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Expedient synthesis of indoles from *N*-Boc arylhydrazines

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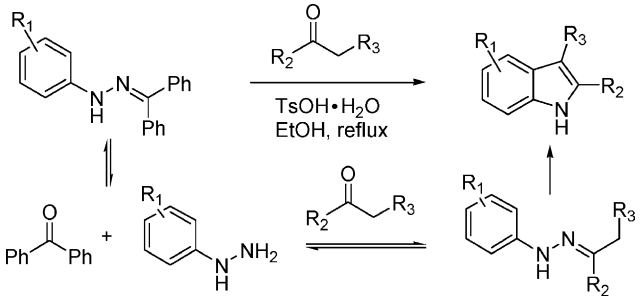
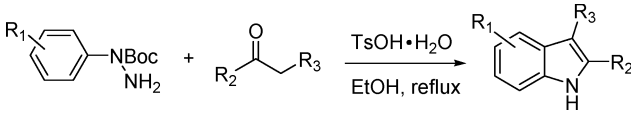
Abstract—The readily available *N*-Boc arylhydrazines undergo efficient Fischer cyclizations to provide the indoles in good yields, when reacted with enolizable ketones.

Indoles have a wide spectrum of physiological activities.[1] While the classical Fischer indole synthesis still remains powerful in the synthesis of indoles, the requisite use of poorly available arylhydrazines limits the scope. Due to their pharmaceutical importance as well as high abundance in nature, many synthetic alternatives have appeared in the literature. Some of the notable recent advances include transition metal catalyzed cyclizations of *o*-alkenylanilines and annulations of *o*-haloanilines with nucleophiles.[2] Attempts to overcome the limitation, while retaining its merits have also been reported. Readily prepared from commercially available benzophenone hydrazone through the coupling with aryl bromides, *N*-aryl benzophenone hydrazone was shown to be an effective surrogate to the less appealing arylhydrazine in the Fischer cycle (Scheme 1).[3]

Despite the usefulness, however, it may not be readily applicable to large scale synthesis as the benzophenone byproduct needs to be chromatographically removed. Herein, we present the use of *N*-Boc arylhydrazines in the Fischer indole cyclization, as an efficient and practical alternative to *N*-aryl benzophenone hydrazones, providing indoles with no inevitable organic byproduct (Scheme 2). The starting *N*-Boc arylhydrazines can be

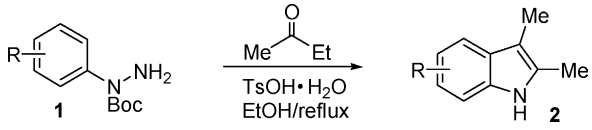


Scheme 1. *N*-Aryl benzophenone hydrazone in the Fischer cycle.



Scheme 2. *N*-Boc arylhydrazines in the Fischer cycle.

Table 1. Indoles from arylhydrazides and 2-butanone



Entry	Arylhydrazide	Time (h)	Indole	Yield (%)
1	**1a** (R = H)	1	**2a** (R = H)	72
2	**1b** (R = *p*-Me)	1	**2b** (R = 4-Me)	94
3	**1c** (R = *p*-OMe)	1	**2c** (R = 4-OMe)	75
4	**1d** (R = *o*-OMe)	1	**2d** (R = 6-OMe)	23
5	**1e** (R = *m*-OMe)	1	**2e** (R = OMe)	87[a]
6	**1f** (R = *p*-*t*-Bu)	1	**2f** (R = 4-*t*-Bu)	92
7	**1g** (R = *p*-Ph)	1	**2g** (R = 4-Ph)	69
8	**1h** (R = *p*-*n*-hexyl)	1	**2h** (R = 4-*n*-hexyl)	79
9	**1i** (R = *p*-COPh)	1	**2i** (R = 4-COPh)	58[b]
10	**1j** (R = *p*-CO_2Et)	1	**2j** (R = 4-CO_2Et)	60[b]

[a] 1:1 Mixture of 2,3,4-trimethyl- and 2,3,5-trimethyl-1*H*-indole.
[b] Heated in toluene at 80 °C.

