Indole Synthesis

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A Variation of the Fischer Indolization Involving Condensation of Quinone Monoketals and Aliphatic Hydrazines**

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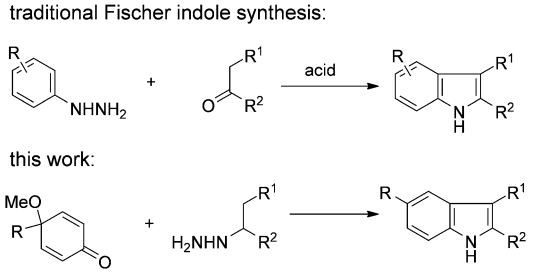
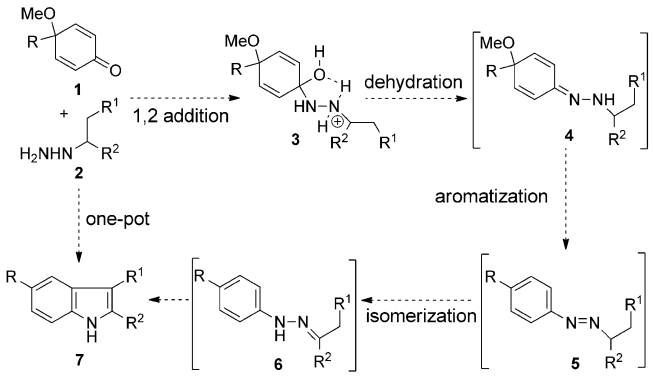
Dedicated to Professors Samuel J. Danishefsky and Ronald Breslow

The indole ring system is one of the most ubiquitous heterocycles in nature. Many indole-containing natural products show a wide scope of biological activities,[1] in particular because they bind to many receptors with high affinity.[2] Since Baeyer's first synthesis of indole from oxindole in 1866 (indigo→isatin→oxindole→indole),[3] numerous methods for the synthesis of indoles have been reported.[4] One of the most efficient and widely employed syntheses is the Fischer indolization discovered in 1883.[5] Compared with other indole syntheses, the importance of Fischer indolization lies in its simplicity and convenience, that is, formation of a critical C–C bond to an unactivated aromatic carbon through a [3,3] sigmatropic rearrangement of enolizable *N*-arylhydrazones.[6] After more than a century of development, the Fischer indole synthesis remains a reliable and versatile method for the preparation of a variety of indole natural products and medicinal compounds.[7] Many new variations have been developed in recent years.[8] Most recently, the first catalytic asymmetric version of Fischer indole synthesis was reported by the group of List.[9] Although the Fischer indole synthesis is widely used, several disadvantages still remain. The classical Fischer indole synthesis starts with arylhydrazines, which are generally made either from anilines through diazonium salts, or from aryl halides through transition-metal-mediated coupling reactions. These processes involve the use of aniline precursors and toxic reagents (nitrous acid, stannous chloride, etc.) and potentially explosive diazonium intermediates, or expensive transition metals. We report herein a novel variation of the Fischer indolization involving a one-pot condensation of quinone monoketals[10] with aliphatic hydrazines[11] (Scheme 1). To the best of our knowledge, this is the first Fischer-type indole synthesis using an aliphatic hydrazine as the nitrogen source and a quinone monoketal as a masked benzene ring.



Scheme 1. Strategies for the synthesis of indoles.

We envisioned that condensation of quinone monoketal **1** and aliphatic hydrazine **2** would ultimately lead to an indole via alkylaryldiazene **5** and arylhydrazone intermediate **6**, as illustrated in Scheme 2. The feasibility of this method relies on the initial formation of alkylaryldiazene **5** from a 1,2-addition/dehydration sequence. It should be noted that there has been no report on the synthesis of alkylaryldiazenes **5** from quinone derivatives and aliphatic hydrazines, although arylaryldiazenes (azobenzenes) have been synthesized from condensations of arylhydrazines with quinones,[12] quinols,[13] quinone monoketals,[14] and quinone bisketals.[15] There is a single report on the condensation of an aliphatic hydrazine (*N*,*N*-dimethylhydrazine) with naphthoquinone monoketal, which, however, gave a 1,4-addition product in high yield.[16] Therefore, our first object was to test the practicality of the



Scheme 2. Synthetic plan.

