **4j** as single regioisomers. 4-Methylbenzyne (from **2c**), by contrast, affords little control in both steps, with indole **4k** being isolated as a mixture of three different isomers. 3-Methoxybenzyne displayed the expected regiocontrol in *N*-arylation, with the nucleophilic hydrazone adding distally to the OMe group. Cyclization would then be expected to favor the 7-OMe substituted indole,[11] which was isolated as the major isomer in 61% yield (entry 12).

In conclusion, we have developed a new entry point into the classic Fischer-indole synthesis using benzyne chemistry. The transformation uses an initial *N*-arylation of widely available tosylhydrazones with aryne precursors **2**, under mild conditions. Subsequent Fischer cyclization, through a Lewis acid added to the same reaction vessel, affords a novel one pot synthesis of *N*-tosyl indoles. The procedure requires no transition-metal catalysis and will compliment existing syntheses that form the aniline C−N bonds of the indole heterocycle.

Acknowledgment. We thank AstraZeneca and the University of Edinburgh for funding. M.F.G. is an EPSRC Leadership Fellow.

Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(6) Hoffman, R. W. *Dehydrobenzenes and Cycloalkynes*; Academic Press, NY, 1967.

(7) Selected recent examples: (a) Hwu, J. R.; Hsu, Y. C. *Chem.—Eur. J.* **2011**, *17*, 4727. (b) Truong, T.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 4243. (c) Bronner, S. M.; Goetz, A. E.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 3832. (d) Laczkowski, K. Z.; Garcia, D.; Pena, D.; Cobas, A.; Perez, D.; Guitian, E. *Org. Lett.* **2011**, *13*, 960. (e) Biju, A. T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 9761. (f) Kirkham, J. D.; Delaney, P. M.; Ellames, G. J.; Row, E. C.; Harrity, J. P. A. *Chem. Commun.* **2010**, *46*, 5154. (g) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 3117. (h) Yoshida, H.; Ohshita, J.; Kunai, A. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 199.

(8) Recent examples: (a) Rogness, D. C.; Larock, R. C. *J. Org. Chem.* **2011**, *76*, 4980. (b) Okuma, K.; Matsunaga, N.; Nagahora, N.; Shioji, K.; Yokomori, Y. *Chem. Commun.* **2011**, *47*, 5822. (c) Smith, A. B., III; Kim, W.-S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6787. (d) Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5925. (e) Hong, D.; Chen, Z.; Lin, X.; Wang, Y. *Org. Lett.* **2010**, *12*, 4608. (f) Wu, C.; Fang, Y.; Larock, R. C.; Shi, F. *Org. Lett.* **2010**, *12*, 2234. (g) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168. (h) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Chem.—Asian J.* **2009**, *5*, 153. (i) Cano, R.; Ramon, D. J.; Yus, M. *J. Org. Chem.* **2010**, *76*, 654. (j) Cant, A. A.; Bertrand, G. H. V.; Henderson, J. L.; Roberts, L.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5199. (k) Zhang, F.; Moses, J. E. *Org. Lett.* **2009**, *11*, 1587.

(9) Whilst this manuscript was under review, Shi, Larock and coworkers described the reaction of aldehyde-derived *N*-tosylhydrazones with arynes to form indazoles: Li, P.; Zhao, J.; Wu, C.; Larock, R. C.; Shi, F. *Org. Lett.* **2011**, ASAP DOI: 10.1021/ol201086g.

(10) A conventional Fischer-indole synthesis of *N*-tosyl indoles would require uncommon *N*-tosylsulfonyl-*N*-arylhydrazines as starting materials. Examples of *N*-benzoyl-*N*-arylhydrazines undergoing Fischer-indole synthesis to the *N*-benzoyl indoles are known: (a) Mills, K.; Al Khawaja, I. K.; Al-Saleh, F. S.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1981**, *2*, 636. (b) Campos, K. R.; Woo, J. C. S.; Lee, S.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 79.

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