Synthesis of Highly Substituted Diphenylacetamides and Diphenylsulfonamides by the Goldberg Coupling Reaction

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We report the synthesis and characterisation of multisubstituted diphenylacetamides, diphenylsulfonamides and diphenylamines (and some observations on cyclisation of the last).

In a preliminary paper on the Goldberg coupling reaction of aryl halides with amides the effect of a variety of substituents in the reactants was investigated and it was shown that the yields are markedly susceptible to the presence of electron withdrawing groups in both reactants\textsuperscript{1}. The effect of substituent methyl groups on the reaction yield was not investigated but this could be important if the products such as 1 or 2 were to be used for the synthesis of 1,4-dimethylcarbazoles 3 (scheme 1) as precursors of ellipticines. Until now, carbazoles have been fruitful precursors of ellipticines\textsuperscript{2}. Apart from possible effects on the yields of the coupled products 1 - 2, the 2,5-dimethyl groups could sterically inhibit the cyclisation to carbazoles 3. It is known that, without 2,5-dimethyl substitution, the cyclisation of diphenylamines with palladium (II) acetate can give good yields
of carbazoles. However, to date this route has led to the synthesis, in poor yield, of only two ellipticines 4 and 5.

Miller and Moock obtained ellipticine 4 by cyclisation of 5,8-dimethyl-6-phenylaminoisoquinoline with palladium (II) acetate. In our hands, the diphenylamine 20g was cyclised to the carbazole 3c and this was then converted to ellipticine 5.

We now report the synthesis of a series of multisubstituted diphenylacetamides 1 and diphenylsulfonamides 2 which embody 2,5-dimethyl substituents, thus extending our earlier work.

The diphenylacetamides (1a-f) were prepared by Goldberg coupling, as shown in the table 1. The different effect of substituents in the coupling components on the yields obtained is noteworthy (16-81%).

The 1H NMR spectra of all the diphenylacetamides in CDCl3 at 25°C showed broad overlapping signals due to hindered rotation which were resolved when the spectra were run in DMSO-d6 at 80°C.

Since the diphenylacetamides 1 were potential precursors of the carbazoles 3 we first attempted the alkaline hydrolysis of the former to diphenylamines (20a-f), [KOH/(EtOH/H2O)].

As expected the diphenylacetamides 1d and 1e with electron-withdrawing groups para and three vacant ortho positions to the amide readily hydrolysed to give high yields of diphenylamines (20d, 84%) and (20e, 85%).

With only two vacant ortho positions, however, i.e. 1a and 1b yields were much lower (20a, 28%) and (20b, 20%).

For diphenylacetamide 1c with only two vacant ortho positions and without an electron withdrawing group in the para position, the hydrolysis was even slower, and after 22 h 15 min. only traces (3%) of the amine 20c and much more of unchanged diphenylacetamide 1c (40%) was recovered. Under forcing conditions (NaOH /ethylene glycol) only the product (20f, 19%) was obtained with improved yield, together with the by product (21, 24%).

We also examined the reactivity of sulfonamides in the Goldberg reaction. The yields of coupling of aryl halides to diphenylsulfonamides were generally lower (2-44%) (table 2) than those obtained for analogous reactions with the acetamides. For example the yield of product 2c
from the bromo compound 11 and sulfonamide 22 was significantly lower (44%) than the yield of the diphenylacetamide 1c (81%) (table 1), also obtained from bromocompound 11.

Attempts to convert the diphenylamines 20d and 20e into the corresponding carbazoles 3a and 3b using palladium (II) acetate gave only very low yields of the desired products. Thus the amine 20d gave 10% of the carbazole 3a together with 11% of the by-product 29; M+ 308.1156 (C18H16N2O3). The NMR spectrum of 29 showed only one singlet at δ 2.74 due to the 4-Me group and three 1 H singlets at δ 7.98, 8.39 and 8.84, assignable to the 2-H and to the methylene protons whilst the aromatic proton of ring A (8-H) gave the expected singlet at δ 7.27.

When the cyclisation of amine 20e was attempted, we isolated only 2% of the bromocarbazole 3b with the alternative oxidation product 30 in a yield of 4%. The 1H NMR spectrum of 30 showed a singlet at δ 5.08, due to the CH2OAc group.

It is significant that under similar conditions we were able to cyclise the 2-fluorodiphenylamine18 31, lacking 2,5-dimethyl substitution, to the 1-fluorocarbazole 3219 in 66% yield.

