A Palladium-Catalyzed Strategy for the Preparation of Indoles: A Novel Entry into the Fischer Indole Synthesis

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Received March 30, 1998

The indole nucleus is an important element in many pharmacologically active compounds.[1] Of the many methods developed for indole synthesis, the oldest and most widely used is the Fischer indole synthesis,[1,2] in which an *N*-aryl hydrazone undergoes acid-catalyzed or thermal sigmatropic rearrangement to generate, after elimination of ammonia, the indole skeleton. Although a number of methods exist for the preparation of *N*-aryl hydrazones,[3] the most common is the condensation of an aldehyde or ketone with an *N*-aryl hydrazine. The *N*-aryl hydrazine, in turn, is typically prepared via reduction of the corresponding aryl diazonium species.[1,2]

The palladium-catalyzed cross coupling of amines with aryl halides has proven to be general in substrate scope with respect to both the amine component and the aryl halide.[4] Due to the success of this reaction, we hoped that this methodology could provide a complementary synthesis of *N*-aryl hydrazones as substrates for Fischer indolizations. In an initial experiment, we found that the palladium-catalyzed coupling of cyclohexanone hydrazone with 4-bromobiphenyl proceeded as evidenced by GC/MS. We found, however, that a more convenient means to access the desired *N*-aryl hydrazones was via the intermediacy of the *N*-aryl hydrazones of benzophenone (Scheme 1). These *N*-aryl benzophenone hydrazones could be prepared by the coupling reaction of benzophenone hydrazone and an aryl bromide with a $Pd(OAc)_2$/BINAP catalyst system.[5] Both electron-rich and electron-poor aryl bromides of a variety of substitution patterns were successfully employed (Table 1, *N*-aryl hydrazones **1**−**7**).

In contrast to simple hydrazones derived from nonaromatic ketones, benzophenone hydrazones could typically be stored for weeks on the benchtop without significant decomposition.[6] Attempts to effect the hydrolysis of these compounds afforded the desired *N*-aryl hydrazine in low yield, along with the corresponding aniline side-product resulting from N−N bond cleavage of the aryl hydrazine. Since we were less interested in the liberated hydrazines than in the hydrazones which could be derived from them, we pursued a modified approach. The hydrolysis of hydrazones can generally be promoted by trapping the liberated hydrazine with an excess of an aldehyde or ketone.[3b] In the case of *N*-aryl benzophenone hydrazones, we felt that conducting the hydrolysis in the presence of a ketone could produce an enolizable hydrazone that would undergo Fischer indolization under the acidic reaction conditions.[7] This would be advantageous from two perspectives. First, it would obviate the need to prepare or isolate potentially sensitive aryl hydrazines. Second, it would provide a potentially very general means to the requisite *N*-aryl hydrazones for Fischer indolization from a single,

Scheme 1

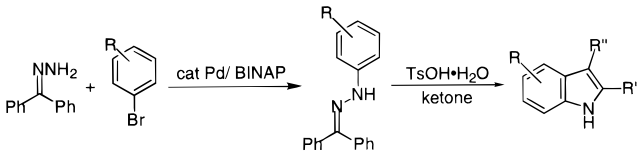
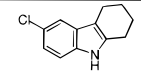
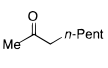
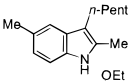
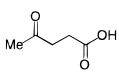
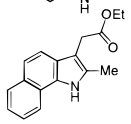
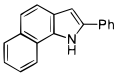
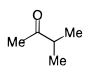
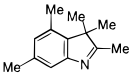
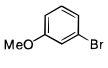
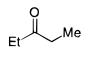
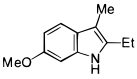
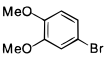
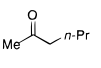
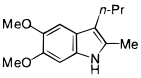
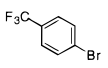
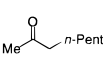
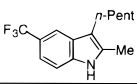


Table 1. Synthesis of N-Aryl Hydrazones and Indoles

entry	aryl bromide	*N*-aryl hydrazone, yield[a]	ketone	indole		yield (%)[d]
1		**1**, 80%			**8**	95 65[e]
2		**2**, 97%[b]			**9**	83 79[e]
3		**3**, 91%			**10**	90
4					**11**	85
5		**4**, 89%			**12**	93
6		**5**, 95%[b]			**13**	74[f]
7		**6**, 85%[b]			**14**	74[g]
8		**7**, 83%[c]			**15**	< 5

Yields refer to the average of two isolated yields of >95% purity as determined by GC, ^{1}H NMR and, for new compounds, elemental analysis. [a]Reactions were run with 1 equiv of aryl bromide, 1−1.1 equiv of benzophenone hydrazone, 1−1.5 mol % $Pd(OAc)_2$, 1−2.3 mol % (*S*)- or (±)-BINAP, 1.4 equiv of NaO*t*-Bu, and 0.5−1 M toluene with respect to benzophenone hydrazone, at 80 °C. [b]Reactions were run at 100 °C, otherwise following reaction conditions described in footnote *a*. [c]The reaction was run with 2.5 mol % $Pd(OAc)_2$, 3.75 mol % (±)-BINAP, and 1.4 equiv of Cs_2CO_3 at reflux, otherwise following reaction conditions previously described in footnote *a*. [d]Reactions were run with 1 equiv of *N*-aryl benzophenone hydrazone, 1.5 equiv of ketone, and 2.0−5.0 equiv of TsOH•H_2O in refluxing EtOH. [e]The intermediate *N*-aryl benzophenone hydrazone was not isolated prior to indolization. [f]The yield refers only to the isolated 6-methoxy indole regioisomer. [g]Indolization was conducted in refluxing THF otherwise following reaction conditions described in footnote *d*.

