

Multiple component Fischer indole reactions

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Abstract—New 3-component variations of the Fischer synthesis of substituted indoles have been developed based on the reaction of organometallic reagents with nitriles or carboxylic acids. The new variations expand the scope and synthetic utility of the method.

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1. Introduction

Multiple component condensation (MCC) reactions, defined as processes ‘in which three or more reactants come together in a single reaction to form a new product that contains portions of all the components,’¹ play a central role in diversity-oriented synthesis. Despite their utility, such reactions remain a small subset of known organic reactions. Recent discoveries by our group² and others³ have expanded the repertoire of useful MCC reactions. However, significant advances in this area might also be achieved by modifying known MCC reactions, either by broadening input types or increasing reaction dimensionality (i.e., >3-component Mannich or >4-component Ugi condensations). Here, we use a combination of those approaches to demonstrate that the well-known 2-component Fischer indole synthesis can be re-engineered into a higher-order, more broadly based 3-component process.

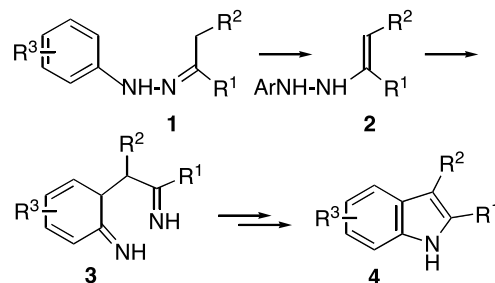
2. Background

Over a century ago Emil Fischer discovered that hydrazones **1**, prepared from arylhydrazines and enolizable ketones, rearranged upon heating in acid with loss of ammonia to afford indoles **4** (Scheme 1).⁴ The process involved initial tautomerization to an ene-hydrazine **2** that underwent a [3,3]-sigmatropic rearrangement to **3** followed by ring closure and aromatization. We reasoned that identifying other reactant combinations leading to intermediates in Scheme 1 might increase the dimensionality of the Fischer indole synthesis, thus widening its scope.

With three contiguous bonds involving two well-differentiated heteroatoms, arylhydrazone **1** presented a particularly attractive target. Such arylhydrazones have previously been formed by Pd-catalyzed cross-coupling of benzophenone hydrazones with aryl bromides, leading to indoles in excellent yield.⁵ Substituted indoles have also been prepared by alkyne hydroamination with hydrazines⁶ and by the tandem hydroformylation/hydrazination of alkenes.⁷ However, each of these methods uses only two variable components.

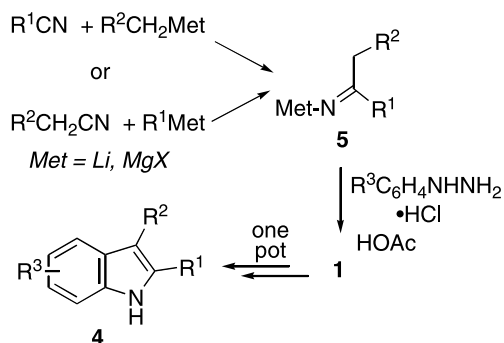
By contrast, metallated ketimines **5** (Scheme 2), generated by the reaction of nitriles with Grignard⁸ or organolithium⁹ compounds, should react in situ (after protonation) with arylhydrazines to form arylhydrazones **1**. Rearrangement to the corresponding indoles would thus incorporate structural diversity from three different inputs. Moreover, species like **5** could in most cases be formed from two complementary reactant combinations as shown, thus making the overall synthesis plan even more flexible.

Here, we report this 3-component condensation can be successfully implemented as a one pot process. By using anhydrous ether as solvent in the addition of organometallic reagents, byproducts arising from competing deprotonation



Scheme 1.

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Scheme 2.

reactions of α -acidic nitriles¹⁰ could be suppressed so as to obtain metallated ketimines **5** in good yield.¹¹

3. Results and discussion

Protonation of **5** and conversion of the corresponding arylhydrazones **1** to indoles **4** was achieved by brief heating (90 °C, 3 h) in glacial acetic acid containing 2.1 equiv of the appropriate arylhydrazine hydrochloride.¹² This method, first reported by Dave, avoids the use of toxic, air- and light-sensitive PhNHNH₂ as well as the customary higher temperatures and more corrosive Lewis acids. Representative examples of the reaction, shown in Table 1, illustrate the scope and generality of the method.

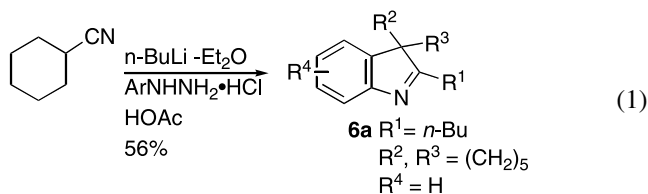
The new 3-component route afforded indoles in yields similar to the classical 2-component Fischer synthesis. In most cases, a small amount (ca. 15% yield based on phenylhydrazine) of PhNHNHCOCH₃ was also obtained as a byproduct.¹³ Condensation of propionitrile with BuLi or BuMgCl led to the same 2:1 mixture of indoles **4h** and **4i**, in agreement with earlier observations on the rearrangement of α,α' -unbranched arylhydrazones.