But when the cyclisation of the fluorodiphenylamine 3320 with 2,5-dimethyl substitution was tried, instead of the required carbazole we obtained only the product of oxidation 34 (19%).

This work shows that the Goldberg coupling of aryl bromides gives significantly better yields for diphenylacetamides than for the corresponding sulfonamides. Hydrolysis of the diphenylacetamides to diphenylamines is difficult to achieve if there are two or less vacant positions ortho to the amide group. This may often be the case for diphenylamides with 2,5-dimethyl substitution.

The palladium acetate cyclisation of diphenylamines to carbazoles seems also to be susceptible to steric hindrance. When the diphenylamines are highly substituted a low yield or none of the carbazoles may be obtained. By-products resulting from oxidation of carbazole, such as 29 or from acetoxylation of diphenylamines, such 34, may be formed.

The general route via Goldberg coupling, hydrolysis and cyclisation by palladium acetate or light has led to some carbazole intermediates used in ellipticines synthesis5, 21, 22. However, due to the limitations described in this paper, the sequence cannot be considered as generally useful to obtain new derivatives of ellipticines.
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Techniques used: \(^1\)H-NMR spectroscopy, mass spectrometry, elemental analysis.

References: 22.

Schemes: 18.

Tables: 4.

**References cited in this synopsis**


Tables

Table 1- The yields for diphenylacetamides (1a-f) prepared by Goldberg coupling

<table>
<thead>
<tr>
<th>Acetamide</th>
<th>Bromide</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>11</td>
<td>1a</td>
<td>68</td>
</tr>
<tr>
<td>13</td>
<td>11</td>
<td>1b</td>
<td>44</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>1b</td>
<td>57</td>
</tr>
<tr>
<td>12</td>
<td>11</td>
<td>1c</td>
<td>81</td>
</tr>
<tr>
<td>16</td>
<td>6</td>
<td>1d</td>
<td>32</td>
</tr>
<tr>
<td>16</td>
<td>15</td>
<td>1e</td>
<td>29</td>
</tr>
<tr>
<td>12</td>
<td>17</td>
<td>1f</td>
<td>31</td>
</tr>
<tr>
<td>18</td>
<td>19</td>
<td>1f</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 2- The yields for diphenylsulfonamides (2a-f) prepared by Goldberg coupling

<table>
<thead>
<tr>
<th>Sulfonamide</th>
<th>Bromide</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>11</td>
<td>2a</td>
<td>16</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>2a</td>
<td>14</td>
</tr>
<tr>
<td>26</td>
<td>11</td>
<td>2b</td>
<td>26</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>2b</td>
<td>17</td>
</tr>
<tr>
<td>22</td>
<td>11</td>
<td>2c</td>
<td>44</td>
</tr>
<tr>
<td>27</td>
<td>25</td>
<td>2d</td>
<td>17a</td>
</tr>
<tr>
<td>23</td>
<td>6</td>
<td>2d</td>
<td>31b</td>
</tr>
<tr>
<td>23</td>
<td>15</td>
<td>2e</td>
<td>2c</td>
</tr>
<tr>
<td>26</td>
<td>25</td>
<td>2e</td>
<td>35</td>
</tr>
<tr>
<td>27</td>
<td>17</td>
<td>2f</td>
<td>8d</td>
</tr>
</tbody>
</table>

\( ^a \) By-product 28 (8%) was also obtained.

\( ^b \) The coupling gave only the by-product 24 instead of the sulfonamide 2d

\( ^c \) By-product 24 (1%) was also obtained.

\( ^d \) By-product 28 (9%) was also obtained.
Schemes and figures

Scheme 1

1. $R_1 = R_2 = R_3 = R_4 = \text{OMe or H}$
   $R_5 = \text{Ac, Tos}$
   $R_6 = \text{H, Br, CN}$

2. $R_1 = R_2 = R_3 = R_4 = \text{OMe or H}$
   $R_5 = \text{Tos, H, Br, CN}$

3. $R_1 = R_2 = R_3 = R_4 = \text{OMe or H}$
   $R_5 = \text{H, Br, CN}$

4. $R = \text{H}$

5. $R = \text{OMe}$
1a R¹ = R² = R⁴ = OMe; R³ = H; R⁵ = CN
1b R¹ = R² = R⁴ = OMe; R³ = H; R⁵ = Br
1c R¹ = R² = R⁴ = OMe; R³ = H; R⁵ = H
1d R¹ = R² = R³ = OMe; R⁴ = H; R⁵ = CN
1e R¹ = R² = R³ = OMe; R⁴ = H; R⁵ = Br
1f R³ = R⁴ = OMe; R¹ = R² = H; R⁵ = H

