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Synthesis of 3-amino-thiochromanes from 4-benzyl 2-thiazolines, via an unprecedented intramolecular electrophilic aromatic substitution†

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A one-pot synthesis of various N-substituted 3-amino-thiochromanes from 4-benzyl-2-methyl thiazoline via a thiazolium salt is described. The obtained 3-amino-thiochromanes are enantiopure, as their precursors derive from chiral 2-aminoalcohols. The reaction involves the formation of a disulfide, which subsequently takes part in an unprecedented intramolecular electrophilic aromatic substitution.

3-Amino-thiochromanes have been described in several publications1 and patents2 as compounds with interesting therapeutic activities. They have been studied for their ability to act on the central nervous system receptors,1,a–c,2a,2c and as antihypertensive3,b,c or cardiovascular agents.2a Only a few synthetic routes for their preparation have been published, and all involve a 1,4-addition of a thiophenol derivative to a Michael acceptor and subsequent cyclisation into thiochromane.2b,c In all the reported syntheses, the amino function is not present in the starting material, but brought after cyclisation by transformation of another functional group such as an oxime,3a a carboxylate,2a or a nitro.2b,c Alternative methods to prepare 3-amino-thiochromanes, especially in enantiopure form,3a are still lacking.

Recently, we described the synthesis of β-aminothiols or their disulfides from β-aminoalcohols and methylthioacetate, via the acidic hydrolysis of a thiazoline or a thiazolium salt.4 When thiazoline (S)-1a (derived from commercial L-phenylalaninol) was subjected to acidic hydrolysis (at 100 °C, in aqueous 5M HCl) in air to access disulfide 2a, the formation of a by-product was observed, in particular when the heating time was longer than 2 days (Scheme 1, eq. I). Therefore, we repeated the experiment by prolonging the reaction time and, after 5 days, a full conversion into the unknown product was obtained. After isolation, the product was analysed by NMR and mass spectroscopy and identified as the 3-amino-thiochromane 3a (Scheme 1, eq. II). The yield was 86%. Very probably, this transformation took place via an aromatic electrophilic substitution involving disulfide 2a, which is first formed by hydrolysis of 1a and then generates a sulfenium cation by protonation with HCl. Indeed, when pure disulfide 2a was submitted to the acidic hydrolysis, compound 3a was obtained in 88% yield, after 4 days of heating (Scheme 1, eq. III). This result highlights an unprecedented intramolecular electrophilic aromatic substitution. Only a few examples of aromatic electrophilic substitution involving a disulfide are reported,3 and, to the best of our knowledge, no intramolecular version has been mentioned.

A single crystal of 3a was isolated and analysed by X-ray diffraction and the absolute configuration was determined to be (S), the same as that of its precursor, the thiazoline 1a. The opposite enantiomer (R)-3a was also synthesized and its structure confirmed by X-ray analysis (Fig. 1).

A second experiment was attempted to synthesize the 3-amino-7-hydroxy-thiochromane 3b starting from thiazoline 1b. The latter was accessible from commercial (S)-tyrosinol by using our described procedure.4b Placed under similar acidic hydrolysis conditions, thiazoline 1b led after 10 days to a mixture of disulfide and thiochromane (1 : 2 ratio). After several washings of the crude product with acetone, pure thiochromane 3b was isolated in 36% yield (Scheme 2). When the O-mesylated derivative of thiazoline 1b was used as the starting material, a complete conversion into the corresponding disulfide was observed, however, even after 20 days of heating under acidic conditions, no trace of the corresponding thiochromane was detected. This is probably due to the presence of

† Electronic supplementary information (ESI) available: Experimental, spectral data, NMR spectra for compounds 3a,b and 6a–e, crystal data for (S)-3a and (R)-3a, CCDC reference numbers 766389 and 766390. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c003050c

Fig. 1 Crystal structures of (S)-3a (at left) and (R)-3a (at right).

Scheme 1 Synthesis of 3-amino-thiochromane 3a.
the mesylate substituent, which should lower the electron density of the aromatic ring and disfavor the electrophilic aromatic substitution.

Then, we examined the possibility of extending the method to the synthesis of 3-amino-thiochromanes possessing a secondary amino function using thiazolinium salts as precursors. The required thiaziolinium salts are easily accessible by N-alkylation of 1a and were prepared according to our described procedure. First, we prepared N-methyl thiaziolinium iodide 4a, and then we placed it in the same reaction conditions as used previously (Scheme 3). After 5 days of heating in 5 M aqueous HCl, the expected N-methyl 3-amino-thiochromane 6a was obtained in 69% yield (Table 1, entry 1). This result shows that it is possible to access variously substituted 3-amino-thiochromanes from thiazolinium salts, in a one-pot reaction. Thus, several thiazolinium salts (4b–e), bearing simple alkyl or functionalized substituents, were prepared and reacted under similar conditions (Scheme 3, Table 1, entries 2–5). In all cases, the corresponding thiochromanes were obtained after a rather long reaction time (5–14 days), although in excellent yields (82 to 89%). To confirm once again that the reaction takes place through a disulfide intermediate, three of these thiochromanes, 6b, 6c and 6d, were also synthesized from the disulfides precursors 5b–d, respectively (Scheme 3, Table 1, entries 6–8). The obtained yields were similar to those obtained starting from the thiaziolinium salts. As expected, the reaction time was a little shorter (3, 6 and 4 days vs. 5, 14 and 6 days, respectively), as an additional time is necessary to transform the thiaziolinium salt into the disulfide.

In conclusion, a new method to synthesize 3-amino-thiochromanes bearing a primary amino group from 4-benzyl thiazolines was found. The method was successfully extended to the preparation of secondary amino-thiochromanes derivatives from thiaziolinium salts, which are versatile precursors enabling easy structural variation. All the obtained 3-amino-thiochromanes are enantiopure (derived from l-phenylalaninol for 3a, 6a–e, or S-tyrosinol for 3b). This one-pot synthesis requires very simple conditions (heating in aqueous 5 M HCl), and involves two steps:

**Table 1**: Synthesis of N-substituted 3-amino-thiochromanes 6a–e.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Starting material</th>
<th>Time/days</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>4a</td>
<td>5</td>
<td>6a</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>Bu</td>
<td>4b</td>
<td>5</td>
<td>6b</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>4c</td>
<td>14</td>
<td>6c</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>CH₂CO₂Et*</td>
<td>4d</td>
<td>6</td>
<td>6d</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>CH₃CH₂OH</td>
<td>4e</td>
<td>7</td>
<td>6e</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>Bu</td>
<td>5b</td>
<td>3</td>
<td>6b</td>
<td>84</td>
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<tr>
<td>7</td>
<td>Bn</td>
<td>5c</td>
<td>6</td>
<td>6c</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>CH₂CO₂H</td>
<td>5d</td>
<td>4</td>
<td>6d</td>
<td>68</td>
</tr>
</tbody>
</table>

*In the starting thiazolinium salt R = CH₂CO₂Et and in the product R = CH₂CO₂H, as a result of the ester hydrolysis.

the formation of a disulfide and a subsequent intramolecular cyclisation. The last step is an interesting example of intramolecular electrophilic aromatic substitution, which merits further investigations.

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**Notes and references**