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Chromone-3-carboxaldehydes in Diels–Alder reactions with indole-*o*-quinodimethane. Synthesis of tetrahydrochromeno[2,3-*b*]carbazoles

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Abstract—An efficient route to a new class of indole derivatives, tetrahydrochromeno[2,3-*b*]carbazoles, has been developed. The cycloaddition reactions of chromone-3-carboxaldehydes with indole-*o*-quinodimethane gave a diastereomeric mixture of Diels–Alder cycloadducts in good yields after in situ deformylation.

The chromone moiety forms the important component of the pharmacophores of a number of biologically active molecules of synthetic as well as natural origin and many of them have useful medicinal applications.[1] Consequently, chromone chemistry continues to draw considerable interest from synthetic organic and medicinal chemists.[2] 3-Formylchromone has emerged as a valuable synthon for incorporation of the chromone moiety into a number of molecular frameworks,[3] but its synthetic utility is limited due to easy opening of the chromone ring[3,4] and strategies are being developed to circumvent this problem.[5]

Indoles too have attracted considerable attention from both synthetic organic and medicinal chemists, due to their biological activity covering a wide range of medicinal applications.[6–9]

Recently, a synthetic approach involving the reaction of chromone-3-carboxaldehydes with *o*-benzoquinodimethane, formed in situ by sulfur dioxide extrusion from 1,3-dihydro-benzo[*c*]thiophene and leading to benzo[*b*]-xanthones appeared in the literature.[10] These results, in combination with our continuing interest in the chemistry of quinodimethanes,[11] encouraged us to investigate the possibility of constructing molecules having both chromone and indole moieties.

Initial experiments involving the reactions of chromone and 6-nitrochromone with indole *o*-quinodimethane (*o*-IQDM) **2** generated in situ through the action of sodium iodide on 2,3-bis(bromomethyl)-1-benzoylindole **1** either in dry refluxing DMF for 30 min or in dry refluxing tolu- ene for 20 h in the presence of 18-crown-6. In all cases, low yields (2–4%) of a mixture of *cis* and *trans* cycloaddition products, tetrahydrochromeno[2,3-*b*]-carbazoles **4**–**7**, were isolated.

In order to enhance the dienophilicity of the chromone moiety, since the yields were very low, we carried out the Diels–Alder reaction on 3-formylchromone **3a** with *o*-IQDM **2** in refluxing DMF, whereupon after separation by column chromatography, two fractions of products were isolated. The first fraction contained a mixture of the two possible *trans* diastereomers, **4a** and **5a** (12% overall yield), inseparable on TLC, in a 10:1 ratio. From this mixture, a pure sample of compound **4a** was obtained by recrystallization from CH_2Cl_2–Et_2O. The second fraction was shown to be a 2:1 mixture of the two possible *cis* diastereomers, **6a** and **7a** (7% overall yield) also inseparable on TLC (Scheme 1). Because the yields were still low, the reaction was repeated in boiling toluene for 10 h, using 18-crown-6 as a phase transfer catalyst, whereupon a substantial improvement was achieved and the same products were isolated in good yields. The **4a**–**5a** mixture was isolated in 31%

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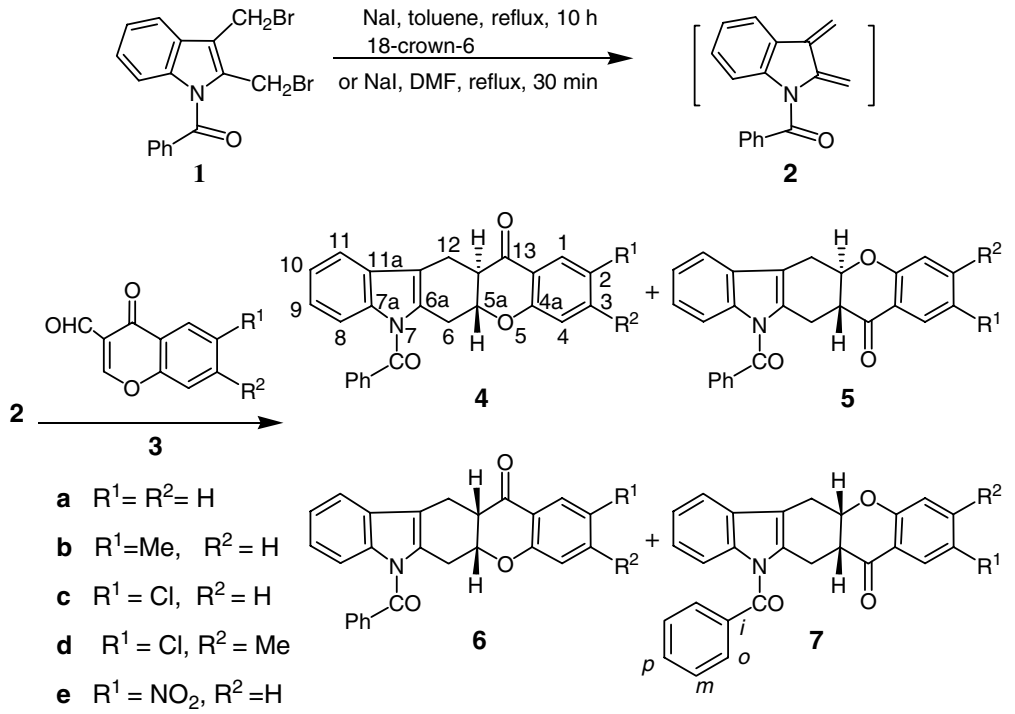