2a R¹ = R² = R⁴ = OMe; R³ = H; R⁵ = CN
2b R¹ = R² = R⁴ = OMe; R³ = H; R⁵ = Br
2c R¹ = R² = R⁴ = OMe; R³ = H; R⁵ = H
2d R¹ = R² = R³ = OMe; R⁴ = H; R⁵ = CN
2e R¹ = R² = R³ = OMe; R⁴ = H; R⁵ = Br
2f R³ = R⁴ = OMe; R¹ = R² = H; R⁵ = CN

20a R¹ = R² = R⁴ = OMe; R³ = H; R⁵ = CN
20b R¹ = R² = R⁴ = OMe; R³ = H; R⁵ = Br
20c R¹ = R² = R⁴ = OMe; R³ = H; R⁵ = H
20d R¹ = R² = R³ = OMe; R⁴ = H; R⁵ = CN
20e R¹ = R² = R³ = OMe; R⁴ = H; R⁵ = Br
20f R³ = R⁴ = OMe; R¹ = R² = R⁵ = H
20g R¹ = R³ = OMe; R² = R⁴ = H; R⁵ = CN
20h R¹ = R² = R³ = H; R⁵ = OH; R³ = OMe

6 R¹ = R⁴ = Me; R² = CN
11 R¹ = R² = R⁴ = OMe; R³ = H
15 R¹ = R⁴ = Me; R² = Br
17 R³ = R⁴ = OMe; R¹ = R² = H
19 R¹ = R⁴ = Me; R² = R³ = H
25 R¹ = R² = R³ = OMe; R⁴ = H

24 NC
28 NC
3a $R^1 = R^2 = R^3 = \text{OME}; \ R^4 = H; \ R^5 = R^6 = \text{Me}; \ R^7 = \text{CN}$
3b $R^1 = R^2 = R^3 = \text{OME}; \ R^4 = H; \ R^5 = R^6 = \text{Me}; \ R^7 = \text{Br}$
3c $R^1 = R^3 = \text{OME}; \ R^2 = R^4 = H; \ R^5 = R^6 = \text{Me}; \ R^7 = \text{CN}$
32 $R^1 = R^2 = R^3 = R^5 = R^6 = R^7 = H; \ R^4 = F$

30 $R^1 = R^2 = R^3 = \text{OME}, \ R^4 = H, \ R^5 = \text{Me}, \ R^6 = \text{CH}_2\text{OCOMe}, \ R^7 = \text{Br}$
31 $R^1 = R^2 = R^3 = R^5 = R^6 = R^7 = H, \ R^4 = F$
33 $R^1 = R^2 = R^3 = R^7 = H, \ R^4 = F, \ R^5 = R^6 = \text{Me}$
34 $R^1 = R^2 = R^3 = R^7 = H, \ R^4 = F, \ R^5 = \text{Me}, \ R^6 = \text{CH}_2\text{OCOMe}$

8 $R^1 = R^2 = R^4 = \text{OME}; \ R^3 = R^5 = H$
9 $R^1 = R^2 = R^4 = \text{OME}; \ R^3 = H; \ R^5 = \text{Tos}$
10 $R^1 = R^2 = R^4 = \text{OME}; \ R^3 = H; \ R^5 = \text{Ac}$
12 $R^1 = R^4 = \text{Me}; \ R^2 = R^3 = H; \ R^5 = \text{Ac}$
13 $R^1 = R^4 = \text{Me}; \ R^2 = \text{Br}; \ R^5 = \text{Ac}$
14 $R^1 = R^4 = \text{Me}; \ R^2 = \text{CN}; \ R^3 = H; \ R^5 = \text{Ac}$
16 $R^1 = R^2 = R^3 = \text{OME}; \ R^4 = H; \ R^5 = \text{Ac}$
18 $R^3 = R^4 = \text{OME}; \ R^1 = R^2 = H; \ R^5 = \text{Ac}$
22 $R^1 = R^4 = \text{Me}; \ R^2 = R^3 = H; \ R^5 = \text{Tos}$
23 $R^1 = R^2 = R^3 = \text{OME}; \ R^4 = H; \ R^5 = \text{Tos}$
26 $R_1 = R_4 = \text{Me}; \ R_2 = \text{Br}; \ R_3 = H; \ R_5 = \text{Tos}$
27 $R_1 = R_4 = \text{Me}; \ R_2 = \text{CN}; \ R_3 = H; \ R_5 = \text{Tos}$