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Aryl Hydrazide beyond as Surrogate of Aryl Hydrazine in the Fischer Indolization: The Synthesis of *N*-Cbz-indoles, *N*-Cbz-carbazoles, and *N,N′*-Bis-Cbz-pyrrolo[2,3-*f*]indoles

In-Keol Park, Sung-Eun Suh, Byeong-Yun Lim, and Cheon-Gyu Cho*

Department of Chemistry, Hanyang University, Seoul 133-791, Korea

ccho@hanyang.ac.kr

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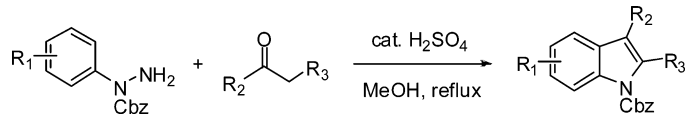
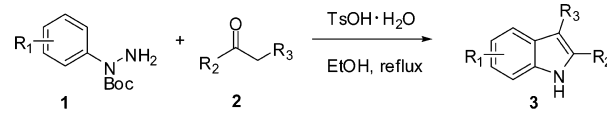
ABSTRACT



Aryl hydrazides underwent the Fischer indolization reactions, while the *N*-carbamate group(s) remained intact to directly provide *N*-Cbz-indoles. This new method allowed the synthesis of various *N*-Cbz-carbazoles and *N,N′*-bis-Cbz-pyrrolo[2,3-*f*]indoles.

The indole nucleus is arguably the most privileged molecular scaffold in nature.[1] A wide variety of important biological activities featured by a plethora of indole-based natural products have driven them to be highly attractive targets for synthesis over the years.[2] A number of elegant synthetic methods and strategies, most notably those based on the Pd-catalyzed C−N bonding formation, have been developed and successfully applied for the synthesis of indoles and related products.[3] The Fischer indole synthesis,[4] reported over 100 years ago, still remains of considerable value, although somewhat compromised by the poor availability of the starting aryl hydrazines. In our previous report,[5] we have demonstrated that aryl hydrazides **1** are effective surrogates of aryl hydrazines in the Fischer indolization reaction. The use of more readily accessed aryl hydrazides **1**[6] (than aryl hydrazines) would thus complement the above limitation in the conventional Fischer method (Scheme 1).[7]

Scheme 1. Fischer Indolization of Aryl Hydrazide **1**



As a part of our ongoing study exploring the synthetic utility of aryl hydrazides,[8] we have elaborated the double Fischer indolization[9] of 1,4-phenylene-bishydrazide **4** toward the synthesis of the indolo[3,2-*b*]carbazole system (Scheme 2). The requisite 1,4-phenylene-bishydrazide **4** was prepared from the Cu(I)-catalyzed coupling reaction of $BocNHNH_2$ with 1,4-diiodobenzene.[6d] A subsequent reaction with cyclohexanone gave bishydrazone **5** in 82% isolated yields.

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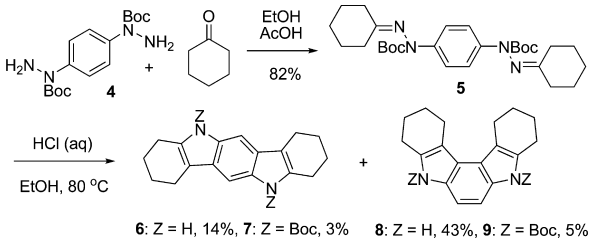
Scheme 2. Fischer Reaction of Bishydrazide **4**



6: Z = H, 14%, **7**: Z = Boc, 3% **8**: Z = H, 43%, **9**: Z = Boc, 5%

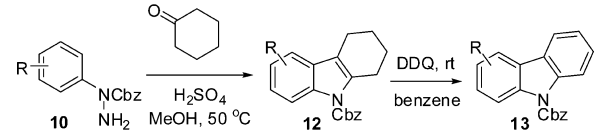
When heated with catalytic amount of HCl(aq) in EtOH, it afforded octahydroindolo[3,2-*b*]carbazole **6** and octahydroindolo[2,3-*c*]carbazole **8** in 14% and 43% yield, respectively, together with various other byproducts including, to our surprise, the carbazoles **7** and **9** bearing Boc groups attached, albeit in low yields.[10]

