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COMMUNICATION

Transition-Metal-Free Synthesis of Carbazoles and Indoles via S\textsubscript{N}Ar-based "Aromatic Metamorphosis" of Thiaarenes

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Dibenzothiophene dioxides, readily prepared through oxidation of the parent dibenzothiophenes, undergo nucleophilic aromatic substitution with anilines intermolecularly and then intramolecularly to yield the corresponding carbazoles in a single operation. The "aromatic metamorphosis" of dibenzothiophenes to carbazoles does not require any heavy metals, thus being useful for organic electronics as well as pharmaceutical industry. This strategy is also applicable to the synthesis of indoles. Since electron-deficient thiaarene dioxides exhibit interesting reactivity that the corresponding electron-rich azaarenes do not, a combination of a thiaarenedioxide-specific reaction with the S\textsubscript{N}Ar-based aromatic metamorphosis allows for transition-metal-free construction of difficult-to-prepare carbazoles.

Carbazoles represent an important class of heteroaromatic compounds, many of which find a wide range of application as biologically active agents in medicinal chemistry\textsuperscript{[1]} and as hole-transport and light-emitting materials in organic electronics.\textsuperscript{[2]}

For the last two decades, transition metal catalysis has attracted attention for constructing a carbazole skeleton via catalytic C-N bond formation, which includes Buchwald-Hartwig or Ullmann-type amination of halobenzyls,\textsuperscript{[3]} oxidative C-H amination of aminobenzyls,\textsuperscript{[4]} or nitrene insertion from azidobenzenes.\textsuperscript{[5]} Despite the high efficiency and reasonably wide scope, residual transition metal impurities could adversely affect the biological properties or device performances of the final products.

Transition-metal-free synthesis of carbazoles has hence undergone a renaissance for the last few years (Scheme 1). Knochel disclosed that halogen-magnesium exchange of 2-iodo-2'-triazenidoaryl resulted in formation of carbazoles.\textsuperscript{[6]} Chang and Antochnich reported intramolecular oxidative C-H amination of aminobenzyls with hypervalent iodine reagents.\textsuperscript{[7]} Studer invented an interesting approach, i.e. reactions of arynes with nitrosoarenes,\textsuperscript{[8]} although the yields were moderate and the regioselectivity were not well controlled as typically observed in arylene chemistry. Tokuyama developed base-mediated cyclization of 2-amino-2'-bromobiphenyls via arynes.\textsuperscript{[9]} From similar precursors, photoinduced cyclization occurs via a radical process to yield carbazoles.\textsuperscript{[10]} Kürti disclosed facile reductive cyclization of 2-nitroaryls by means of PhMgBr.\textsuperscript{[11]} Regardless of these elegant protocols, there still remains ample room to develop novel strategies to prepare carbazoles without recourse to transition metal catalysts.

Recently, our group has been interested in developing "aromatic metamorphosis", which represents a transformation of an aromatic system to a different one through partial disassembly of the starting aromatic ring.\textsuperscript{[12-14]} Along this line, here we report transition-metal-free S\textsubscript{N}Ar-based aromatic metamorphosis of dibenzothiophenes to carbazoles via dibenzothiophene dioxides.

Our strategy begins with smooth oxidation of dibenzothiophenes with aqueous hydrogen peroxide (see Supporting Information (SI)).\textsuperscript{[15]} This conventional process is useful as the first step of the aromatic metamorphosis.