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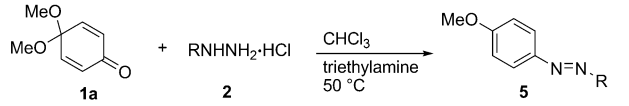
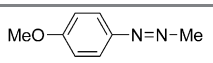
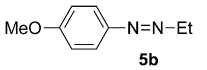
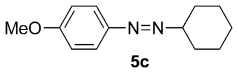
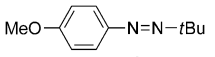
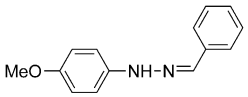
synthesis of alkylaryldiazenes **5** through a 1,2-addition of aliphatic hydrazines to quinone monoketals.

Not surprisingly, when we treated methyl hydrazine or *N*,*N*-dimethylhydrazine with quinone monoketal **1a**, only polar intractable products formed. The desired nonpolar alkylaryldiazene could not be detected. After extensive experimentation, we found that when acetic acid was added to deactivate methylhydrazine, nonpolar methyldiazene **5a** was isolated in a 23% yield as a 40:1 *E*/*Z* isomeric mixture (Table 1, entry 1). The minor *Z* isomer was identified by the characteristic upfield resonances of the arylazo *ortho* protons in its ^{1}H NMR spectrum.[17] The remainder of the mass balance for this reaction is an unidentified mixture of polar side products. The fact that diazene **5a** was formed, albeit in low yield, suggested that general acid catalysis facilitates the dehydration of carbinolhydrazine **3**.[18] Under similar conditions the reaction of *N*,*N*-dimethylhydrazine also led to diazene **5a** as product, presumably through the demethylation of a diazenium cation intermediate.[19] Higher yields were obtained when more-hindered alkyl hydrazine hydrochloride/oxalate salts were used, possibly owing to steric hindrance, which could disfavor the 1,4 addition (Table 1, entries 2–4). A screening of various solvents (MeOH, $CHCl_3$, CH_2Cl_2, PhH, THF, CH_3CN, $ClCH_2CH_2Cl$, and HOAc) for the condensation determined that methanol, chloroform, and dichloroethane were optimal. The reactions are easily monitored by thin layer chromatography because the product diazenes are colored.

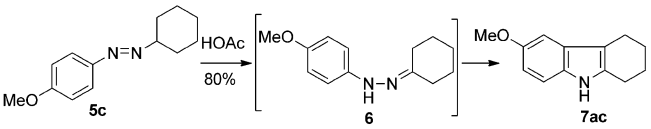
Table 1: Diazene synthesis.



Entry	R	Product	Yield [%][a]
1	Me (Me_2NNH_2)	 **5a**	23; *E*/*Z* 40:1 (37; *E*/*Z* 20:1)
2	Et[b]	 **5b**	62; *E*/*Z* 30:1
3	*c*Hex	 **5c**	65
4	*t*Bu	 **5d**	60; *E*/*Z* 25:1
5	Bn	 **8**	45

[a] The yield of the isolated product. [b] Oxalate salt.

Once the diazenes were in hand, we next turned to the isomerization of diazenes into arylhydrazones (**5**→**6**) and then cyclization to indoles (**6**→**7**). It has been previously reported that alkylaryldiazenes can be isomerized into the corresponding hydrazones by catalysis with acid or base.[20] Indeed, when benzylhydrazine hydrochloride was used in the condensation with quinone monoketal **1a**, we isolated the isomerized arylhydrazone **8** instead[21] (Table 1, entry 5). This facile diazene→hydrazone isomerization is presumably owing to the higher acidity of the benzylic protons. Bellamy and Guthrie reported acid-mediated indole formation directly from alkylaryldiazenes.[22] Recently, the groups of Heinrich[23] and Knochel[8s,t] utilized this chemistry for indole synthesis using diazonium salts as starting material. When we treated diazene **5c** with acetic acid tetrahydrocarbazole **7ac** was indeed isolated in 80% yield (Scheme 3).



Scheme 3. Indole formation from diazene.

We next attempted to find optimized conditions for diazene formation, isomerization, and indole formation in a one-pot process from quinone monoketals and aliphatic hydrazines. The development of a one-pot synthesis is attractive for two reasons. First, it could obviate the isolation and purification of diazenes. Second, it would provide higher yield as the isomerized hydrazones and even 1,4-addition intermediates can ultimately lead to indole under one-pot conditions. The reaction of quinone monoketal **1a** with cyclohexylhydrazine hydrochloride **2c** in the presence of triethylamine gives diazene **5c**; addition of excess acetic acid to the reaction mixture then gives tetrahydrocarbazole **7ac** in 57% yield . But as this one-pot procedure uses both base (triethylamine) and acid (acetic acid), it is not optimal with regards to atom economy. Considering that we use hydrazine hydrochlorides as condensation partners, we reasoned that a weak base would accelerate diazene formation (**1**+**2**→**5**) and its conjugate acid (hydrochloride salt) could mediate diazene to hydrazone (**5**→**6**) isomerization, hydrazone to ene-hydrazine isomerization, and [3,3] sigmatropic rearrangement to the indole[6] (**6**→**7**). After screening a range of organic bases (Et_3N, pyridine, picoline, lutidine, quinoline, *N*-methylmorpholine, and 1,8-diazabicyclo[5.4.0]undec-7-ene) we found the best yield is achieved when pyridine is used. When **1a** and **2c** are heated in chloroform with 2 equivalents of pyridine in a sealed vial, **7ac** is obtained in 68% yield.[24]

