SYNTHESIS OF NEW (+)-TRANS-3,4-DISUBSTITUTED 3,4-DIHYDROISOCOUMARINS

M.Bogdanov1, M.Kandinska1, B. Yliev2 and M.Palamareva1
1 University of Sofia, Faculty of Chemistry, Department of Organic Chemistry
2 Organisch-chemisches Institut der Universität Zürich

Summary – The reaction between homophthalic anhydride and thiophene-2-carbaldehyde or N-methyl-carbazol-3-carboxaldehyde in dry chloroform, at room temperature and presence of 4-dimethylaminopyridine afforded as main products the expected 3-substituted trans-3,4-dihydroisocoumarin-4-carboxylic acids 3a,b. In two steps the carboxylic group of 3a,b was transformed with cyclic secondary amines in amide groups yielding the new 3,4-dihydroisocoumarins 5-14 with expected pharmacological activities. The reaction with acyclic secondary amines goes in another direction.

Results and discussion

The reaction between 1 and aldehydes 2a,b was carried out at room temperature in the presence of DMAP/chloroform (Scheme 1). The consumption of homophthalic anhydride was monitored by TLC. The expected trans-acids 3a and 3b were the main products in this reaction. The trans configuration of the isolated acids was assigned on the basis of the observed values of $^3J_{3,4}$: 5.7 and 8.0 Hz for 3a and 3b, respectively. It was deduced that the intermediate values of $^3J_{3,4}$ [2] for this type of compounds are based on the existing conformational equilibrium (Figure 1) between the conformations with synclinal (sc, torsion angle 60°) and antiperiplanar (ap, torsion angle 180°) H-3 and H-4. It is worth noting that the bulky substituent N-methyl-carbazol at C-3 influenced slightly the conformational equilibrium where both conformers (sc and ap) are of approximately equal quantities.

Key words: synthesis, dihydroisocoumarin, conformation

The 3,4-dihydroisocoumarins constitute a class of natural products [7], which exhibit a wide range of pharmacological activities such as antifungal [13], antiulcer [17], antileucemic [4], antiallergic [20], etc. Most of these natural products possess an aryl or alkyl substituents at C-3. The synthesis of this type of 3,4-dihydroisocoumarins have been achieved by different methods [1,10,11,16,19] depending of the bond formation in the pyranone ring.

The reaction of homophthalic anhydride (1) with carbonyl compounds is a one-step reaction for synthesis of 3-substituted dihydroisocoumarin-4-carboxylic acids. Such a reaction has been performed under various reaction conditions including different basic or acidic catalysts [6,8,12,14,15].

This study aims at the synthesis of new substituted dihydroisocoumarins. It is related to our previous investigations on the reaction of homophthalic anhydride with compounds containing activated double bonds [3,9,18]. Recently, we have reported [3] that 4-dimethylaminopyridine (DMAP) is a good catalyst in the reaction between homophthalic anhydride and aromatic aldehydes (Scheme 1). The reaction leads preferable to cyclic products and is highly stereoselective towards the trans-acids of type 3. We tried to obtain in this way new compounds of type 3 and to subject them to subsequent transformations of the carbonylic group at C-4 with preparation of new compounds with expected pharmacological activities.
Table 1. Synthesis of dihydroisocoumarins 5-14.

<table>
<thead>
<tr>
<th>No</th>
<th>NuH with 3a</th>
<th>%</th>
<th>No</th>
<th>NuH with 3b</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
<td>69</td>
<td>10</td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>50</td>
<td>11</td>
<td></td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>71</td>
<td>12</td>
<td></td>
<td>41</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>75</td>
<td>13</td>
<td></td>
<td>51</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>66</td>
<td>14</td>
<td></td>
<td>39</td>
</tr>
</tbody>
</table>

Scheme 1 also gives the route of acids 3a,b to the target compounds 5-14. The pathway is similar to that used by Haimova et al. [5] to prepare a given tetrahydroisoquinolinone having a cyclic amino-carbonyl group at position 4. The acids 3a,b were converted into acidic chlorides in boiling benzene and presence of thionyl chloride. The target compounds 5-14 were obtained by treatment of the corresponding acidic chlorides with the cyclic secondary amines shown in Table 1. In these cases, the reactions always lead to the expected 4-amino-carbonyl derivatives. When 1-oxo-3-thiophen-2-yl-isocoumarin-4-carbonyl chloride reacted with bulky secondary acyclic amines such as diisopropyl amine or dicyclohexyl amine, the product obtained was the known Perkin-type anhydride 15, i.e. the reaction went in an undesired direction. All compounds were isolated in solid state, after column chromatography and recrystallization, and were characterized by spectral methods (\(^1\)H-, \(^13\)C-NMR- and IR-spectra).