(1) For a description of the biological activity of indoles, see: Sundberg, R. J. *Indoles*; Academic Press: London, 1996, and references therein.

(2) For a recent review on the Fischer indole synthesis, see: Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 607.

(3) For preparative routes to *N*-aryl hydrazones, see: (a) Robinson, B. *The Fischer Indole Synthesis*; John Wiley & Sons: Chichester, 1982; pp 48−59. (b) Smith, P. A. S. *Derivatives of Hydrazine and Other Hydronitrogens Having N−N Bonds*, 2nd ed.; The Benjamin/Cummings Publishing Company: Reading, MA, 1983; Chapter 2.

(4) For lead references on the palladium-catalyzed coupling of amines with aryl halides see: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* Submitted for publication. (b) Hartwig, J. F. *Synlett* **1997**, 329. (c) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (d) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.

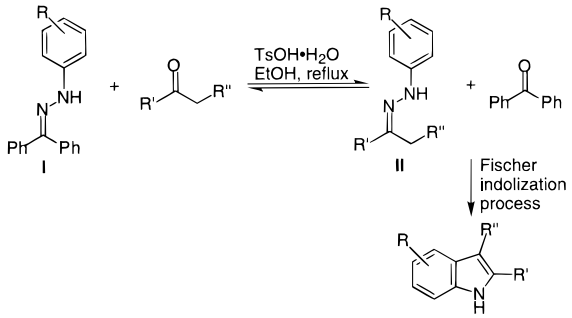
(5) In a related process, benzophenone imine undergoes palladium-catalyzed cross-coupling with aryl halides: (a) Wolfe, J. P.; Åhman J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367. (b) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827.

(6) Hydrazones of aromatic ketones are more resistant to azine formation as compared to hydrazones derived from aliphatic ketones: Szmant, H. H.; McGinnis, C. *J. Am. Chem. Soc.* **1950**, *72*, 2890. Additionally, crystalline hydrazones may be stored for longer periods of time without decomposition than undiluted liquid hydrazones.[10]

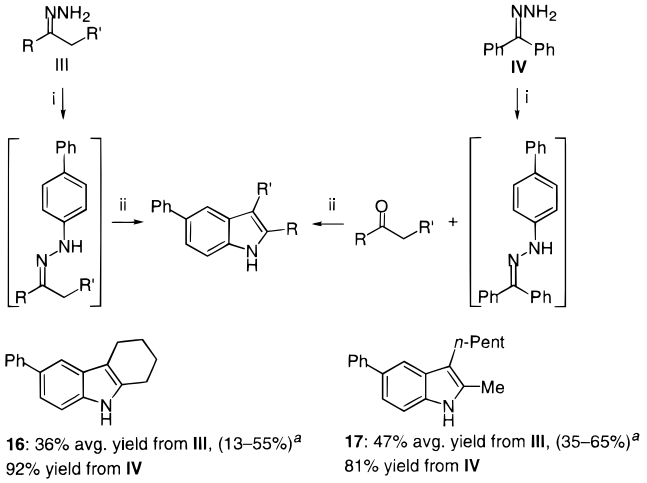
(7) It has been reported that heating an acetic acid solution of acetophenone phenylhydrazone or benzaldehyde phenylhydrazone in the presence of cyclohexanone results in the formation of tetrahydrocarbazole in 50% and 5% yield, respectively. This was ascribed to have resulted from transhydrazonation followed by Fischer cyclization: Gore, P. H.; Hughes, G. K.; Ritchie, E. *Nature* **1949**, *164*, 835.

S0002-7863(98)01045-2 CCC: $15.00
Published on Web 06/18/1998

Scheme 2



Scheme 3



Reagents and conditions: (i) 4-bromobiphenyl (1.0 equiv), $Pd(OAc)_2$ (5 mol %), (±)-BINAP (5 mol %), NaO*t*-Bu (1.4 equiv), toluene, 100 °C. (ii) TsOH·H_2O (2 equiv), refluxing EtOH. [a]The range of yields which were obtained from four reactions run under identical conditions.

commercially available precursor. In fact, the reaction of *N*-(4-chlorophenyl)benzophenone hydrazone **1** with cyclohexanone[8] in the presence of concentrated hydrochloric acid solution in refluxing THF gave the desired indole **8** in 64% yield. After examining a number of acids commonly employed in Fischer indolization procedures,[3a] we found that the best results were obtained using *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O). In this way a 95% yield of **8** was realized. We have found that the *p*-TsOH·H_2O generally provides a sufficient amount of water to effect hydrolysis of the *N*-aryl benzophenone hydrazone. Although THF was found to be a satisfactory solvent in this procedure, protocols which utilized ethanol were frequently found to be preferable.