When cyclohexylhydrazine hydrochloride (**2c**) was used in our optimized process, tetrahydrocarbazoles, which can be oxidized upon exposure to air, were obtained as the major products (Table 2, entries 1–3). Therefore, we decided to survey the scope of quinone monoketals[25] by using (2-phenylethyl)hydrazine hydrochloride (**2e**)[26] as the condensation partner, since **2e** is more reactive than **2c** and leads to cleaner products.[27] Unsubstituted quinone monoketals generally lead to indoles in good yields (Table 2, entries 4–6). Halogenated indoles can be easily made from halogen-substituted quinone monoketals. For quinone monoketals **1d**–**1g**, excellent combined yields of separable regioisomers were obtained (Table 2, entries 7–10). Quinone monoketal **1h** gave a lower yield, presumably owing to the lower reactivity of its vinylogous ester carbonyl group (Table 2, entry 11). For

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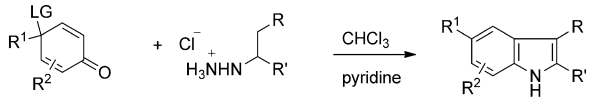
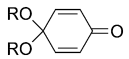
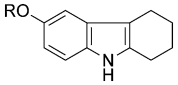
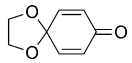
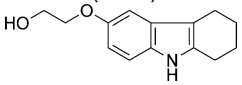
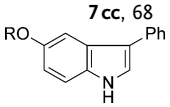
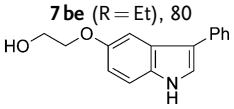
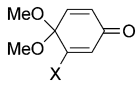
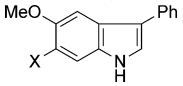
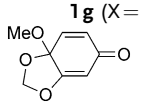
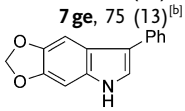
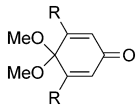
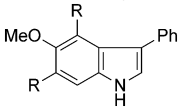
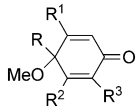
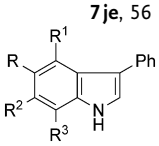
Table 2: Indole synthesis by a one-pot condensation.



1 2 7

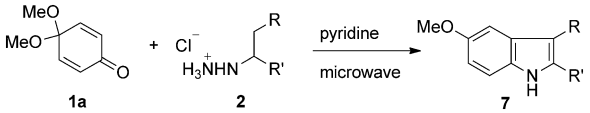
Entry	Quinone monoketal	Hydrazine	Indole/Yield [%][a]
			
1	**1a** (R = Me)	**2c**	**7ac** (R = Me), 68
2	**1b** (R = Et)	**2c**	**7bc** (R = Et), 66
			
3	**1c**	**2c**	**7cc**, 68
			
4	**1a**	**2e**	**7ae** (R = Me), 75
5	**1b**	**2e**	**7be** (R = Et), 80
			
6	**1c**	**2e**	**7ce**, 68%
			
7	**1d** (X = I)	**2e**	**7de**, 61 (17)[b]
8	**1e** (X = Br)	**2e**	**7ee**, 84 (13)[b]
9	**1f** (X = Cl)	**2e**	**7fe**, 84 (11)[b]
10	**1g** (X = F)	**2e**	**7ge**, 75 (13)[b]
			
11	**1h**	**2e**	**7he**, 41
			
12	**1i** (R = Me)	**2e**	**7ie**, 81
13	**1j** (R = Cl)	**2e**	**7je**, 56
			
14	**1k** (R = Me, $R^1 = R^2 = R^3 = H$)	**2e**	**7ke**, 93
15	**1l** (R = Et, $R^1 = R^2 = R^3 = H$)	**2e**	**7le**, 84
16	**1m** (R = Ph, $R^1 = R^2 = R^3 = H$)	**2e**	**7me**, 93
17	**1n** ($R = R^1 = R^2 = Me$, $R^3 = H$)	**2e**	**7ne**, 95
18	**1o** ($R = R^3 = Me$, $R^1 = R^2 = H$)	**2e**	**7oe**, 63
19	**1p** ($R, R^1 = -(CH_2)_4-$, $R^2 = R^3 = H$)	**2e**	**7pe**, 74

[a] Yield of the isolated product. [b] Yields in parenthesis are the yields of separable 4-haloindole isomers. LG = leaving group.