These unprecedented results[11] prompted us to reinvestigate our previous study (Scheme 1) and screen the conditions that may tolerate the presence of an *N*-Boc group. A series of control experiments were then conducted on the Fischer reaction of phenyl hydrazide **1a** (R_1 = H) with 2-butanone, as a model, which involved variation of reaction temperature, solvent, and acid catalyst. Running the reaction in MeOH at 50 °C with 2 equiv of conc. H_2SO_4 turned out to be the best, which furnished 2,3-dimethyl-*N*-Boc-indole, but only up to 20% yield.

With no further improvement availed, aryl hydrazide **10a** bearing a less acid labile *N*-Cbz group was prepared from the Cu(I)-catalyzed coupling reaction of $CBzNHNH_2$ with phenyl iodide (Supporting Information for details). To our delight, its reaction with ketone **2a** in boiling MeOH provided *N*-Cbz-indole **11a** in 95% yield (entry 1, Table 1). The reactions with various other aryl hydrazides **10b**−**10j** also proceeded smoothly to afford *N*-Cbz indoles **11b**−**11l** in fair to excellent isolated yields.

Further extension to the synthesis of *N*-Cbz-carbazoles was elaborated by first preparing tetrahydro-*N*-Cbz-carbazoles **12a**−**12l** from the reactions of aryl hydrazides **10a**−**10l** with cyclohexanone (Table 2). The substrates with a *meta*-substituent provided a mixture of two regioisomers (entries 7 and 8). Subsequent oxidative aromatization with DDQ in benzene afforded the corresponding *N*-Cbz-carbazoles **13a**−**13l** mostly in good yields, except the one with the methyl ester group (**12d**, entry 4).[12] In entry 7, the isomeric products **12j** and **12j′** were separated by column chromatography and subjected individually to the aromatization reaction to give **13j** and **13j′**.

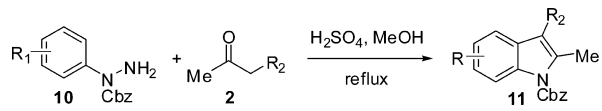
Table 2. Syntheses of *N*-Cbz-carbazoles



entry	arylhydrazide	time	12 (yield)	time	13 (yield)
1	**10a** (R_1 = H)	2 h	**12a** (86%)	1 h	**13a** (87%)
2	**10b** (R_1 = *p*-OMe)	2 h	**12b** (98%)	1 h	**13b** (85%)
3	**10c** (R_1 = *p*-Me)	2 h	**12c** (98%)	1 h	**13c** (80%)
4	**10d** (R_1 = *p*-CO_2Me)	5 h	**12d** (70%)	3 h[a]	**13d** (49%)
5	**10e** (R_1 = *p*-*t*-Bu)	6 h	**12e** (85%)	1 h	**13e** (86%)
6	**10f** (R_1 = *p*-Ph)	6 h	**12f** (86%)	1 h	**13f** (86%)
7	**10j** (R = *m*-OMe)	6 h	**12j** (53%)[b]	1 h	**13j** (80%)
			12j′ (32%)[b]	1 h	**13j′** (88%)
8	**10k** (R = *m*-Me)	3 h	**12k** (87%)[c]	1 h	**13k** (67%)[c]
9	**10l** (R_1 = *p*-hexyl)	6 h	**12l** (87%)	1 h	**13l** (77%)

[a] At 50 °C. [b] Two regioisomers **12j** (R = 6-OMe) and **12j′** (R = 4-OMe) were separated and subjected to aromatization. [c] For a mixture of two regioisomers.

