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Uncatalyzed addition of indoles and *N*-methylpyrrole to 3-formylchromones: synthesis of (chromon-3-yl)bis(indol-3-yl)methanes and *E*-2-hydroxy-3-(1-methylpyrrol-2-ylmethylene)chroman-4-ones under solvent-free conditions

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Abstract—(Chromon-3-yl)bis(indol-3-yl)methanes and *E*-2-hydroxy-3-(1-methylpyrrol-2-ylmethylene)chroman-4-ones have been obtained in good yields from 3-formylchromones on reaction with indoles and *N*-methylpyrrole under solvent-free conditions.

3-Formylchromone is a highly reactive and well studied compound which can serve as the starting material for the syntheses of a whole series of heterocycles due to the presence of three electrophilic centers in this molecule.[1] However, published data on the reactions of 3-formylchromones with azoles, such as indoles and pyrroles, are scarce. It is known that they react with pyrrole at the aldehyde group to form *meso*-tetrakis(chromon-3-yl)porphyrins.[2] At the same time, indoles and pyrroles react readily with aldehydes and ketones to form bis(indolyl)methane[3] and dipyrromethane[4] derivatives, which are important bioactive metabolites of terrestrial and marine origin.[5] Chromones are more widely distributed in Nature, especially in the plant kingdom, and exhibit low toxicity along with a wide spectrum of useful properties. They have been shown to be tyrosine and protein kinase C inhibitors, as well as antifungal, antiviral, antitubulin, and antihypertensive agents. Chromone derivatives are also active at benzodiazepine receptors and on lipoxygenases and cyclooxygenases.[6] We envisaged that the combination of a chromone system with indole or pyrrole rings would allow the development of a new class of biologically active molecules and useful synthetic building blocks in organic and medicinal chemistry.

In this context, our attention was drawn to the fact that, although 1,2-addition of nucleophilic indoles and pyrroles to carbonyl compounds has been well studied,[3,4] the use of 3-formylchromone as an acceptor in the reaction with azoles as nucleophiles has never been reported. Based on the literature data,[1] one could assume that the reactions of π-electron-rich azoles and 3-formylchromones would proceed at either the CHO group (1,2-addition) or at the C-2 atom (1,4-addition). The latter reaction is usually accompanied by pyrone ring-opening followed by recyclization due to the phenolic hydroxyl and aldehyde group. We have shown quite recently[7] that the reaction of 3-(polyfluoroacyl)chromones with indoles and *N*-methylpyrrole proceeds solely through 1,4-addition, and after recyclization involving the OH and R^FCO groups, affords a mixture of *Z*- and *E*-isomers of 3-(azolylmethylene)-2-hydroxy-2-(polyfluoroalkyl)chroman-4-ones substantially favoring the *Z*-isomer.

In the present study we found that, unlike 3-(polyfluoroacyl)chromones,[7] 3-formyl- and 6-methyl-3-formylchromones **1a**,**b** react with excess indole or *N*-methylindole (3 equiv) to give (chromon-3-yl)bis(indol-3-yl)methanes **2a**–**d**. The reaction occurs at 85–90 °C in 5 h and requires no solvent or catalyst (solvent-free conditions). As in the case of aromatic aldehydes, this reaction does not stop after mono-addition but affords bis-adducts **2a**–**d** in 54–78% yields (Scheme 1).[8] The same compounds were formed but in lower yields when 1 equiv of indole was used. Since the 3-position of indole is

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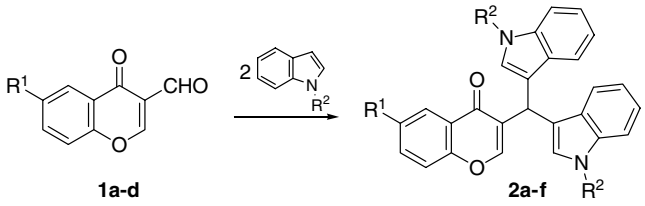


Chromone	R^1	R^2	Product	Yield (%)	Mp (°C)
1a	H	H	**2a**	54	233–234
1a	H	Me	**2b**	65	265–266
1b	Me	H	**2c**	68	252–254
1b	Me	Me	**2d**	78	262–263
1c	Cl	H	**2e**	55	235–236
1d	NO_2	H	**2f**	58	204–205

Scheme 1.