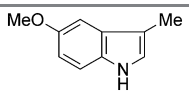
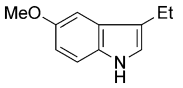
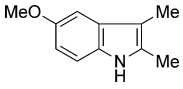
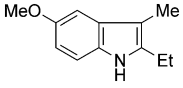
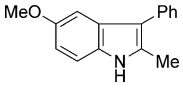
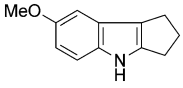
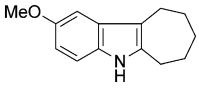
disubstituted quinone monoketals **1i** and **1j**, tetra-substituted indoles **7ie** and **7je** were obtained (Table 2, entries 12–13). Quinol ethers are also suitable condensation partners and afford substituted indoles in good to excellent yields (Table 2, entries 14–19).

To further explore the scope of this reaction, we next focused on the generality of the condensation partner, that is the aliphatic hydrazine hydrochlorides, which can be easily prepared either in one step from alkyl halides[26a] or in two steps from ketones/aldehydes and Boc hydrazine through reductive hydrazination and deprotection[26b] (see the Supporting Information). Under microwave conditions, *N-n*-alkylhydrazines afforded indoles in moderate to good yields (Table 3, entries 1 and 2). *N-sec*-alkylhydrazines gave 2,3-substituted indoles in good yields (Table 3, entries 3–5). For unsymmetrical hydrazine **2h**, regioselective cyclization product **7ah** was obtained, presumably due to the weak acidity of our reaction medium. It is known that the direction of Fischer indole cyclization was governed by the acidity of the reaction medium.[28] For **2j**, conjugation with a phenyl ring is an additional important factor for regioselective hydrazone to ene-hydrazine isomerization. The reactions of cyclopentyl and cycloheptyl hydrazines **2k** and **2l** gave the desired products in a similar yield to that for **7ac** (Table 3, entries 6 and 7 and Table 2, entry 1).

Table 3: Scope of the aliphatic hydrazines.



1a 2 7

Entry	Hydrazine	Indole/Yield [%][a]
1	**2f** (R = Me, R′ = H)	 **7af**, 62
2	**2g** (R = Et, R′ = H)	 **7ag**, 37
3	**2h** (R = Me, R′ = Me)	 **7ah**, 71
4	**2i** (R = Me, R′ = Et)	 **7ai**, 58
5	**2j** (R = Ph, R′ = Me)	 **7aj**, 80
6	**2k** (R,R′ = $-(CH_2)_3-$)	 **7ak**, 68
7	**2l** (R,R′ = $-(CH_2)_5-$)	 **7al**, 69

[a] Yield of the isolated product.

Thus, our method, using readily accessible phenols[29] as starting materials, offers a simple alternative to the traditional Fischer indole synthesis. For example, by the traditional

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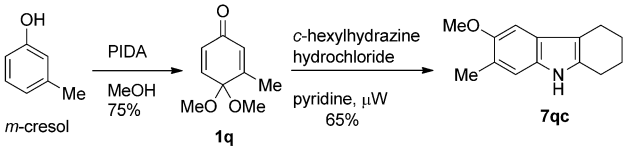
Fischer indole synthesis indole **7qc** was made from 4-methoxy-3-methylaniline and cyclohexanone.[30] In contrast, our method afforded **7qc** from inexpensive *m*-cresol (Scheme 4).[31] Furthermore, we use aliphatic hydrazines as



Scheme 4. Synthesis of tetrahydrocarbazole from *m*-cresol. PIDA = (-diacetoxy)iodobenzene.

the nitrogen source of indoles and avoid arylhydrazines, which are more difficult to prepare and handle in some cases.

In summary, we have developed a new variation of Fischer indole synthesis. Starting with readily available phenols and aliphatic hydrazines it affords 5-substituted indoles in a two-step procedure, and avoids the use of arylhydrazines, diazonium intermediates, and transition metals. Applications of this method to synthesis of natural and synthetic therapeutic products are currently underway in our laboratory.

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