Although aryl sulfones are known to undergo S\textsubscript{N}Ar reactions, the scope of the substitution is limited.\textsuperscript{[16-19]} Another difficulty should originate from the second intramolecular S\textsubscript{N}Ar reaction that would involve formal elimination of $K_{SO}$ of high energy.\textsuperscript{[20]} The realization of the second, and the last step, sequential inter/intramolecular nucleophilic aromatic substitution, hence required screening of reaction conditions. We selected the reaction of dibenzo[b,df]thiophene 5,5-dioxide (1a) with $p$-toluidine (2a) as a model reaction for optimization (eq. 1). The reaction of 1a (1.0 equiv) with 2a (2.0 equiv) by means of lithium hexamethyldisilazide (3.0 equiv) in dioxane at $80 ^\circ C$ for 16 h did not produce the desired carbazole 3a. Interestingly, 3a was obtained in 50% yield when NaN(SiMe$_3$)$_2$ was employed. To our delight, KN(SiMe$_3$)$_2$ (potassium hexamethyldisilazide, KHMD, 0.5 M toluene solution) gave the best result to isolate 3a in 94% yield. Other potassium bases such as K$_2$CO$_3$, K$_3$PO$_4$, KOAc, and KOBu were totally ineffective. Dioxane has proved to be the best co-solvent with toluene from KHMD. The reactions in 1,2-dimethoxyethane/toluene and in toluene as a sole solvent delivered 3a in 91% and 61% yields, respectively. Reducing the amount of 2a or KHMD led to lower yields of 3a.
With the optimized conditions in hands, the scope of amines was examined (Table 1). The reactions proceeded efficiently with electron-rich or neutral amines to yield 3b–l in high yields. The vinyl functionality was tolerated under the reaction conditions to afford 3l in moderate yield. TIPS protection of 2g partly survived under the reaction conditions to yield a mixture of protected 3g and unprotected 3h quantitatively in 1:2.6 ratio. Unfortunately, unprotected p-aminophenol (2h) reacted sluggishly. Despite its steric hindrance, mesitylamine (2i) participated in the reaction to give 3i in high yield. Moderately electron-withdrawing halo groups retarded the reaction as well as partly underwent dehalogenation. The reaction with 4-chloroaniline (2m) yielded a 4:1 mixture of desired 3m and hydrodechlorinated byproduct 3b in 64% yield. The fluoro analog 2n was less reactive to afford 3n in 30% yield, and the fluoro group was partly substituted with 2n via an S,S,Ar reaction to yield N-(4-(9-carbazolyl)phenyl)-4-fluoroaniline (3n) as a byproduct. Alkylamines such as p-methoxybenzylamine reacted moderately (34% yield with p-methoxybenzylamine in 18 h), possibly due to the less acidic NH protons. Attempted phenylation of carbazole with diphenyl sulfoxide under similar conditions resulted in no conversion probably because of the lower nucleophilicity of potassium carbazolide.

Table 1. Scope of amines

<table>
<thead>
<tr>
<th>R</th>
<th>time [h]</th>
<th>3</th>
<th>yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>24</td>
<td>3b</td>
<td>77</td>
</tr>
<tr>
<td>4-MeO</td>
<td>16</td>
<td>3c</td>
<td>94</td>
</tr>
<tr>
<td>4-Bu</td>
<td>16</td>
<td>3d</td>
<td>92</td>
</tr>
<tr>
<td>4-MeN</td>
<td>17</td>
<td>3e</td>
<td>91</td>
</tr>
<tr>
<td>4-CH2=CH</td>
<td>17</td>
<td>3f</td>
<td>60</td>
</tr>
<tr>
<td>4-TIPS</td>
<td>17</td>
<td>3g</td>
<td>28 (72%)</td>
</tr>
<tr>
<td>4-HO</td>
<td>24</td>
<td>3h</td>
<td>26(3)</td>
</tr>
<tr>
<td>3-MeO</td>
<td>16</td>
<td>3i</td>
<td>70</td>
</tr>
<tr>
<td>3,5-Bu</td>
<td>17</td>
<td>3j</td>
<td>98</td>
</tr>
<tr>
<td>3,4-OCH3</td>
<td>17</td>
<td>3k</td>
<td>65</td>
</tr>
<tr>
<td>2,4,6-Me3</td>
<td>16</td>
<td>3l</td>
<td>67</td>
</tr>
<tr>
<td>4-Cl</td>
<td>18</td>
<td>3m</td>
<td>51 (13%)</td>
</tr>
</tbody>
</table>

[4-F] The yield of 3h as a byproduct. [b] Dioxane (6.0 mL), 100 °C. [c] The yield of 3b as a byproduct. [d] 2.0 equiv of KHMD. [e] The yield of 3n as a byproduct.

