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Rearrangement of 3,3-Disubstituted Indolenines and Synthesis of 2,3-Substituted Indoles

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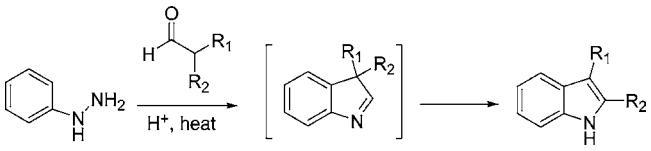
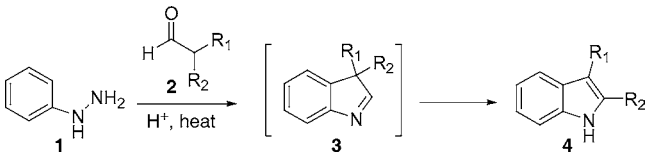
ABSTRACT



Synthesis of 2,3-substituted indoles from phenylhydrazine and α-branched aldehydes via rearrangement of 3,3-disubstituted indolenine intermediates is reported.

In our efforts to synthesize 3,3-disubstituted oxindoles from arylhydrazines (**1**) and α-branched aldehydes (**2**),[1] we found the intermediate indolenines (**3**) rearrange to afford 2,3-disubstituted indoles (**4**) when heated to elevated reaction temperatures for prolonged periods (Scheme 1). Although

Scheme 1



Rodriguez[2,3] reported many years ago that rearrangement of spiroindolenines of type **3** can occur with an acid catalyst to give cycloalkanoindoles, detailed studies on this rearrangement and examination of the acyclic variant have not been reported. Our initial results prompted us to investigate the rearrangement in greater detail in the hopes of expanding the scope. Herein, we report the results of our studies on this rearrangement and its application to the synthesis of 2,3-disubstituted indoles.

During the course of our investigation, we first explored the effect of solvents and catalysts on a typical reaction of phenylhydrazine (**1**) with cyclohexanecarboxaldehyde (**2a**). We were interested in the potential effects on the rearrangement of the indolenine intermediate (**3a**) and the subsequent formation of indole product **4a** (Table 1). A typical experiment was performed by heating a mixture of **1** and **2a** in a solvent at 60 °C for 30 min followed by elevating the temperature to 110 °C for 6 h in the presence of a catalyst. Close monitoring of the reaction showed that with all solvents studied, the hydrazone intermediate was formed rapidly at room temperature. In most cases, Fischer indole reaction was complete or proceeded to a great extent to give indolenine **3a** after 30 min at 60 °C. Running this reaction under mildly acidic conditions (AcOH), a typical procedure for facile Fischer indole reactions,[4,5] afforded clean formation of indolenine **3a**, although the rearrangement was sluggish (entry 1, Table 1). Stronger acids, such as TFA and HCl, were utilized as catalysts to potentially accelerate the

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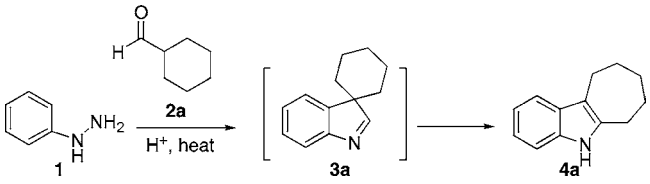
Table 1. Effects of Solvents and Acid Catalysts on Rearrangement of 3,3-Disubstituted Indolenine[a]