Table 1. Double Fischer Indolization of **10**

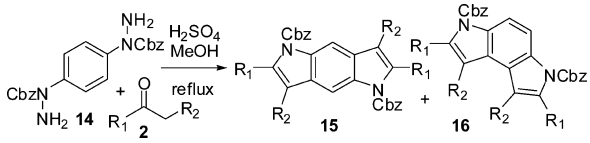


entry	10	2	time	*N*-CBz-indole
1	**10a** (R_1 = H)	**2a** (R_2 = Me)	2 h	**11a** (95%)
2	**10b** (R_1 = *p*-OMe)	**2a** (R_2 = Me)	2 h	**11b** (91%)
3	**10c** (R_1 = *p*-Me)	**2a** (R_2 = Me)	2 h	**11c** (84%)
4	**10d** (R_1 = *p*-CO_2Me)	**2a** (R_2 = Me)	72 h	**11d** (50%)
5	**10a** (R_1 = H)	**2b** (R_2 = nBu)	4 h	**11e** (71%)
6	**10b** (R_1 = *p*-OMe)	**2c** (R_2 = CH_2CO_2Me)	24 h	**11f** (73%)
7	**10e** (R_1 = *p*-tBu)	**2a** (R_2 = Me)	4 h	**11g** (77%)
8	**10f** (R_1 = *p*-Ph)	**2a** (R_2 = Me)	8 h	**11h** (93%)
9	**10g** (R_1 = *p*-Br)	**2a** (R_2 = Me)	12 h	**11i** (75%)
10	**10h** (R_1 = *p*-NH_2)	**2a** (R_2 = Me)	12 h	**11j** (77%)
11	**10i** (R_1 = *o*-Me)	**2a** (R_2 = Me)	2 h	**11k** (40%)
12	**10j** (R_1 = *m*-OMe)	**2a** (R_2 = Me)	12 h	**11l** (91%)[a]

[a] 6:4 mixture of two regioisomers.

For the synthesis of the pyrrolo[2,3-*f*]indole system, we prepared 1,4-phenylene bishydrazide **14** from 1,4-diiodobenzene via the Cu(I)-catalyzed coupling reaction with benzyl carbazate (75% yield). The double Fischer reactions of bishydrazide **14** with ketones **2** afforded a mixture of pyrrolo[2,3-*f*]indoles **15** and pyrrolo[3,2-*e*]indoles **16** in good to fair total yields (Table 3). Although inseparable on column chromatography, pyrrolo-indoles **15a**−**15g** and **16a**−**16g** are readily separable based on their solubility difference in EtOAc (**15a**−**15g**, insoluble; **16a**−**16g**, soluble; see Supporting Information for the structural assignment).[13] Simple trituration with or recrystallization from EtOAc afforded pure **15a**−**15g**. This new protocol is of particular interest and value as there are no other general methods available in the literature for the synthesis of pyrrolo[2,3-*f*]indoles.[14]

Table 3. Syntheses of *N*,*N*′-Bis-Cbz-pyrrolo[2,3-*f*]indoles



entry	ketone	time	yield (ratio)[a]
1=	$R_1 = R_2 =$ Me	12 h	95% (**15a**:**16a** = 3:2)
2	R_1 = Me, R_2 = nBu	12 h	90% (**15b**:**16b** = 1:2)
3	R_1 = Me, $R_2 = CH_2CO_2Me$	72 h	55% (**15c**:**16c** = 5:1)
4	R_1 = Me, $R_2 = CH_2Ph$	12 h	76% (**15d**:**16d** = 1:2)
5	R_1 = Ph, R_2 = Me	12 h	57% (**15e**:**16e** = 1:1)
6	R_1 = Ph(2-F), R_2 = Me	12 h	50% (**15f**:**16f** = 1:1)
7	R_1 = Ph(4-Br), R_2 = Me	24 h	47% (**15g**:**16g** = 2:3)

[a] Total isolated yield (ratio determined by ^{1}H NMR).

In summary, aryl hydrazides underwent the Fischer indolization reactions while the *N*-carbamate group(s) remained intact, to provide *N*-Cbz-indoles, *N*-Cbz-carbazoles, and *N*,*N*′-bis-Cbz-pyrrolo[2,3-*f*]indoles.

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Supporting Information Available: Details of experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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