The scope of dibenzothiophene dioxide derivatives is wide (Chart 1). Substituted or π-extended carbazoles were obtained efficiently. Gratifyingly, sterically demanding 4d was obtained in high yield. The reactions of substrates bearing bromo or methoxy groups gave slightly complex mixtures to isolate 4h or 4i in moderate yield. Notably, we could synthesize 2,7-diphenyl-9-p-tolylicarbazoles (4c) in a controlled manner. While electron-rich dibenzothiophene as well as carbazole undergoes electrophilic bromination at the 3,6-positions with exclusive regioselectivity, dibenzothiophene dioxide is electron-deficient to deliver the 2,7-dibromo product (Scheme 2).[15a,22] By changing the oxidation state of sulfur, we could hence alter the positions of substituents in the final carbazoles 4c and 4d.[21]

Benzene-1,4-diamine reacted with 1a smoothly to afford bis(carbazolyl)benzene (5), an important structural unit that has found diverse applications in electronic devices.[23] (eq 2). Usually, bis(carbazolyl)benzenes were obtained in moderate...
yields through palladium-catalyzed or copper-mediated reactions of 1,4-dihalobenzene with carbazole at 170–200 °C.

\[
\text{H}_2\text{N-} \xrightarrow{4.0 \text{ equiv } 1a} \xrightarrow{6.0 \text{ equiv } \text{KHMDS}} \text{N}\text{-} \xrightarrow{100 \text{ °C, } 68 \text{ h}} \text{N} \quad (2)
\]

Scheme 2. Amination of isobenzofuran

Our S$_2$Ar-based amination was applicable to the synthesis of indoles (Scheme 3). Although 2,3-diaryl groups are necessary to avoid undesired conjugate addition onto the vinyl sulfoxide unit, densely arylated indoles 7a–d$^{[21]}$ were formed in excellent yields. The reaction of 6 with 4-(9-carbazolyl)aniline (2o) yielded an unsymmetric indole-carbazole hybrid 7d, which will find applications in organic EL.$^{[24]}$

\[
\text{Ar} \quad 2.0 \text{ equiv } 2a \\
\xrightarrow{3.0 \text{ equiv KHMDS}} \text{dioxane/toluene, 80 °C} \\
\xrightarrow{\text{p-tolyl}} \quad 89\% (20 \text{ h}) \\
\text{Ar} \quad 90\% (20 \text{ h}) \\
\text{2-naphthyl} (7c) \quad 97\% (24 \text{ h}) \\
\quad p = \text{p-tolyl}
\]

Scheme 3. S$_2$Ar-based synthesis of indoles

Electron-deficient benzo thiophene dioxide 8 showed uniquely high reactivity as a dienophile in the Diels-Alder reaction with isobenzofuran 9a$^{[20]}$ whereas indoles do not react with 9a. Taking advantage of the Diels-Alder reaction, we could extend \( \pi \)-conjugation to form benzonaphthothiophene dioxide 10 (Scheme 4). Eventually, \( \pi \)-extended benzocarbazole 11 was obtained in good overall yield from commercially available 8.

\[
\text{Ph} + \quad \text{toluene, reflux, then } p = \text{p-TsOH, reflux ref } [25] \\
\xrightarrow{4.0 \text{ equiv } 2a} \xrightarrow{3.0 \text{ equiv KHMDS}} \text{dioxane/toluene} \\
\xrightarrow{80 °C, 19 h} \quad \text{Me} \quad 65\%
\]

Scheme 4. Sequential Diels-Alder reaction/carbazole formation

We applied this Diels-Alder-based approach to achieve significantly \( \pi \)-extended dibenzoindolo[3,2-b]carbazoles 14 (Scheme 5). The precursor bis sulfone 13 was obtained from rather small aromatic compound 12 in 89% yield. Subsequently, expected quadruple C–N bond formations occurred to give 14d and 14j in 38% and 22% yields, respectively. In comparison with elegant yet burdensome construction of similar dibenzoindolo[3,2-b]carbazoles for OFET devices,$^{[26,27]}$ this overall transformation highlights the synthetic potential of our carbazole synthesis.