The Dave conditions for Fischer cyclization, originally applied only to PhNHNH₂·HCl, could be extended to ring-substituted arylhydrazine hydrochloride salts leading to 4, 5, 6, and 7-substituted indoles (e.g., **4b**, **4c**, **4f**, **4j**), albeit in slightly lower yields. Cyclizations leading to 2-arylidoles required somewhat longer heating (15–19 h).

Table 1 also showed that the scope of the method could be extended beyond commercially available organometallic reagents. For example, the synthesis of indoles **4e**, **4f** and **4k** demonstrated the successful use of organolithium reagents prepared by halogen–metal exchange methods, which significantly expanded the utility of the 3CC indole synthesis.

One limitation of the method was encountered in efforts to transform halo-substituted nitriles (e.g., 3-bromopropionitrile, 4-chlorobutyronitrile) into the correspondingly functionalized indoles. All attempts to trap metallated imine **5**, the corresponding ketone or hydrazone **1** failed, suggesting that **5** might be susceptible to inter- or intramolecular decomposition.

The method was successful in preparing indolenines by way of α -branched arylhydrazones. Reaction of cyclohexylcarbonitrile with BuLi followed by PhNHNH₂·HCl afforded **6a** (Eq. 1) in 56% yield, in accordance with literature precedent.¹⁴



An alternative 3-component route to indoles has also been devised from the well-known reaction of a carboxylic acid with 2 equiv of an organolithium reagent in ether.¹⁵ The method affords a useful synthetic approach to ketones, by hydrolysis of the intermediate dialkoxides **7** (Scheme 3).

In the present variation, stepwise reaction of a carboxylic acid with RLi was followed by the addition of a sufficient quantity of arylhydrazine hydrochloride. By using 3.1 equiv of ArNHNH₂·HCl in HOAc, it proved possible to protonate dianion **7** and generate the corresponding ketone. Arylhydrazone formation in situ and Fischer cyclization catalyzed by the residual hydrochloride salt in glacial HOAc at 90 °C afforded indoles **4**. Table 2 presents representative examples of indoles that could be prepared in this fashion.

The higher-order variants of the Fischer synthesis reported

Table 1. 3-Component condensations of nitriles, RMet and ArNHNH₂ leading to indoles **4**^a

Nitrile	RMet	ArNHNH ₂ Ar =	Product (% yield)
PhCN	BuLi	Ph ^b	4a 2-Phenyl-3-propylindole (60)
PhCN	BuLi	<i>m</i> -Cl-Ph ^b	4b 4-Chloro-2-phenyl-3-propylindole (19), 4c 6-Chloro-2-phenyl-3-propylindole (19)
PhCN	BuMgCl	Ph	4a (42)
<i>n</i> -C ₅ H ₁₁ CN	PhLi	Ph	4d 3-Butyl-2-phenylindole (49)
<i>n</i> -C ₅ H ₁₁ CN	PhMgCl	Ph	4d (45)
<i>n</i> -C ₅ H ₁₁ CN	<i>p</i> -OMe-C ₆ H ₄ Li	Ph ^a	4e 3-Butyl-2-(<i>p</i> -CH ₃ OPh)-indole (64)
<i>n</i> -C ₅ H ₁₁ CN	<i>p</i> -OMe-C ₆ H ₄ Li	<i>o</i> -Cl-Ph ^b	4f 3-Butyl-7-chloro-2-(<i>p</i> -CH ₃ OPh)-indole (34)
<i>n</i> -C ₅ H ₁₁ CN	CH ₃ Li	Ph	4g 3-Butyl-2-methylindole (54)
CH ₃ CH ₂ CN	BuLi	Ph	4h R ¹ = 2-butyl-3-methylindole (46), 4i 2-Ethyl-3-propylindole (23)
CH ₃ CH ₂ CN	BuMgCl	Ph	4h (40); 4i (20)
CH ₃ CH ₂ CN ^c	PhMgBr	<i>p</i> -OMe-Ph	4j 5-Methoxy-3-methyl-2-phenylindole (32)
CH ₃ CH ₂ CN	3,5-Dibromo-PhLi	Ph ^b	4k 2-(3',5'-Dibromophenyl)-3-methylindole (57)

^a The nitrile was combined with RMet in ether, followed by the addition of ArNHNH₂·HCl. The ether was removed in vacuo and HOAc added. The reaction mixture was then heated at 90 °C.

^b ArNHNH₂·HCl (2.6 equiv) added.

^c Nitrile added in C₆H₆.

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