



# Synthesis of 2-(9*H*-carbazol-1-yl)anilines from 2,3'-biindolyl and ketones

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## ABSTRACT

Twenty-nine examples of 2-(9*H*-carbazol-1-yl)anilines were obtained in yields from 27 to 95% by refluxing 2,3'-biindolyl (1 equiv.) and ketones (1 equiv.) in ethanolic HCl. Alkyl, cyclic, and aryl ketones were found to be compatible with this method, however, aldehydes are not. Because the reaction proceeds by addition of the carbonyl C atom to the biindolyl 3-position, this method has high regioselectivity. One example is presented of bridging the two N atoms in the carbazolyaniline product with an acetaldehyde synthon to give a benzodiazepino[*lm*]carbazole. Also, one example is given of installing a dimethylamino group at the  $\alpha$ -position of the starting ketone to give an indolo[3,2-*c*]carbazole.

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## 1. Introduction

Carbazoles are heterocyclic compounds that are commonly observed in naturally occurring alkaloids<sup>1</sup> and synthetic derivatives, many of which show a wide range of biological activities including anticancer and antitumor,<sup>2</sup> anti-inflammatory,<sup>3</sup> antibacterial,<sup>4</sup> anti-oxidative,<sup>5</sup> and neuroprotective properties,<sup>6</sup> among others.<sup>7</sup> Carbazoles also have potential applications in optoelectronic materials,<sup>8</sup> polymers,<sup>9</sup> and synthetic dyes.<sup>10</sup> Hence, carbazoles have maintained the interest of the chemistry community, and synthetic strategies continue to be developed for accessing new carbazole derivatives with good regioselective control. Transition-metal-catalyzed syntheses of carbazoles have been extensively explored to accomplish such objectives.<sup>11</sup>

Several examples of transition-metal-free carbazole syntheses have also been reported. These include a modified Fischer-Borsche carbazole synthesis (Scheme 1a),<sup>12</sup> an intramolecular electrophilic amination of arene C–H bonds (Scheme 1b),<sup>13</sup> an intramolecular dehydrogenative annulation using iodine (III) reagents (Scheme 1c),<sup>14</sup> and a Diels-Alder-oxidation cascade (Scheme 1d).<sup>15</sup> Collectively, these four examples cover a wide range of carbazoles. However, the first three examples have limited control over

regioselection due to multiple annulation possibilities, the second example is limited to functional groups that don't interfere with magnesium transmetalation, and the last two examples require substitution at the carbazole N atom.

Past reports have shown that 2,3'-biindolyl **3** is a versatile building block for synthesis of cycloheptadiindoles, indolocarbazoles, and related aza analogs.<sup>16,17</sup> Here, we disclose access to 2-(9*H*-carbazol-1-yl)anilines *via* cyclizative condensation of **3** with alkyl, cyclic, and aryl ketones under metal- and oxidant-free conditions.

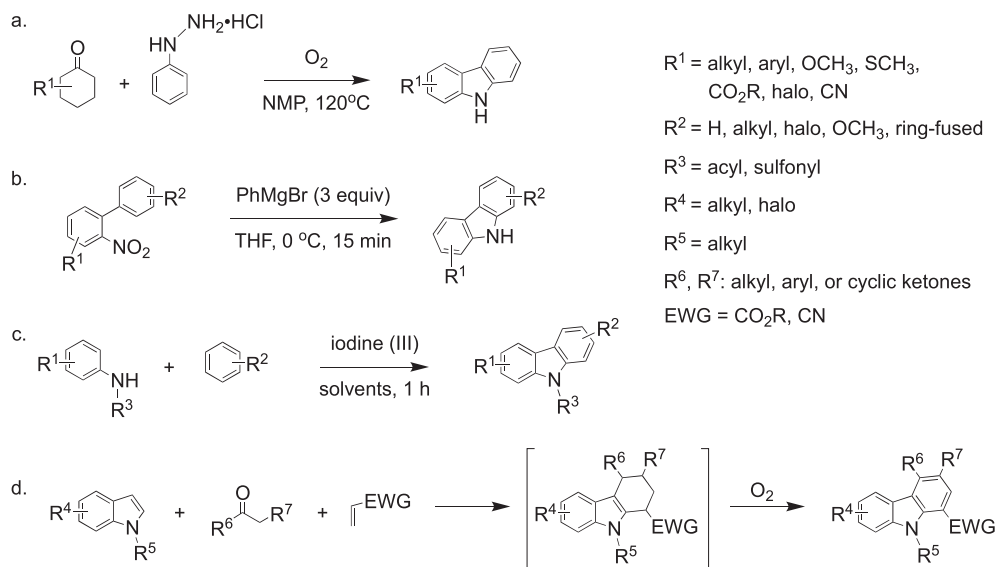
## 2. Results and discussion

Compound **3** was prepared according to the literature<sup>16a</sup> by the dimerization of indole **1** in anhydrous hydrochloric ether, followed by palladium-catalyzed dehydrogenation of dimer **2** in refluxing toluene in 65% overall yield (Scheme 2a). Compound **3** has also been prepared in metal-free conditions, by the addition bromine to a solution of **1** in acetonitrile in 80% yield (Scheme 2b).<sup>18</sup>