Figure 1 shows the UV/visible and fluorescence spectra of 14j in dichloromethane.$^{[23]}$ The lowest energy absorption maximum was observed at 496 nm, which is significantly red shifted compared to typical absorption of indolo[3,2-b]carbazoles (420–440 nm).$^{[20]}$ Compound 14j showed bright green fluorescence that has its intensity maximum at 511 nm with a fluorescence quantum yield of 34%. Our S$_2$Ar-based approach is thus useful to explore \( \pi \)-extended carbazoles that show interesting functions.

The most likely mechanism would be the sequential inter/intramolecular S$_2$Ar reactions with highly nucleophilic potassium amides (Scheme 6). The first intermolecular S$_2$Ar reaction would be faster than the second intramolecular reaction of 15,$^{[30]}$ and the carbazole formation necessitates a high temperature. The following experiments strongly support the mechanism (Scheme 7): 1a reacted with 2a with the aid of KHMDS at room temperature to isolate zwitterionic 16.$^{[21]}$ Subsequent exposure of 16 to KHMDS at 80 °C afforded 3a quantitatively. Although there are several debatable reaction pathways for aromatic substitution of aryl sulfones,$^{[18]}$ the isolation of 16 strongly indicates the intermediacy of 15 and hence the S$_2$Ar pathway in our case.
Figure 1. UV/visible (solid line) and fluorescence (dotted line) spectra of 14j in CH₂Cl₂

Scheme 6. Plausible mechanism

Scheme 7. Elucidation of mechanism

In conclusion, we have reported a new powerful and practical strategy to prepare carbazoles without recourse to transition metal catalysts. Dibenzothiophene dioxide derivatives undergo sequential inter/intramolecular nucleophilic aromatic substitution with anilines with the aid of KHMD to afford a wide range of carbazoles in one shot. Considering that dibenzothiophene dioxides are readily available by oxidation of the parent dibenzothiophenes, one can concisely achieve aromatic metamorphosis of dibenzothiophenes to carbazoles. Since electron-deficient thiophene dioxides exhibit reactivity different from that of the corresponding electron-rich azaharzenes, coupling a thiaarene-dioxide-specific reaction with the S₄Ar carbazole synthesis opens up a new route to easily-access carbazoles. Current efforts are directed toward exploring new aromatic metamorphosis in our laboratory.

Acknowledgements

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Keywords: Nucleophilic aromatic substitution • Amination • Nitrogen heterocycles • Sulfur heterocycles • Aromatic metamorphosis

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[19] Reactive azazulene sulfones such as tetrathiazole sulfones are well known to undergo intermolecular S₄Ar substitution with a variety of nucleophiles. For instance: a) P. J. Kocienski, A. Bell, P. R. Blakemore, Synlett 2000, 365; b) C. Aissa, J. Org. Chem. 2006, 71, 360; c) P. Janowski, K. Plesniak, J. Wicha, Org. Lett. 2003, 5, 2789.
[21] X-ray crystallographic analysis unambiguously revealed the structure. For details, see SI.


[28] The photophysical properties of 14d are very similar to those of 14j. For details, see SI.


[30] The elimination of elusive and high-energy $K_2SO_2$ is unlikely. After many experiments, at this stage we speculate that trimethylsilylation of 15 with $HN(SiMe_3)_2$ generated in situ would take place to afford 15', which should undergo a smoother $S_N$Ar reaction.
Dibenzothiophene dioxides undergo sequential inter- and intramolecular nucleophilic aromatic substitution with anilines to yield the corresponding carbazoles in a single operation. This approach to carbazole needs no heavy metals, thus being useful for organic electronics as well as pharmaceutical industry. Coupling a thiaarene-dioxide-specific reaction with the S_{N}Ar carbazole synthesis allows for construction of uneasy-to-access carbazoles.

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