Fig. 1. Structure and conformational equilibrium of 3a,b and 5-14

The \(^1\)H-NMR spectrum of the synthesized compounds showed two doublets closed to \(\delta = 6.10\) ppm and 4.64 ppm for 5-9 and 5.92 ppm and 5.40 ppm for 10-14, respectively for H-3 and H-4. The values
of $^{3}J_{3,4}$ in these cases varied from 9.9 to 10.7 Hz, indicating that the preferred conformation for compounds 5-14 is I with diequatorial substituents at C-3 and C-4 (see Figure 1).

Conclusions

We extended the procedure for synthesis of 3,4-disubstituted 3,4-dihydroisocoumarins by a reaction catalyzed by DMAP, of homophthalic anhydride with aldehydes. The main products were trans-acids 3a,b. Moreover, the acidic chlorides of the latter reacted with secondary cyclic amines yielding numerous new 3,4-disubstituted 3,4-dihydroisocoumarins with trans-configuration.

The examination of the pharmacological activities of the newly synthesized compounds is been accomplishing by Johnson & Johnson, Pharmaceutical Research and Development, Janssen Pharmaceutica, Belgium.

Experimental

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The IR spectra were recorded on a Specord 75. Nujol was used for all acidic products and chloroform for all other compounds. The $^1$H NMR spectra were obtained on a Bruker AM300 NMR spectrometer at 300.13 MHz. The $^{13}$C NMR spectra were obtained on a Bruker AM300 NMR spectrometer at 75 MHz. The chemical shift is given in ppm ($\delta$) relative to tetramethylsilane as internal standard. The integrals in the $^1$H NMR spectra show that any compound was isolated in purity more than 98%.

The acids 3a,b were synthesized as we have described in Ref.3. The isolated products showed similar spectral characteristics.

General procedure for preparation of compounds 5-14

To a boiling solution of corresponding acid 3a or 3b in dry benzene, thionyl chloride (3 equiv.) was added. The reaction mixture was stirred at 65 °C for 2.5 h. The solvents were evaporated under reduced pressure and the residue was dissolved in dichloromethane. The cooled solution was treated with corresponding amine (3 equiv.) (See Table 1) and was stirred for an hour. At the end of the reaction, the reaction mixture was diluted with ethyl acetate and was washed with water (pH = 7). The organic layer was dried (sodium sulfate), filtered and the solvent was then evaporated under reduced pressure. The products were isolated after column chromatography of the residue and recrystallization from ethyl acetate.

$(\pm)$-trans-4-[4-(2-Methoxy-phenyl)-piperazine-1-carbonyl]-3-thiophen-2-yl-isochroman-1-one (5)

This compound was obtained as colorless prisms. Yield: 0.48 g (69%), mp 129–131 °C; IR: (CO) 1735, 1645 cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ = 2.58-2.83 (2H, m, H-14), 3.01-3.16 (2H, m, H-15), 3.65-3.78 (3H, m, H-12a, H-13), 3.86 (3H, s, -OCH$_3$), 3.92-4.01 (1H, m, H-12b), 4.66 (1H, d, H-4, J= 10.5Hz), 6.12 (1H, d, H-3, J= 10.5Hz), 6.80-7.08 (5H, m, H-Th, H-Phe), 7.17-7.20 (2H, m, H-Th, H-Phe), 7.34 (1H, dd, H-Th, J= 1.5 Hz and 5.1 Hz), 7.48 (1H, t, H-Ph, J= 7.6 Hz), 7.61 (1H, dt, H-Ph, J= 1.3 Hz and 7.4 Hz), 8.19 (1H, dd, H-8, J= 1.3 Hz and 7.6 Hz). $^{13}$C-NMR (CDCl$_3$): $\delta$ = 167.58, 163.88, 152.28, 139.44, 138.13, 134.53, 130.85, 128.59, 127.51, 126.93, 126.37, 125.91, 124.79, 123.90, 121.10, 118.52, 111.49, 78.38, 55.49, 51.06, 50.68, 47.73, 46.63, 42.43.