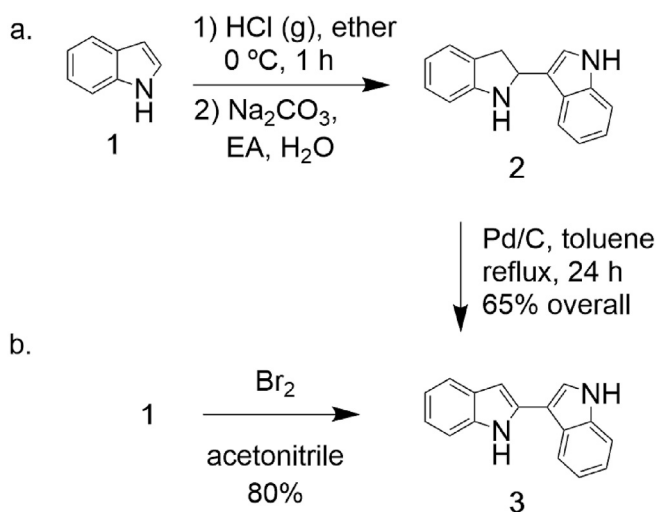
Based on previous work in our laboratories,<sup>19</sup> refluxing ethanolic hydrochloric acid was a reasonable starting point for the optimization of reaction conditions (Table 1, entry 1). Cyclohexanone **4e** was chosen as the test substrate, because of its low cost and good behavior in preliminary trials. Among the different acid and solvent mixtures attempted, hydrochloric acid in refluxing ethanol or acetonitrile (Table 1, entries 1–2) gave the highest yields of **5e**, 88

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Scheme 1. Selected transition-metal-free syntheses of substituted carbazoles.



Scheme 2. The preparation of **3** from **1** via (a) acid-catalyzed dimerization and then dehydrogenation; (b) bromine-promoted oxidative dimerization of **1**.

and 91% respectively, and the lowest yields of side products. *p*-TsOH and TFA gave mixtures of **5e** with **6e** and **7e** (Table 1, entries 3–11), while dilute AcOH was too mild (Table 1, entries 12–15). The original condition (Table 1, entry 1) was chosen as the optimized condition because of much faster conversion of **3** into **5e** versus use of acetonitrile, with a minimal loss of yield.

A selection of 30 alkyl, cyclic, aryl, and heterocyclic ketones were exposed to the optimized conditions on a gram scale or larger (Scheme 3). Alkyl ketones **4a–c** required relatively long reaction times compared to the other types of ketone. For cyclic ketones, ring sizes 5–8 **4d–g** performed better than alkyl ketones. The larger ring sizes **4h–k** reacted more slowly. Cyclobutanone **8** gave an inseparable, tarry mixture.

Monosubstituted acetophenones with electron-donating substituents (*i.e.*, **4m** and **4p**) gave lower yields than those with electron-withdrawing substituents (*i.e.*, **4q** and **4r**), or **4n**, which probably is protonated in solution. The use of propiophenone **4s** gave slightly lower yield than that of acetophenone **4l**, but interestingly outperformed 4-methylacetophenone **4m**.

Multisubstituted acetophenones **4t** and **4u** both gave comparatively high yields. The yields from heteroaryl ketones **4v** and **4x–z** were near the middle of the aryl ketone range. In spite of being electron-deficient, 2-acetylpyridine **4w** gave a low yield. Neither aryl ketones 2-acetyl-*N*-methylpyrrole **9** and 3-acetylidole **10**, nor hindered 3,3-dimethyl-2-butanone **11** gave any identifiable products. Several alkyl aldehydes were also tried, giving complex, tarry mixtures that were not explored further.

The easiest method of isolating products **5a–z** from the reaction mixtures was to first obtain the corresponding hydrochloride salts by removing the ethanol at reduced pressure. Trituration of the resulting residue with ether removed most of the leftover ketone, except for **4n**, which was highly persistent, before and after neutralization or chromatography. The resulting residues were neutralized with a biphasic mixture of ethyl acetate and aqueous sodium carbonate, followed by separation by column chromatography. For many of the methyl aryl ketone-derived products **5l–w**, residual solvents could not be removed completely.

The preceding ketones are either symmetrical (Scheme 4a) or have one quaternized  $\alpha$ -position (Scheme 4b), allowing only one regioisomer of type **5** products to form. To test the regioselectivity of this method, 2-pentanone **12** was allowed to condense with **3** (Scheme 4c). Products **13** and **14** were obtained as a 15:1 mixture, which could not be resolved by flash chromatography nor fractional crystallization. The major product is the more highly substituted carbazole **13**.

In two examples, plain biindolyl **3** was replaced by substituted biindolyls, **16** and **19** (Scheme 5). Compound **16** was prepared from 5-methoxyindole **15** by the same sequence used to prepare **3**.<sup>16a</sup> For compound **19**, the dehydrogenation was replaced by oxidation by DDQ, because complications were encountered that were probably derived from oxidative addition of the aryl bromide to palladium. Although the yields of substituted biindolyls **16** and **19** were substantially lower than the yield of **3**, the cyclizative condensation portion of the synthesis gave products **17e** in 89% yield, higher than **4e** condensing with **3** (84%). Product **20e** was obtained in somewhat lower yield (59%), indicating that this method could be most compatible with electron-rich or electron-neutral biindolyls.

The aforementioned work was inspired by previous work in our laboratory, in which condensation reactions of indole **1** with cyclic ketones in the presence of Brønsted acids were explored.<sup>19</sup> The

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