

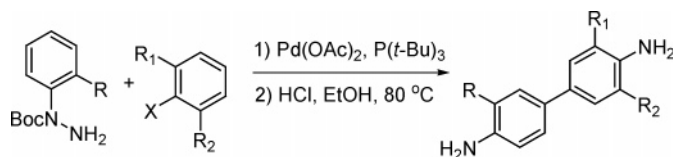
Regioselective [5,5]-Sigmatropic Rearrangement Reactions of Aryl Hydrazides

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Received February 21, 2006

ABSTRACT

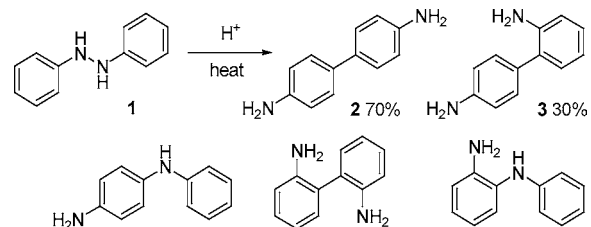


N,N'-Aryl hydrazides with substituents at the ortho or meta positions undergo highly regioselective [5,5]-sigmatropic rearrangement reactions to furnish benzidines in good to excellent isolated yields. The presence of single substituent at either the ortho or meta position provides sufficient bias, effectively suppressing the formation of diphenylene, the major byproduct of the conventional benzidine rearrangement reaction.

The acid-catalyzed rearrangement of hydrazobenzenes, known as the benzidine rearrangement, affords 4,4'-diaminobiaryls (benzidines).¹ Benzidines are useful synthetic building blocks to polyimides, polyfluorenes, and other aromatics.² In addition, their *N*-arylated compounds are important hole-transporting materials in the fabrication of light-emitting displays for their π -electron-donating properties.³ Despite their long history and extensive mechanistic studies, the synthetic utility of the benzidine rearrangement has been collectively disregarded in the literature because it gives a substantial amount of byproducts, mostly diphenylene **3**, along with *o*- and *p*-semidines, not separable with flash column chromatography (Scheme 1).⁴

The lack of adequate synthetic methods to the starting hydrazobenzenes⁵ further limited the reaction as a synthetic protocol for the generation of benzidines and related products.

Scheme 1. Benzidine Rearrangement of Hydrazobenzene **1**



N,N'-Diaryl hydrazides are readily available from the Pd-catalyzed coupling reactions of *N*-aryl hydrazides and aryl halides and are effective synthetic equivalents of hydrazobenzenes, undergoing [3,3]-sigmatropic rearrangement to provide 2,2',-diamino-1,1'-biaryls, when heated in the presence of an acid.⁶ In light of this, we explored the benzidine rearrangement reactions of *N,N'*-diaryl hydrazides with particular interest in controlling the regiochemical outcome of the reaction. For this venture, we prepared a series of *N,N'*-diaryl hydrazides with substituents at the ortho position, anticipating that the ortho substituent would suppress the

(1) (a) Hoffman, A. W. *Proc. R. Soc. (London)* **1863**, *12*, 576. (b) Dewar, M. J. S. In *Molecular Rearrangement*; de Mayo, P., Ed.; Interscience: New York, 1969; Vol. 1, p 323. (c) Banthorpe, D. V. *Chem. Rev.* **1970**, *70*, 295. (d) Olah, G. A.; Dunne, K.; Kelly, D. P.; Mo, Y. K. *J. Am. Chem. Soc.* **1972**, *94*, 7438. (e) Cox, R. A.; Buncel, E. In *The Chemistry of the Hydrazone, Azo, and Azoxy Groups*; Patai, S., Ed.; Wiley: New York, 1975; p 775. (f) Bunton, C. A.; Rubin, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 4236. (g) Park, K. H.; Kang, J. S. *J. Org. Chem.* **1997**, *62*, 3794. (h) Benniston, A. C.; Clegg, W.; Harriman, A.; Harrington, R. W.; Li, P.; Craig, S. *Tetrahedron Lett.* **2003**, *44*, 2665.

(2) (a) Chen, R.-F.; Fan, Q.-L.; Zheng, C.; Huang, W. *Org. Lett.* **2005**, *8*, 203. (b) Chan, K. L.; McKiernan, M. J.; Towns, C. R.; Holmes, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 21, 7662.