$(\pm)$-trans-4-(4-Methyl-piperazine-1-carbonyl)-3-thiophen-2-yl-isochroman-1-one (6)

This compound was obtained as colorless prisms. Yield: 0.35 g (50 %), mp 139–141 °C; IR: (CO) 1730, 1640 cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ = 1.89-1.97 (1H, m, H-14a), 2.08-2.16 (1H, m, H-14b), 2.25 (3H, s, N-CH$_3$), 2.39-2.53 (2H, m, H-15), 3.48-3.59 (3H, m, H-12a, H-13), 3.78-3.89 (1H, m, H-12b), 4.64 (1H, d, H-4, J= 10.5 Hz), 6.09 (1H, d, H-3, J= 10.5 Hz), 7.00 (1H, dd, H-Th, J= 3.6 Hz and 5.1 Hz), 7.10 (1H, d, H-Phe, J= 7.8Hz), 7.14 (1H, d, H-Th, J= 3.6 Hz), 7.35 (1H, dd, H-Th, J= 1.0 Hz and 5.0 Hz), 7.47 (1H, t, J= 7.6Hz, H-Phe), 7.60 (1H, dt, H-Ph, J= 1.5 Hz and 7.6 Hz), 8.17 (1H, dd, H-8, J= 1.2 Hz and 7.8 Hz). $^{13}$C-NMR (CDCl$_3$): $\delta$ = 167.54, 163.86, 139.48, 138.08, 134.51, 130.82, 128.58, 127.45, 126.88, 126.33, 125.90, 124.76, 78.38, 55.06, 54.68, 47.75, 46.14, 45.76, 42.07.

$(\pm)$-trans-4-(2-Hydroxy-ethyl)-piperazine-1-carbonyl]-3-thiophen-2-yl-isochroman-1-one (7)

This compound was obtained as colorless prisms. Yield: 0.5 g (71 %), mp 122–125 °C; IR: (CO) 1735, 1670 cm$^{-1}$; $^1$H-NMR (CDCl$_3$): $\delta$ = 1.98-2.10 (1H, m, H-14a), 2.19-2.31 (1H, m, H-14b), 2.47-2.75 (5H, m, H-15, H-16, -OH), 3.47-3.59 (3H, m, H-12a, H-13), 3.58-3.68 (2H, m, H-17), 3.81-3.94 (1H, m, H-12b), 4.65 (1H, d, H-4, J= 10.5 Hz), 6.09 (1H, d, H-3, J= 10.5 Hz), 7.00 (1H, t, J= 4.8 Hz, H-Th), 7.10 (1H, d, H-Phe, J= 7.8 Hz), 7.15 (1H, d, H-Th, J= 2.5 Hz), 7.35 (1H, d, H-Th, J= 4.8 Hz), 7.48 (1H, t, H-
This compound was obtained as colorless prisms. Yield: 0.52 g (75 %), mp 152–154 °C; IR: (CO) 1735, 1640 cm⁻¹; ¹H-NMR (CDCl₃): δ = 1.15-1.25 (1H, m, H-14a), 1.30-1.41 (1H, m, H-14b), 1.50-1.63 (4H, m, H-15, H-16), 3.29-3.44 (2H, m, H-13), 3.46-3.58 (1H, m, H-12a), 3.81-3.92 (1H, m, H-12b), 4.66 (1H, d, H-4, J = 10.5 Hz), 6.12 (1H, d, H-3, J=10.5 Hz), 6.99 (1H, dd, H-Th, J=3.4 Hz and 5.0 Hz), 7.10 (1H, d, H-Ph, J = 7.6Hz), 7.16 (1H, d, H-Th, J= 2.8 Hz), 7.34 (1H, dd, H-Th, J = 1.1 Hz and 4.6 Hz), 7.46 (1H, t, H-Ph, J = 7.6 Hz), 7.59 (1H, dt, H-Ph, J = 1.3 Hz and 7.4 Hz), 8.18 (1H, dd, H-8, J = 1.2 Hz and 7.7 Hz). ¹³C-NMR (CDCl₃): δ = 167.17, 63.98, 139.66, 138.32, 134.46, 130.78, 128.46, 127.41, 126.78, 126.19, 125.86, 124.81, 78.47, 47.70, 47.52, 43.38, 26.63, 25.79, 24.39.

