



# A practical one-pot synthesis of 2,3-disubstituted indoles from unactivated anilines

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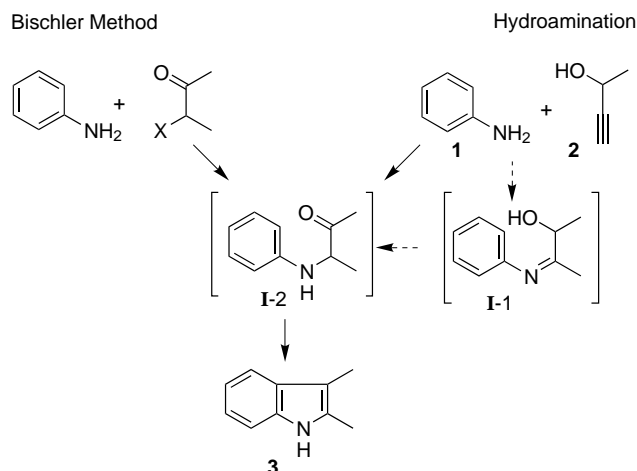
**Abstract**—2-Substituted-3-methyl indoles are synthesized with good regioselectivity from readily available substrates and catalysts, i.e. the reaction of anilines with propargyl alcohols in the presence of 0.36–1 mol% Ru<sub>3</sub>(CO)<sub>12</sub>. © 2001 Elsevier Science Ltd. All rights reserved.

The indole skeleton is an important element in many pharmacologically active compounds and there is still a strong demand for a versatile, efficient, and regioselective synthesis.<sup>1</sup> The classical Fischer indole synthesis<sup>2</sup> has been used for more than 100 years and is the most common and versatile method known, but has difficulties associated with the use of arylhydrazine precursors to produce an arylhydrazone intermediate. Recently, this precursor has been elegantly bypassed by a palladium-catalyzed method that furnishes arylhydrazones directly.<sup>3</sup> On the other hand, the equally classical Bischler<sup>4,5</sup> indole synthesis, i.e. the reaction of aniline with  $\alpha$ -haloketones, has only been used in limited cases,<sup>6</sup> probably due to the low accessibility of  $\alpha$ -haloketones.<sup>7</sup> Concerning the aniline part, however, the Bischler synthesis does not require anilines with an *o*-functional group, e.g. a parent aniline can be used. In many other approaches to indoles,<sup>8</sup> *o*-functionalized anilines have frequently been applied. For example, *o*-haloanilines are inevitable reagents or precursors in the palladium-catalyzed cross-coupling synthesis of indoles.<sup>8e–h</sup> The purpose of the present study was to develop a new Bischler-type indole synthesis that would avoid the use of haloketones, thereby making it a halogen-free, versatile, practical process for the preparation of 2,3-disubstituted indoles.

The reaction is based on the intermolecular addition of anilines to terminal alkynes, which we have recently

developed, and is efficiently catalyzed by a commercially available ruthenium carbonyl/additive mixture.<sup>9,10</sup> Furthermore, the reaction conditions are unique for an organometallic reaction in that it can be carried out *in open air* and basically *without solvent*. We have found that by using propargylalcohol derivatives as the terminal alkyne, the Bischler intermediate (**I-2** in Scheme 1) is readily formed via isomerization of the hydroamination product (**I-1**).

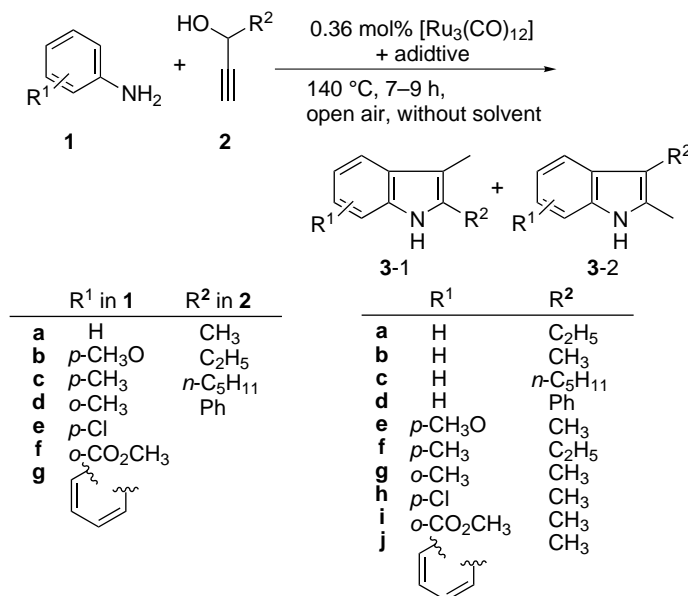
Thus, the one-pot reaction of aniline (**1a**, Scheme 2) with 1-pentyn-3-ol (**2b**) was found to give two isomeric