Scheme 1. Formation of indole *o*-QDM **2** and its reaction with some substituted chromenones **3**.

and the **6a**–**7a** in 26% overall yields, respectively. Taking this further, the reactions with substituted 3-formylchromones, **3b**–**e**, were performed under these conditions and the results are presented in Table 1. Attempting the reaction in boiling xylene resulted only in polymerization of the quinodimethane and no addition products were isolated. Under the reaction conditions, deformylation of the expected initial cycloadducts always occurred yielding the products **4**–**7**. This type of deformylation has been previously reported,[10,12] but from the reactions carried out at higher temperatures. It is also notable that in the reactions studied, opening of the pyran ring was never observed.

From the results shown in Table 1, we conclude that the electron-withdrawing substituents at C3 of the chromone ring considerably enhance the reaction yield. The Diels–Alder cycloaddition proceeds in a *cis* manner giving a mixture of diastereomers, **6** and **7**. The formation of the *trans* diastereomers, **4** and **5** can be explained by enolization of the *cis* diastereomers **6** and **7** during separation on the silica gel column leading to the more stable *trans* products. The observed regioselectivity of the reaction (**6**:**7**, Table 1) is in agreement with the results obtained from FMO calculations (AM1).

Table 1. Reaction yields (%) for compounds **4**–**7**

	4+**5**[a]	**6**+**7**
a	31	26 (2:1)
b	3	44 (2.5:1)
c	29	34 (4:1)
d	23	32 (2.5:1)
e	27	59 (3:1)

[a] In all cases compound **5** is present in ~3%.

Concerning the stereochemistry of the cycloaddition products, the structure of **4a** was deduced from the following data.[13] For the saturated protons, H_A–H_F (Fig. 1a), one proton multiplets at 4.62, 3.50, 3.46, 3.31, 3.10 and 2.82 δ were observed in the ^{1}H NMR spectrum. The most downfield multiplet at 4.62 δ was attributed to the H_A proton next to the chromone oxygen. This proton shows COSY correlations with the 3.10 δ proton and also with the 3.46 and 3.31 δ protons attached to the 32.07 ppm carbon, whereas the 3.10 δ proton shows correlations with the 4.62 δ proton and also with the 3.50 and 2.82 δ protons attached to the 19.82 ppm carbon. Moreover, from the coupling constants of $J_{AD} = 9.6$ Hz, $J_{AE} = 13.3$ Hz and $J_{EF} = 10.8$ Hz, an *axial–axial* (*trans*) relationship between these protons could be deduced, whereas the coupling constants of $J_{AC} = 6.1$ Hz and $J_{BE} = 6.1$ Hz indicated an *axial–equatorial* relationship of these protons.[14] On the other hand, COLOC correlations between H_C with

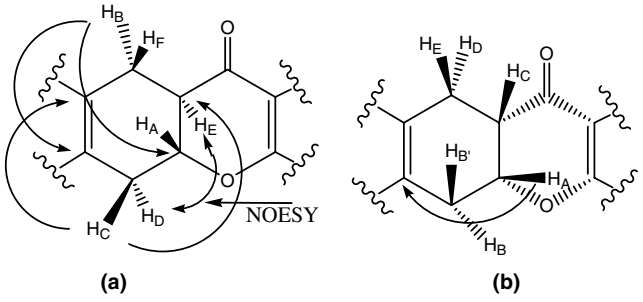

Figure 1. NOESY and COLOC correlations between protons and carbons in the saturated part of the skeleton of compounds **4a** (a) and **6e** (b).

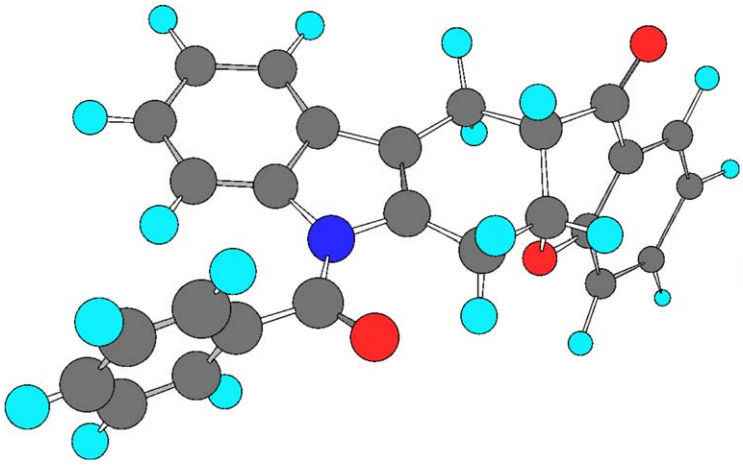

Figure 2. Minimized conformation of compound **6e** calculated by AM1 method.

carbons at 45.67 and 115.87 ppm and between H_B with carbons at 131.55 and 77.72 ppm indicated that these protons occupy equatorial positions on the cyclohexene ring. The more downfield shift of H_C compared to H_F can be attributed to its vicinity of the NCO carbonyl also causing a slight broadening to the H_C multiplet. Thus for the minor component, structure **5a** was deduced.