Keywords: Indoles; Fischer indole synthesis; *N*-Boc arylhydrazines.
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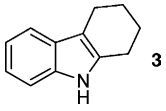
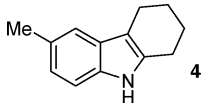
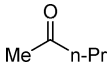
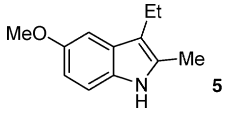
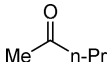
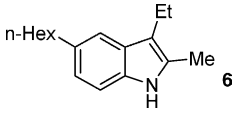
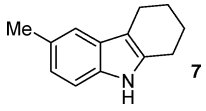
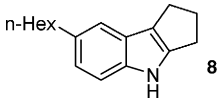
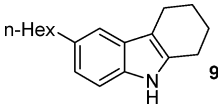
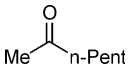
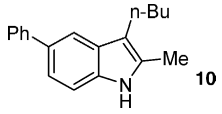
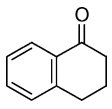
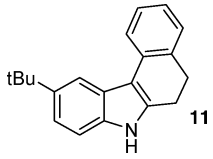
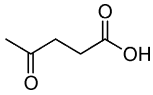
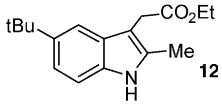
readily prepared from various types of aryl or heteroaryl halides according to the literature methods, securing structural diversity in the arylhydrazine part.[4]

Table 1 summarizes the results on the cyclizations of various substituted *N*-Boc arylhydrazines with 2-butanone.[5]

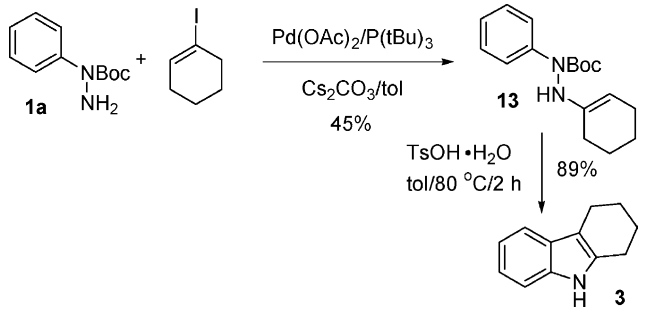
Evidently, the Boc protecting group is removed in situ prior to the subsequent Fischer cyclization to the corresponding indoles. The hydrazide with substituent at the *ortho*-position (entry 4) gave only marginal yield, while the one with substituent at the *meta*-position provided a 1:1 mixture of two regioisomeric indoles (entry 5). The Fischer cyclizations with other enolizable ketones also proceeded to the corresponding indoles within an hour in good to excellent yields in most cases (Table 2).

In addition to the cyclizations with enolizable ketones, *N*-Boc arylhydrazines can be directly coupled with various vinyl halides to generate the coupling products,

Table 2. The indole synthesis with other ketones

Entry	Hydrazide	Ketone	Indole	Yield (%)
1	R = H		 **3**	89
2	R = Me		 **4**	90
3	R = OMe		 **5**	53
4	R = *n*-Hex		 **6**	78
5	R = OMe		 **7**	90
6	R = *n*-Hex		 **8**	57[a]
7	R = *n*-Hex		 **9**	90
8	R = Ph		 **10**	83
9	R = *t*-Bu		 **11**	74
10	R = *t*-Bu		 **12**	54

[a] Heated in THF under reflux.



Scheme 3. Coupling followed by the Fischer cyclization.

which undergo facile Fischer cyclizations to the corresponding indoles when heated in the presence of an acid (Scheme 3). The intermediate coupling products need not be isolated, but can be directly subjected to the Fischer cyclization condition to the indole.

In summary, we have found that *N*-Boc arylhydrazines readily undergo cyclization reactions to indoles when heated with enolizable ketones in the presence of an acid. Unlike the cases with *N*-aryl benzophenone hydrazones, the reactions with *N*-Boc arylhydrazines do not give organic byproducts need to be removed chromatographically. In this new synthesis, the product indole can be isolated from the reaction mixture in an essentially pure form with a simple water workup, suitable for a large scale preparation.

Acknowledgements

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References and notes

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5. Representative procedure: A mixture of *N*-Boc phenyl hydrazine (**1a**, 50 mg, 0.24 mmol), cyclohexanone (35 mg, 0.36 mmol), TsOH monohydrate (274 mg, 1.44 mmol) in 3 mL of EtOH was heated under reflux for 1 h. The reaction mixture was then concentrated and filtered through a plug of silica gel to give 37 mg of **3** in 89% yield.