### (±)-trans-4-(Piperidine-1-carbonyl)-3-thieno-2-yli-isochroman-1-one (8)

This compound was obtained as colorless prisms. Yield: 0.22 g (34 %), mp 224–226 °C; IR: (CO) 1730, 1640 cm⁻¹; ¹H-NMR (DMSO-d₆): δ = 2.20-2.28 (1H, m, H-12a), 2.42-2.47 (1H, m, H-12b), 3.10-3.24 (2H, m, H-11), 3.35-3.41 (1H, m, H-9a), 3.60-3.71 (3H, m, H-9b, H-10), 3.74 (3H, s, -NCH₃), 5.40 (1H, d, H-4, J = 10.3 Hz), 5.94 (1H, d, H-3, J = 10.3 Hz), 6.81 (1H, dd, Ph-H, J = 2.0 Hz and 8.2 Hz), 6.93 (1H, s, Ph-H), 7.03 (1H, d, Ph-H, J = 7.8 Hz), 7.17-7.29 (3H, m, Ph-H), 7.45 (1H, dt, Ph-H, J = 1.2 Hz and 8.2 Hz), 7.49-7.65 (4H, m, Ph-H), 7.71 (1H, dt, Ph-H, J = 1.5 Hz and 7.5 Hz), 8.08 (1H, dd, Ph-H, J = 1.4 Hz and 7.6 Hz), 8.12 (1H, d, Ph-H, J = 7.6 Hz), 8.29 (1H, s, Ph-H).

### (±)-trans-3-(Methyl-9H-carbazol-3-yl)-4-[4-(3-trifluoromethyl-phenyl)piperazine-1-carbonyl]-isochroman-1-one (11)

This compound was obtained as colorless crystals. Yield: 0.24 g (41 %), mp 190–193 °C; IR: (CO) 1735, 1640 cm⁻¹; ¹H-NMR (DMSO-d₆): δ = 1.95-2.02 (2H, m, H-10), 2.33-2.42 (2H, m, H-12), 3.35-3.43 (1H, m, H-9a), 3.64-3.71 (1H, m, H-9b), 3.89 (3H, s, -NCH₂), 5.35 (1H, d, H-4, J = 10.3 Hz), 5.93 (1H, d, H-3, J = 10.3 Hz), 7.18 (1H, d, Ph-H, J = 7.6 Hz), 7.24 (1H, dt, Ph-H, J = 1.0 Hz and 7.8 Hz), 7.45-7.64 (5H, m, Ph-H), 7.71 (1H, dt, Ph-H, J = 1.5 Hz and 7.6 Hz), 8.07 (1H, dd, Ph-H, J = 1.2 Hz and 7.6 Hz), 8.14 (1H, d, Ph-H, J = 7.6 Hz), 8.30 (1H, s, Ph-H).

### (±)-trans-3-(Methyl-9H-carbazol-3-yl)-4-[4-(3-trifluoromethyl-phenyl)piperazine-1-carbonyl]-isochroman-1-one (12)

This compound was obtained as colorless crystals. Yield: 0.24 g (41 %), mp 190–193 °C; IR: (CO) 1735, 1640 cm⁻¹; ¹H-NMR (DMSO-d₆): δ = 1.95-2.02 (2H, m, H-10), 2.33-2.42 (2H, m, H-12), 3.35-3.43 (1H, m, H-9a), 3.64-3.71 (1H, m, H-9b), 3.89 (3H, s, -NCH₂), 5.35 (1H, d, H-4, J = 10.3 Hz), 5.93 (1H, d, H-3, J = 10.3 Hz), 7.18 (1H, d, Ph-H, J = 7.6 Hz), 7.24 (1H, dt, Ph-H, J = 1.0 Hz and 7.8 Hz), 7.45-7.64 (5H, m, Ph-H), 7.71 (1H, dt, Ph-H, J = 1.5 Hz and 7.6 Hz), 8.07 (1H, dd, Ph-H, J = 1.2 Hz and 7.6 Hz), 8.14 (1H, d, Ph-H, J = 7.6 Hz), 8.30 (1H, s, Ph-H).
Yield: 0.20 g (39 %), mp 185–187 °C; IR: (CO) (pyrrolidine-1-carbonyl)-isochroman-1-one (13)

This compound was obtained as colorless prisms. Yield: 0.29 g (51 %), mp 180–182 °C; IR: (CO) (piperidine-1-carbonyl)-isochroman-1-one (14)

This compound was obtained as colorless crystals. Yield: 0.20 g (39 %), mp 185–187 °C; IR: (CO) (pyrrolidine-1-carbonyl)-isochroman-1-one (13)

References

Address for correspondence:
M.Bogdanov
University of Sofia
Faculty of Chemistry
1, J. Bourchier blv. 1164 Sofia
Tel.: +359 2 8161 228
e-mail: mbogdanov@chem.uni-sofia.bg

Адрес за кореспонденция:
М. Богданов
Софийски Университет
Химически факултет
бул. Дж.Баучер №1 1164 София
Тел.: +359 2 8161 228
e-mail: mbogdanov@chem.uni-sofia.bg