Concerning the two *cis* addition products **6** and **7**, recrystallization of the nitro-substituted mixture from ethanol gave a pure sample of **6e**. The structure of **6e** was based on the following data.[15] H_A showed a dt multiplet at 5.17 δ, a triplet due to the $H_BH_{B'}$ protons ($J = 4.2$ Hz) and a doublet due to H_C ($J = 2.75$ Hz) (Fig. 1b). In addition, H_A showed a COLOC correlation with the quaternary carbon at 131.33 ppm, revealing its equatorial configuration. On the contrary, H_C showed a ddd multiplet at 3.22 δ ($J_{CE} = 9.35$, $J_{CD} = 6.70$, $J_{AC} = 2.75$ Hz). The structure, which suits these data must have the chromene moiety almost perpendicular to the indole–cyclohexene moiety (Fig. 2).

In conclusion, an efficient route for the synthesis of a new class of fused benzopyranocarbazoles has been described. The new products are formed by the combination of two biologically extremely active components and such polycyclic molecules are known to display substantial biological activities.[16] Further applications of these very interesting reactions are being studied.

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13. Selected data for compound **4a**. White solid, mp 235–237 °C (CH_2Cl_2–Et_2O); ν_{max} (KBr): 1682, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.82 (m, 1H), 3.10 (m, 1H), 3.31 (m, 1H), 3.46 (m, 1H), 3.50 (m, 1H), 4.62 (m, 1H), 6.99 (m, 1H), 7.02 (m, 1H), 7.06 (m, 1H), 7.08 (m, 1H), 7.22 (m, 1H), 7.51 (m, 1H); 7.52 (m, 1H), 7.54 (m, 2H), 7.67 (m, 1H); 7.74 (m, 2H), 7.97 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.82 (C-12), 32.07 (C-6), 45.67 (C-12a), 77.72 (C-5a), 114.72 (C-8), 115.87 (C-11b), 117.91 (C-4), 118.37 (C-9), 120.72 (C-13a), 121.69 (C-2), 123.05 (C-10), 123.78 (C-11), 127.25 (C-1), 128.88 (C-*m*), 128.94 (C-11a), 129.48 (C-*o*), 131.55 (C-6a), 132.83 (C-*p*), 135.42 (C-*i*), 136.14 (C-3), 137.06 (C-7a), 161.27 (C-4a), 169.00 (NCO), 193.49 (C-13). EIMS *m/z* (%) 393 (4, $M^{+\cdot}$), 392 (57), 391 (50), 373 (8), 288 (40), 269 (45), 166 (95), 143 (27), 130 (35), 105 (45), 104 (62), 77 (100). Anal. Calcd for $C_{26}H_{19}NO_3$ (393.43): C, 79.37; H, 4.87; N, 3.56%. Found: C, 79.25; H, 4.92; N, 3.50%.

14. The spin system of the saturated protons has been studied also by simulation (SpinWorks ver. 2.2.0).
15. Spectral data for compound **6e**. Light yellow solid, mp 227–232 °C (EtOH); ν_{max} (KBr): 1705, 1683, 1614 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.03 (m, 2H), 3.23 (m, 1H), 3.45 (m, 2H), 5.17 (m, 1H), 6.81 (m, 1H), 7.04 (m, 1H), 7.11 (m, 1H), 7.19 (m, 1H), 7.40 (m, 1H), 7.53 (m, 2H); 7.67 (m, 1H), 7.53 (m, 2H), 8.35 (m, 1H), 8.85 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.00 (C-12), 29.55 (C-6), 43.87 (C-12a), 76.50 (C-5a), 114.70 (C-8), 115.32 (C-11b), 118.15 (C-11), 119.37 (C-4), 123.05 (C-10), 123.81 (C-9), 124.19 (C-1), 128.90 (C-*m*), 128.96 (C-11a), 129.49 (C-*o*), 129.53 (C-13a), 130.49 (C-3), 131.33 (C-6a), 132.93 (C-*p*), 135.30 (C-*i*), 136.59 (C-7a), 142.58 (C-2), 164.72 (C-4a), 169.12 (NCO), 192.12 (C-13). Anal. Calcd for $C_{26}H_{18}N_2O_5$ (438.43): C, 71.23; H, 4.14; N, 6.39%. Found: C, 71.15; H, 4.20; N, 6.48%.
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