As shown in Table 1, reaction conditions described above are applicable to the synthesis of a wide variety of indoles. Note that a large excess of ketone is not necessary; in general 1.5 equiv were sufficient. As shown in Scheme 2, **I** and **II** are in dynamic equilibrium. Hydrazone **II**, however, is irreversibly consumed in the Fischer indolization process, thus driving the reaction to completion. We have found that purification of the intermediate *N*-aryl benzophenone hydrazone is not required. Filtration of the crude product from the palladium-catalyzed coupling reaction through Celite/silica gel followed by the removal of solvent and subjecting the crude material to Fischer indolization conditions affords the indole product in overall yields comparable to the stepwise protocol (see Table 1, entries 1−2 and Scheme 3). In testing the limits of this methodology, we find that when the *N*-aryl group is *p*-CF_3 substituted (hydrazone **7**), condensation of the corresponding *N*-aryl hydrazine with 2-hexanone occurs cleanly, but subsequent indolization does not occur. This is consistent with previous findings that such hydrazones do not readily undergo Fischer indolization even under forcing conditions.[9]

The regioselectivity of the indolization with respect to the *N*-aryl group was as expected.[2] In the case of *meta*-substituted hydrazone **5**, indolization gave a 4:1 mixture of the 6-methoxy- and the 4-methoxyindole regioisomers, with the 6-substituted isomer predominating. In the case of dimethoxy hydrazone **6**, only the product resulting from indolization at the less hindered site of the aryl group was observed. Regioselectivity with respect to the ketone component was consistent with rate-limiting sigmatropic rearrangement of the more substituted ene-hydrazine. Thus, indolization of dimethoxyhydrazone **6** with 2-hexanone provided the corresponding 2-methyl-3-propyl indole (**14**). In all cases where unsymmetrical ketones were employed, only one regioisomer of the product was observed.

While the palladium-catalyzed *N*-arylation of nonbenzophenone-derived simple hydrazones does proceed, this method is less convenient. Preparation of these simple hydrazones requires the use of anhydrous hydrazine.[10,11] Moreover, decomposition of the hydrazones was apparent under the conditions of the palladium-catalyzed coupling reaction, leading to variable yields (see Scheme 3).[12] *N*-Aryl hydrazones formed from these coupling reactions were not stable to chromatography, though the crude product could be directly subjected to Fischer indolization. Yields of indoles derived from these nonbenzophenone simple hydrazones were lower compared to those derived from the benzophenone hydrazone protocol under otherwise identical reaction conditions. For example, the combination of cyclohexanone hydrazone with 4-bromobiphenyl gave **16** in an average yield of 36%. A 92% overall yield was realized by using the procedure via the intermediacy of the *N*-aryl benzophenone hydrazone, which was converted to indole **16** without purification. Likewise, the latter procedure produced **17** in substantially higher yield (81%) than when simple hydrazone **III** was employed (47% average yield).

In summary, we have developed a method that provides an alternative source of substrates for Fischer indolizations. Central to this strategy was the application of a palladium-catalyzed coupling procedure to prepare *N*-aryl benzophenone hydrazones, and their use as general precursors to intermediates in the classical Fischer Indole Synthesis. We are currently applying this and related methodologies toward the preparation of *N*-alkyl and *N*-aryl indoles, pyrroles, furans, and benzofurans, as well as the synthesis of pharmaceutical targets and indole libraries.

Acknowledgment. This research was funded by the National Science Foundation. We also thank Pfizer Inc. for additional support. B.H.Y. is a trainee of the National Cancer Institute (NCI Training Grant NCI No. 5T32CA09112). S.W. gratefully acknowledges the Ford Foundation for a Predoctoral Fellowship. We thank Professor John Hartwig for informing us of his work on the coupling reactions of benzophenone hydrazone.

Supporting Information Available: Preparation and characterization of **1**−**17** (12 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA981045R

(8) In this initial experiment, 10 equiv of cyclohexanone were employed.

(9) Troitskaya, V. I.; Oksengendler, I. G.; Pazenok, S. V.; Lyubich, M. S.; Larina, S. M. *Chem. Heterocycl. Compd.* **1982**, *18*, 39.

(10) Newkome, G. R.; Fishel, D. L. *J. Org. Chem.* **1966**, *31*, 677.

(11) Day, A. C.; Whiting, M. C. *Organic Syntheses*; John Wiley & Sons: New York, 1970; Vol. 50, pp 3−6.

(12) Azine byproducts were irreversibly formed during the coupling reaction of nonbenzophenone derived simple hydrazones, as determined by GC/MS. For discussions on the stability of simple hydrazones, see refs 6, 10, and 11.