

Aryl Hydrazone 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

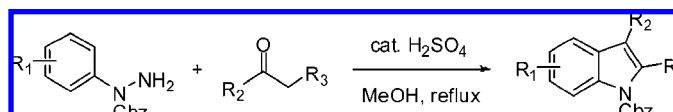
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ABSTRACT

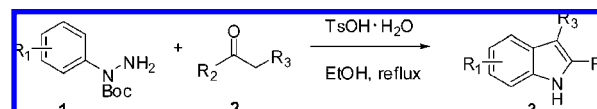


Aryl hydrazides underwent the Fischer indolization reactions, while the *N*-carbamate group(s) remained intact to directly provide *N*-Cbz-indoles. This new method allowed the synthesis of various *N*-Cbz-carbazoles and *N,N'*-bis-Cbz-pyrrolo[2,3-*f*]indoles.

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 Hydrazone **1**



As a part of our ongoing study exploring the synthetic utility of aryl hydrazides,⁸ we have elaborated the double Fischer indolization⁹ 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 BocNHNH₂ with 1,4-diiodobenzene.^{6d} A subsequent reaction with cyclohexanone gave bishydrazone **5** in 82% isolated yields.

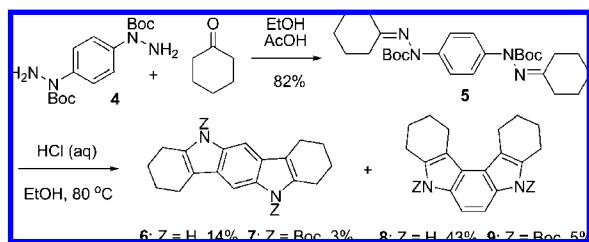
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Scheme 2. Fischer Reaction of Bishydrazide **4**



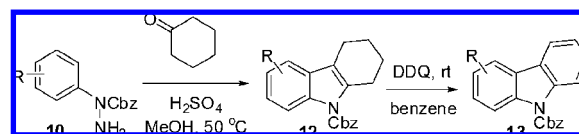
When heated with catalytic amount of HCl(aq) in EtOH, it afforded octahydroindolo[3,2-*b*]carbazole **6** and octahydroindolo[2,3-*c*]carbazole **8** in 14% and 43% yield, respectively, together with various other byproducts including, to our surprise, the carbazoles **7** and **9** bearing Boc groups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

These unprecedented results¹¹ 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** ($R_1 = \text{H}$) 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 CBzNHNH₂ 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–11j** 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*-

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

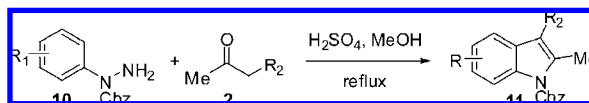


entry	arylhydrazide	time	12 (yield)	time	13 (yield)
1	10a ($R_1 = \text{H}$)	2 h	12a (86%)	1 h	13a (87%)
2	10b ($R_1 = p\text{-OMe}$)	2 h	12b (98%)	1 h	13b (85%)
3	10c ($R_1 = p\text{-Me}$)	2 h	12c (98%)	1 h	13c (80%)
4	10d ($R_1 = p\text{-CO}_2\text{Me}$)	5 h	12d (70%)	3 h ^a	13d (49%)
5	10e ($R_1 = p\text{-t-Bu}$)	6 h	12e (85%)	1 h	13e (86%)
6	10f ($R_1 = p\text{-Ph}$)	6 h	12f (86%)	1 h	13f (86%)
7	10j ($R = m\text{-OMe}$)	6 h	12j (53%) ^b 12j' (32%) ^b	1 h	13j (80%) 13j' (88%)
8	10k ($R = m\text{-Me}$)	3 h	12k (87%) ^c	1 h	13k (67%) ^c
9	10l ($R_1 = p\text{-hexyl}$)	6 h	12l (87%)	1 h	13l (77%)

^a At 50 °C. ^b Two regioisomers **12j** ($R = 6\text{-OMe}$) and **12j'** ($R = 4\text{-OMe}$) were separated and subjected to aromatization. ^c For a mixture of two regioisomers.

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 1. Double Fischer Indolization of **10**

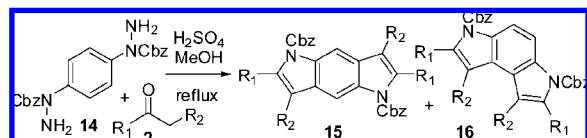


entry	10	2	time	<i>N</i> -Cbz-indole
1	10a ($R_1 = \text{H}$)	2a ($R_2 = \text{Me}$)	2 h	11a (95%)
2	10b ($R_1 = p\text{-OMe}$)	2a ($R_2 = \text{Me}$)	2 h	11b (91%)
3	10c ($R_1 = p\text{-Me}$)	2a ($R_2 = \text{Me}$)	2 h	11c (84%)
4	10d ($R_1 = p\text{-CO}_2\text{Me}$)	2a ($R_2 = \text{Me}$)	72 h	11d (50%)
5	10a ($R_1 = \text{H}$)	2b ($R_2 = n\text{Bu}$)	4 h	11e (71%)
6	10b ($R_1 = p\text{-OMe}$)	2c ($R_2 = \text{CH}_2\text{CO}_2\text{Me}$)	24 h	11f (73%)
7	10e ($R_1 = p\text{-tBu}$)	2a ($R_2 = \text{Me}$)	4 h	11g (77%)
8	10f ($R_1 = p\text{-Ph}$)	2a ($R_2 = \text{Me}$)	8 h	11h (93%)
9	10g ($R_1 = p\text{-Br}$)	2a ($R_2 = \text{Me}$)	12 h	11i (75%)
10	10h ($R_1 = p\text{-NH}_2$)	2a ($R_2 = \text{Me}$)	12 h	11j (77%)
11	10i ($R_1 = o\text{-Me}$)	2a ($R_2 = \text{Me}$)	2 h	11k (40%)
12	10j ($R_1 = m\text{-OMe}$)	2a ($R_2 = \text{Me}$)	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

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 ₂ CO ₂ Me	72 h	55% (15c : 16c = 5:1)
4	R ₁ = Me, R ₂ = CH ₂ Ph	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 ¹H NMR).

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

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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