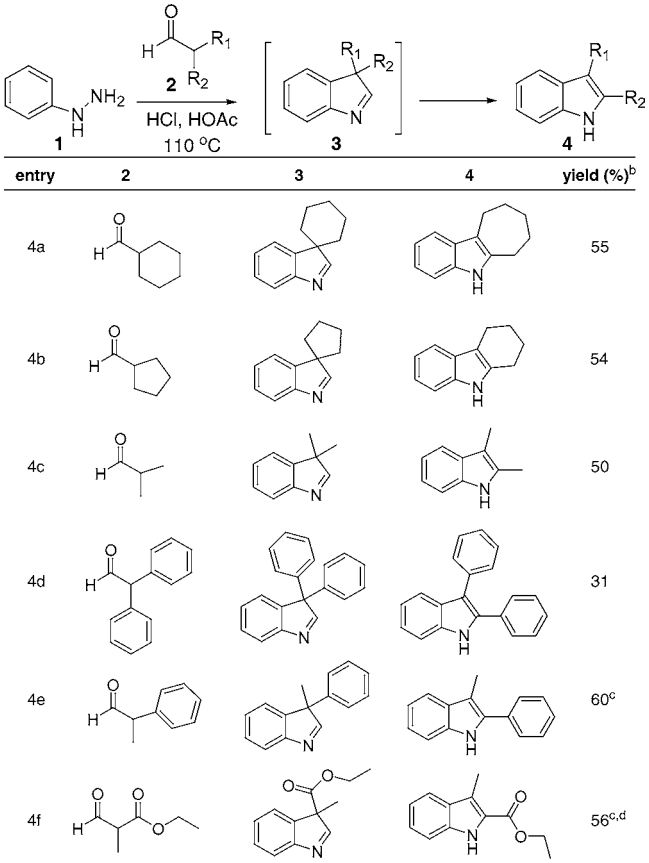
entry	solvent	catalyst	equiv	ratio (**3a**:**4a**)[b]
1	AcOH			30:70
2	AcOH	TFA	1.0	15:85
3	AcOH	HCl	1.0	0:100
4	AcOH	HCl	2.0	0:100
5	AcOH	$ZnCl_2$	1.0	100:0
6	AcOH	H_2SO_4	1.0	multiple products
7	AcOH	MsOH	1.0	0:100
8	toluene	HCl	1.0	87:13
9	toluene	HCl	2.0	0:100
10	toluene	TFA	1.0	97:3
11	toluene	$ZnCl_2$	2.0	hydrazone
12	toluene	H_2SO_4	0.5	multiple products
13	toluene	MsOH	1.0	63:37
14	toluene	MsOH	2.0	100:0
15	EtOH	HCl	1.0	95:5
16	1,4-dioxane	HCl	1.0	95:5
17	n-BuOH	HCl	1.0	multiple products
18	DMA	HCl	1.0	multiple products
19	$HO(CH_2)_2OH$	HCl	1.0	multiple products

[a] Reaction conditions: **1** (1.68 mmol), **2a** (1.68 mmol), solvent (16.8 mL), 110 °C, 6 h. [b] Ratio (**3a**:**4a**) determined by LC-MS based on peak integration at 254 nm.

reaction. While TFA had a modest effect on the reaction rate, addition of 1−2 equiv of HCl greatly facilitated the transformation of **3a** to **4a** at 110 °C (entries 2−4, Table 1). Several other acid catalysts including $ZnCl_2$, H_2SO_4, and methanesulfonic acid were also explored with AcOH as the solvent, and only methanesulfonic acid proved equal to the effects of HCl (entries 5−7, Table 1). Our investigation of alternate solvents looked at the effects of nonacidic solvents with addition of the various acid catalysts as before (entries 8−19, Table 1). In all instances these conditions were inferior to the AcOH protocol and gave either reduced reaction rates or mixtures containing a multitude of undesired products.

With the optimal reaction protocol in place we then sought to investigate and possibly expand the scope of the rearrangement. A variety of aldehyde substrates including acyclic and unsymmetrical α-branchedaldehydes were examined and are listed in Table 2. The rearrangement proceeded well with both cyclic and acylic aldehyde substrates (entries 4a−4d) affording products in moderate to good yields. Somewhat to our surprise, in the cases of 2-phenylpropionaldehyde and 2-formylpropionic acid ethyl ester (entries 4e and 4f, Table 2), the respective phenyl or carbonyl moieties migrated exclusively to provide a single regioisomer. The proposed mechanism for the rearrangement is depicted in Scheme 2. In this hypothesis, the rearrangement occurs through a cationic intermediate that upon aromatization provides the indole product. The exclusive and somewhat unanticipated migration of the phenyl group, rather than the methyl group (entry 4e, Table 2), suggests that stabilization of the carbocation is not the determining factor in deciding the migratory aptitude in this instance. This regiospecific migration may be facilitated by formation of a $\pi-\pi$ electronic interaction between these groups and the imine C=N bond.

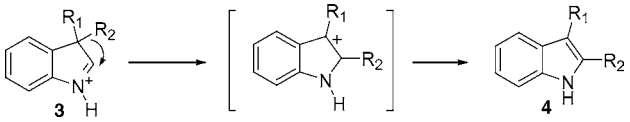
Table 2. Rearrangement of a Variety of 3,3-Disubstituted Indolenines to Yield 2,3-substituted Indoles[a]



[a] Reaction conditions: **1** (1.68 mmol), **2** (1.68 mmol), 4 N HCl in dioxane (1.68 mmol, 0.42 mL), HOAc (16.8 mL), 110 °C, 6 h. [b] Yields are isolated yields after chromatography. [c] Only one isomer was obtained, and structures were determined by 2-D NMR. [d] Combined yield of ester and hydrolyzed acid products.

In summary, we have studied the rearrangement of 3,3-disubstituted indolenines by exploring a number of catalysts and solvents and further examined the scope of the rearrangement by expanding it to include acyclic systems. This rearrangement provides an alternative method to the traditional Fischer indole synthesis and can afford products in a

Scheme 2



more regiospecific manner. The application of this rearrangement to the syntheses of pharmaceutically interesting compounds is currently under investigation.

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Supporting Information Available: Spectral data for all final compounds along with detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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