Scheme 1.

**Keywords:** indoles; anilines; propargyl alcohols; ruthenium complexes; hydroamination.

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Scheme 2.

indoles **3a-1** and **3a-2** in good yield under the standard reaction conditions at 140°C and by using NH<sub>4</sub>PF<sub>6</sub> as the additive or co-catalyst (Table 1, entry 1).<sup>11,12</sup> Aniline hydrochloride **1a**·HCl (Table 1, entry 2) is a less-effective additive for indole formation than NH<sub>4</sub>PF<sub>6</sub>. However, by using a larger amount, at least a 20-fold excess of **1a**·HCl versus Ru<sub>3</sub>(CO)<sub>12</sub>, indoles are produced in good yield (Table 1, entries 3 and 4). Moreover, reactions with **1a**·HCl as the additive result in better regioselectivities (**3a-1/3a-2**: 9.2 and 8.7 in Table 1, entries 3 and 4, versus 6.1 in entry 1). The use of a 1.3 molar excess of **2** rather than the calculated molar amount improves the yield (Table 1, entry 5).<sup>13</sup>

A variety of substituents on the aniline ring have been examined: *p*-methoxy (**1b**), *p*-methyl (**1c**), *o*-methyl (**1d**), and *p*-chloro (**1e**) anilines, and 1-naphthylamine (**1g**) all gave the corresponding indoles in good yields (Table 1, entries 9–12 and 14), while the reaction was very slow with *o*-methoxycarbonyl aniline (**1f**) (Table 1, entry 13). Obviously, anilines with electron-donating groups react more smoothly than those with electron-withdrawing groups, in accordance with the tendency known in the Bischler synthesis.<sup>5,14</sup> The reaction does not require solvents in general, but ethylene glycol may be used when the reaction mixture becomes too viscous (Table 1, entries 11, 12, and 14).

Table 1. Synthesis of 2,3-disubstituted indoles **3** from **1** and **2**<sup>a</sup>

Entry	<b>1</b>	<b>2</b>	Additive	<b>1</b> /Additive/ <b>2</b> (mmol)	<b>3</b>	Yield (%)	<b>3-1/3-2</b>
1	<b>1a</b>	<b>2b</b>	NH <sub>4</sub> PF <sub>6</sub>	7/0.25/7	<b>3a</b>	75	6.1/1
2	<b>1a</b>	<b>2b</b>	<b>1a</b> ·HCl	6.75/0.25/7	<b>3a</b>	<5	–
3	<b>1a</b>	<b>2b</b>	<b>1a</b> ·HCl	6.5/0.5/7	<b>3a</b>	71	9.2/1
4	<b>1a</b>	<b>2b</b>	<b>1a</b> ·HCl	6/1/7	<b>3a</b>	76	8.7/1
5	<b>1a</b>	<b>2b</b>	<b>1a</b> ·HCl	6/1/9	<b>3a</b>	95	9.3/1
6	<b>1a</b>	<b>2a</b>	<b>1a</b> ·HCl	6/1/9	<b>3b</b>	90	
7	<b>1a</b>	<b>2c</b>	<b>1a</b> ·HCl	6/1/9	<b>3c</b>	75	11/1
8	<b>1a</b>	<b>2d</b>	<b>1a</b> ·HCl	6/1/9	<b>3d</b>	72	16/1
9	<b>1b</b>	<b>2a</b>	<b>1b</b> ·HCl	6/1/9	<b>3e</b>	89	
10	<b>1c</b>	<b>2b</b>	<b>1c</b> ·HCl	6/1/9	<b>3f</b>	97 <sup>b</sup>	8.4/1
11 <sup>c,d</sup>	<b>1d</b>	<b>2a</b>	NH <sub>4</sub> PF <sub>6</sub>	7/0.75/9	<b>3g</b>	91	
12 <sup>c,e</sup>	<b>1e</b>	<b>2a</b>	NH <sub>4</sub> PF <sub>6</sub>	5/0.75/7	<b>3h</b>	80	
13 <sup>f</sup>	<b>1f</b>	<b>2a</b>	NH <sub>4</sub> PF <sub>6</sub>	7/0.7/9	<b>3i</b>	5	
14 <sup>c,g</sup>	<b>1g</b> <sup>h</sup>	<b>2a</b>	NH <sub>4</sub> PF <sub>6</sub>	7/0.7/9	<b>3j</b>	82	