(3) (a) Popovic, Z. D.; Aziz, H. *J. Appl. Phys.* **2005**, *98*, 13510. (b) Tung, C.-H.; Zhang, L.-P.; Li, Y.; Cao, H.; Tanimoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 5348.

(4) (a) Cheng, J. D.; Shine, H. J. *J. Org. Chem.* **1975**, *40*, 703. (b) Zhu-Ohlbach, A.; Gleiter, R.; Bleiter, R.; Schmidt, H. L.; Reda, T. *Eur. J. Org. Chem.* **1998**, *11*, 2409. (c) Buncel, E. *Can. J. Chem.* **2000**, *78*, 1251.

formation of diphenylenes, the major byproduct of the benzidine rearrangement reaction.

Shown in Table 1 are the Pd-catalyzed coupling reactions

Table 1. Synthesis of Aryl Hydrazides

entry	R	R ₁	R ₂	6 (% yield) ^a
1	4a (R = H)	H	H	6a (96)
2	4b (R = Me)	H	H	6b (99)
3	4b (R = Me)	H	Me	6c (99)
4	4b (R = Me)	Me	Me	6d (74)
5	4c (R = OMe)	Me	Me	6e (64)
6	4d (R = CO ₂ Et)	Me	H	6f (94)

^a Isolated yield.

of *N*-aryl hydrazides **4** with aryl halides **5**, which provided various ortho-substituted *N,N'*-diaryl hydrazides **6**.

The coupling reactions proceeded in good to excellent yields, even in the cases with three ortho substituents.⁷

We next examined reaction conditions to effect the [5,5]-sigmatropic rearrangement. Heating at reflux in EtOH with a catalytic amount of aqueous HCl proved optimal for both product yield and operational ease. The product yields peaked mostly after 1–2 h and gradually decreased thereafter, owing to decomposition of the benzidine products. The results are summarized in Table 2.⁸

The unsubstituted hydrazide **6a** (entry 1, Table 2) furnished an inseparable 2:1 mixture of the benzidine **2** and diphenylene **3**, the [3,5]-sigmatropic rearrangement product, along with small amounts of other byproducts, similar to hydrazobenzene. However, the *N,N'*-diaryl hydrazides with ortho substituents (entries 2–6) cleanly rearranged to afford the corresponding benzidines **7b–f** in good to excellent isolated yields. No difference was observed between the substrates

(5) They are generally prepared from nitroarenes via the reductive coupling reaction with NaBH₄ or from azobenzenes through Zn-mediated reduction process that are moderately effective only for symmetric hydrazobenzenes. (a) Feiring, A. E.; Auman, B. C.; Wonchoba, E. R. *Macromolecules* **1993**, *26*, 2779. (b) Shine, H. J.; Trisler, J. C. *J. Am. Chem. Soc.* **1960**, *82*, 4054.

(6) (a) Lee, K. S.; Lim, Y. K.; Cho, C. G. *Tetrahedron Lett.* **2002**, *43*, 7463. (b) Lim, Y. K.; Lee, K. S.; Cho, C. G. *Org. Lett.* **2003**, *5*, 979. (c) Lim, Y. K.; Pang, S. J.; Paik, S. U.; Cho, C. G. *Bull. Korean Chem. Soc.* **2003**, *24*, 543. (d) Lim, Y. K.; Choi, S.; Park, K. B.; Cho, C. G. *J. Org. Chem.* **2004**, *69*, 2603. (e) Lim, Y. K.; Jung, J. W.; Lee, H. Cho, C. G. *J. Org. Chem.* **2004**, *69*, 5778. (f) Kim, K. Y.; Shin, J. T.; Lee, K. S.; Cho, C. G. *Tetrahedron Lett.* **2004**, *45*, 117.

(7) **Representative Procedure.** To a round flask were charged 329 mg (1.58 mmol) of aryl hydrazide **4b**, 267 mg (1.32 mmol) of iodobenzene, 5 mol % of Pd(OAc)₂, 5 mol % of P(*t*-Bu)₃·iHBF₄, 602 mg (1.85 mmol) of Cs₂CO₃, and 5 mL of anhydrous toluene at rt. The reaction mixture was stirred for 30 min at rt and refluxed for 2 h. The resulting mixture was concentrated and purified by flash column chromatography (hexanes/EtOAc = 20: 1) to afford 389 mg of product **6b** in 99% yield.