<sup>a</sup> For reaction conditions, see Scheme 2.

<sup>b</sup> Yield of crude product.

<sup>c</sup> Ethylene glycol was used as the solvent.

<sup>d</sup> 17 h.

<sup>e</sup> 0.5 mol% catalyst was used.

<sup>f</sup> 1.0 mol% catalyst was used, 23 h.

<sup>g</sup> 20 h.

<sup>h</sup> 1-Naphthylamine.

<sup>i</sup> 2,3-Dimethylbenzylindole.

**Table 2.** Formation of indoles from a 1:1 mixture of **I-1** and **I-2**

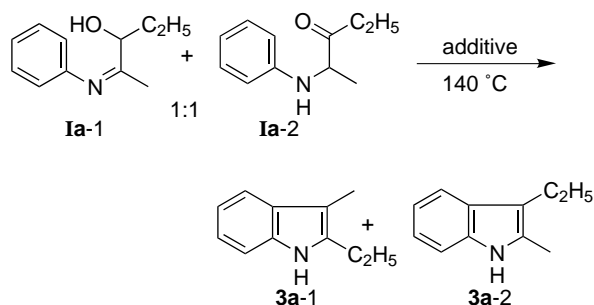
Entry	Additive	Equiv.	Time (min)	Yield (%)	<b>3a-1/3a-2</b>
1 <sup>a</sup>	<b>1a</b> ·HCl	1.0	5	90	8.6/1
2 <sup>b</sup>	<b>1a</b> ·HCl	1.0	5	87	4.2/1
3 <sup>b</sup>	<b>1a</b> ·HCl	0.1	210	86	3.6/1
4 <sup>b</sup>	<b>1a</b> ·HCl <sup>c</sup>	0.1	210	80	3.6/1
5 <sup>b</sup>	2,6-(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> NH <sub>2</sub> ·HCl	1.0	90	65	4.5/1
6 <sup>b</sup>	<b>1c</b> ·HCl	1.0	10	97 <sup>d</sup>	4.2/1 <sup>d</sup>

<sup>a</sup> Aniline was used as the solvent.

<sup>b</sup> Ethylene glycol was used as the solvent.

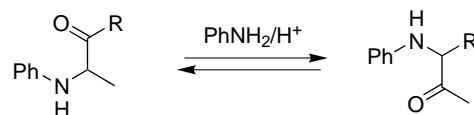
<sup>c</sup> In the presence of 0.36 mol% [Ru<sub>3</sub>(CO)<sub>12</sub>].

<sup>d</sup> A 1:1 mixture of **3f** and **3a** was formed and both have the same **3-1/3-2** ratio of 4.2/1.

**Scheme 3.**

All of the secondary propargyl alcohols examined (**2a–d**, R<sup>2</sup>=alkyl or aryl) gave high yields of the desired products, and the best regioselectivity (**3d-1/3d-2**: 16) was observed with 1-phenyl-2-propyne-1-ol (**2d**) (Table 1, entry 8).<sup>15</sup> When the parent propargyl alcohol (R<sup>2</sup>=H) was used, however, the reaction mixture resulted in an untidy solution, probably due to side reactions of the unstable **I-2**-type formylaniline intermediate, and eventually gave a ca. 1:1 mixture of 2- and 3-methylindoles in low yield (GC yield ≈10%).