(8) **Representative Procedure.** To a round flask were charged 110 mg (0.39 mmol) of *N,N'*-aryl hydrazide **6b**, 3 mL of ethanol, and 3 drops of concd HCl at rt. The reaction mixture was refluxed for 1 h, cooled to 0 °C, neutralized with aq NaHCO₃, filtered, concentrated, and purified by flash column chromatography (CH₂Cl₂/EtOAc = 2: 1) to afford 59 mg of **7b** in 76% yield.

Table 2. Benzidine Rearrangement of Aryl Hydrazides

entry	6	R	R ₁	R ₂	7 (% yield) ^a
1	6a	H	H	H	7a (89) ^b
2	6b	Me	H	H	7b (76)
3	6c	Me	Me	H	7c (81)
4	6d	Me	Me	Me	7d (72)
5	6e	OMe	Me	Me	7e (91)
6	6f	CO ₂ Et	Me	H	7f (88)

^a Isolated yields. ^b Combined yield of the 2:1 inseparable product mixture of **2/3**.

bearing electron-donating and electron-withdrawing groups, in terms of the yield and rate (entries 5 and 6). Notably, the presence of single methyl group at the ortho position (entry 2) provides sufficient bias to effectively suppress the formation of the diphenylene byproduct, affording the benzidine product **7b** in 86% isolated yield.

Gratified with the successful control of the regiochemical outcomes, we extended our protocol to multiple benzidine rearrangement reactions. Tables 3 and 4 summarize the

Table 3. Synthesis of Bis-aryl Hydrazides

entry	5	time (h)	9 (% yield) ^a
1	5a (R = R ₁ = H)	3	9a (57)
2	5b (R = H ₁ , R ₁ = Me)	3	9b (59)
3	5c (R = R ₁ = Me)	3	9c (57)
4	5d (R = H ₁ , R ₁ = CO ₂ Me)	2	9d (64)

^a Isolated yields.

Table 4. Synthesis of Bis-aryl Hydrazides

entry	4	time (h)	9 (% yield) ^a
1	4a (R = H)	2	9e (99)
2	4b (R = Me)	3	9f (99)
3	4c (R = OMe)	2	9g (85)

^a Isolated yields.

synthesis of the bis-aryl hydrazides employing two slightly different strategies.

The corresponding compounds **9a–d** (Table 3) were prepared by reacting bis-hydrazide **8**⁹ with aryl iodide **5**. Mono-hydrazides **4** were coupled with 3,5-dibromotoluene to afford **9e–g** in excellent yields (Table 4).

The double-benzidine rearrangement reactions of **9a–g** were conducted under the conditions shown in Table 1 (Table 5).

Table 5. Double Benzidine Rearrangement

entry	9	R	R ₁	R ₂	10 (% yield)
1	9a	H	H	H	10a (75) ^b
2	9b	H	H	Me	10b (56)
3	9c	H	Me	Me	10c (61)
4	9d	Me	H	CO ₂ Me	10d (N/A) ^c
5	9e	Me	H	H	10e (45)
6	9f	Me	Me	H	10f (61)
7	9g	Me	H	OMe	10g (54)

^a Combined yield; **10a** and traces of inseparable by-products. ^b Isolated yield. ^c MeOH was used, the product decomposes upon standing.

Table 6. Synthesis of Tris-aryl Hydrazides

entry	4	time (h)	11 (% yield) ^a
1	4a (R = H)	2	11a (98)
2	4b (R = Me)	3	11b (84)
3	4c (R = OMe)	2	11c (99)

^a Isolated yield.

As in the cases of mono-benzidine rearrangement reactions, the presence of ortho substituents suppressed the formation of byproducts, yielding mainly the benzidines **10b–f** in good isolated yields, except entry 4. The unsubstituted bis-aryl hydrazide **9a** furnished **10a**, which was contaminated with small amounts of byproducts, not separable with flash column chromatography, in a combined yield of 75% (72% based on GC analysis with internal standard).

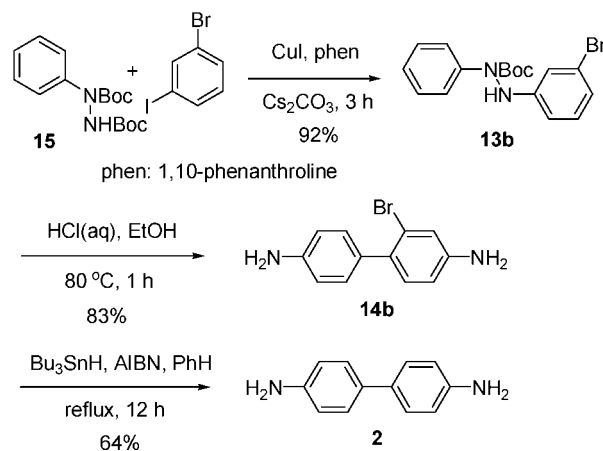
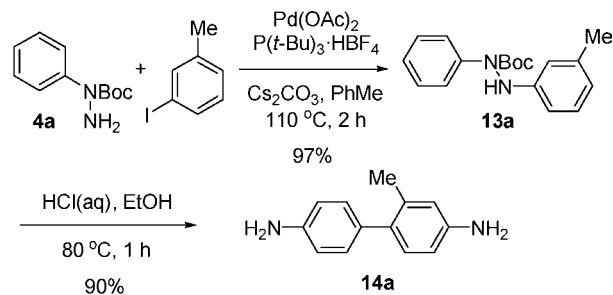
(9) Compound **8** was prepared from the Cu(I)-mediated coupling reaction of BocNHNH₂ with 1,3-dibromobenzene according to Buchwald's conditions. Kwong, F. Y.; Klapsars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581.

Table 7. Triple Benzidine Rearrangement

entry	11	12 (% yield) ^a
1	11a (R = H)	12a (46)
2	11b (R = Me)	12b (56)
3	11c (R = OMe)	12c (45)

^a Isolated yield.

Scheme 2. Benzidine Rearrangement Reactions of Aryl Hydrazides with Substituent at *Meta*-position



Further extension to triple benzidine rearrangement reactions was made with tris-aryl hydrazides **11** which were prepared from the coupling reactions of *N*-aryl hydrazides **4** with tribromobenzene in excellent yields (Table 6). Table 7 summarizes the rearrangement reactions providing novel trisubstituted triaminobenzenes **12a–c** in good isolated yields.

The effect of a meta substituent on the benzidine rearrangement reaction was then investigated.¹⁰ Despite our initial expectation that it might promote the [3,5]-sigmatropic rearrangement product, i.e., diphenylene **3**, the aryl hydrazide

13a, bearing a methyl group at the meta position, cleanly provided the benzidines **14a** in 90% yield (Scheme 2).

The aryl hydrazide **13b** with bromine at the meta position can be conceived as a chemical equivalent of aryl hydrazine **1** which can provide the parent benzidine **2**, otherwise difficult to be obtained in chemically pure form through the two-step sequence involving the rearrangement to **14b** and the reductive removal of the bromine group (Scheme 2).¹¹

In conclusion, we have shown that aryl hydrazides with substituent(s) at the ortho or meta positions undergo highly regioselective [5,5]-sigmatropic rearrangement reactions to

(10) Park, K. H.; Park, M.-K.; Cho, Y. H. *Bull. Korean. Chem. Soc.* **1998**, *19*, 1090.

(11) The Pd-catalyzed coupling reaction of **4** with 1-bromo-3-iodobenzene gave the coupling product in only 47% yield.

(12) All of the new benzidines were completely characterized with ¹H, ¹³C NMR, IR, and HRMS.

an array of structurally novel benzidines¹² in good to excellent isolated yields. Our new route would certainly shed light on the synthetic utility of the long-standing and mostly unexploited benzidine rearrangement reaction to its full potential.

Acknowledgment. This work was supported by the grant from the Korea Science and Engineering Foundation through the Center for Bioactive Molecular Hybrids (CBMH), Yonsei University. K.H.-M. is grateful for a BK21 fellowship.

Supporting Information Available: Experimental procedures and details of compound characterization for all unknown aryl hydrazides and benzidines. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL060451+