At a lower temperature (100°C), the reaction of **1a** and **2b** with NH<sub>4</sub>PF<sub>6</sub> as the additive gave the expected intermediates **Ia-1** and **Ia-2** in a ca. 3:7 ratio in the crude mixture, as confirmed by NMR spectra. Purification of this mixture by silica-gel column chromatography yielded a pure fraction with a **I-1/I-2** ratio of 1. Starting from this 1:1 mixture of **Ia-1** and **Ia-2**, cyclization to **3a-1** and **3a-2** (Scheme 3) was examined at 140°C in the presence of different additives (Table 2).<sup>16</sup> The formation of indoles **3a** proceeded readily with 1.0 equiv. of aniline hydrochloride (**1a**·HCl), so that the reaction was completed in 5 min (Table 2, entries 1 and 2), to give the indole with a total yield and **3-1/3-2** ratio similar to those in the one-pot synthesis (cf. Table 1, entry 4). Therefore, it is very likely that the metal does not participate in hydrogen migration (**I-1** to **I-2**) or cyclization in the original one-pot synthesis, but participates only in the first hydroamination step to form **I-1**. A considerably longer reaction time was necessary when a catalytic amount of **1a**·HCl (0.1 equiv.) was added, but the reaction remained clean (Table 2, entry 3). As expected, addition of 0.36 mol% of Ru<sub>3</sub>(CO)<sub>12</sub> (Table 2, entry 4) did not produce any change from

**Scheme 4.**

entry 3. The observation that the hydrochloride of the bulky aniline, 2,6-(CH<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>NH<sub>2</sub>·HCl, effects indole formation much more slowly (Table 2, entry 5) than **1a**·HCl does (Table 2, entry 2) suggests that the aniline part is involved in indole core formation. Indeed, the reaction with 1.0 equiv. of *p*-toluidine hydrochloride (**1c**·HCl) gave a 1:1 mixture of 5-CH<sub>3</sub> (**3f**)- and 5-H (**3a**)-substituted indoles, and both of these have almost the same **3f-1/3f-2** and **3a-1/3a-2** ratio of 4.2 (Table 2, entry 6).

All of these observations depicted in Table 2 are consistent with the mechanistic studies made on the original Bischler reaction in the 1940s.<sup>5,17</sup> It is known that there is apparent fast interconversion of the regioisomers of aminoketones in the presence of aniline hydrochloride (Scheme 4) so that different aminoketones often give the same indole.<sup>17</sup>

In conclusion, we have developed a highly atom-economical, practical, and regioselective method for the preparation of 2,3-disubstituted indoles, which uses easily accessible, and often commercially available, anilines and propargyl alcohols.<sup>18</sup> This one-pot reaction consists of three steps: hydroamination of the C≡C triple bond, hydrogen migration of the resulting aminoalcohol to aminoketone (to the Bischler-type intermediate), and cyclization to give the indole ring. A detailed mechanism of the reaction, including the role of acid and the reason for the high regioselectivity of the cyclization, is currently under investigation.

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11. In these catalytic hydroamination reactions, a small amount of additive ( $\text{NH}_4\text{PF}_6$ ) was crucial. See Ref. 9.
12.  $[\text{RuCl}_2(\text{PPh})_3]$  exhibited similar activity on this one-pot indole formation (140°C) whereas it showed low activity for the first amination step (100°C).
13. Typical procedure: A round-bottomed flask was charged with  $[\text{Ru}_3(\text{CO})_{12}]$  (16.0 mg, 0.025 mmol), aniline (559 mg, 6.0 mmol), aniline hydrochloride (129.6 mg, 1.0 mmol), and 3-butyn-2-ol (631 mg, 9.0 mmol) and was then stirred at 140°C for 8 h. After cooling, the product was separated by silica-gel column chromatography (hexane- $\text{CH}_2\text{Cl}_2$ , 4:1 then 1:1). Special care does not need to be taken to remove air and moisture from the system. In the case of solid substrate, ethylene glycol was used as the solvent. When the reaction gave a mixture of two regioisomeric indoles, crude product was isolated to determine its ratio by  $^{13}\text{C}$  NMR (NNE mode; gated decoupling without NOE), representative signal:  $\delta$  8.0–9.7 (3-Me), 10.6–11.7 (2-Me).
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