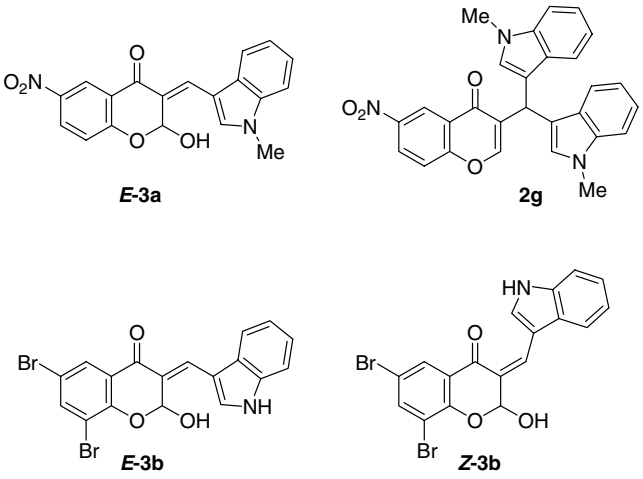


Figure 1.

the preferred site for electrophilic reactions, substitution occurred exclusively at this position, and N-substituted products were not detected in the reaction mixture. Note that under classical conditions (reflux in solvent in the presence of acid or base), 3-formylchromones reacted with indoles to give complicated mixtures of products.

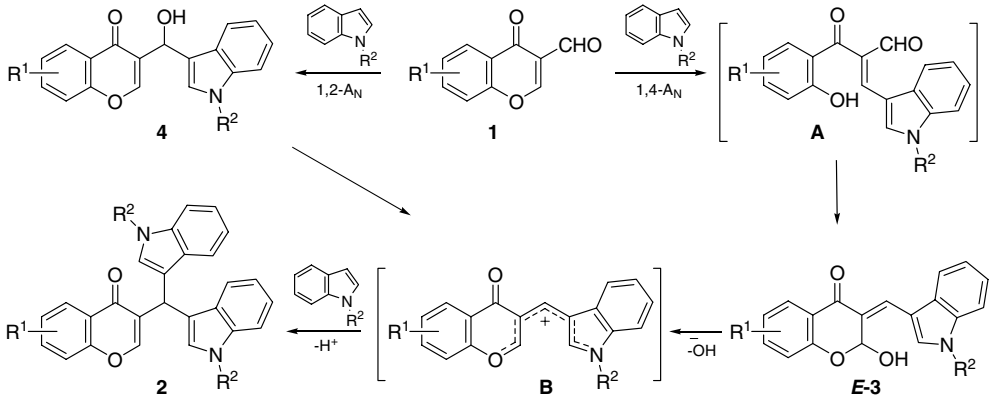
The reaction turned out to be very sensitive to the nature of the substituent at C-6 of **1**. Reaction of 6-chloro-3-formylchromone **1c** and 3-formyl-6-nitrochromone **1d** with indole under solvent-free conditions gave polymeric products, which were insoluble in standard solvents. However, the use of butanol as solvent in the presence of catalytic amounts of $HClO_4$ at ~20 °C made it possible to produce bis-adduct **2e** in 55% yield from **1c** and indole. Under similar conditions, the reaction of indole with **1d** resulted in resinification of the reaction mixture, and bis-adduct **2f** was synthesized on heating of the reactants in water at 90 °C for 5 h (for **1c** these conditions were inappropriate, and only a polymeric product was isolated instead of **2e**). Interestingly, the solvent-free reaction between **1d** and *N*-methylindole afforded a mixture of bis-adduct **2g** and *E*-2-hydroxy-6-nitro-3-(1-methylindol-3-ylmethylene)chroman-4-one **3a** in a ratio of 33:67, respectively. It is noteworthy that the formation of **2g** can be explained by both 1,2- and 1,4-addition reactions, whereas structure **3a** indicates unambiguous attack at C-2 followed by recyclization. A similar reaction of 6,8-dibromo-3-formylchromone **1e** with indole proceeded exclusively via 1,4-addition followed by recyclization to form a diastereomeric mixture of *E*-**3b** (91%) and *Z*-**3b** (9%) (Fig. 1).

Mechanistically we suppose that indole initially attacks C-2 of the chromone ring. A plausible pathway includes nucleophilic 1,4-addition of indoles with concomitant opening of the pyrone ring and subsequent intramolecular cyclization of intermediate **A** at the CHO group to chromanone **3**, which through highly delocalized cation **B** affords bis-adducts **2**. The presence of an electron-withdrawing substituent on the benzene ring of the chromones inhibits the bis-addition due to destabilization of intermediate carbocation **B**, which stops the reaction after the first step (compounds **3**). However, we cannot exclude the alternative 1,2-addition (compounds **4**), as occurs in the case of aromatic aldehydes[3] (Scheme 2).

The ^{1}H NMR spectra of compounds **2a**–**f** are characterized by the doubled number of the indole protons and two singlets or doublets ($J = 0.6$–0.8 Hz) due to the CH and H-2 protons at δ 6.03–6.05 and 7.88–8.01 ppm, respectively. The geometrical isomers **3b** were identified by comparison of the ^{1}H NMR chemical shifts of the olefinic and indole H-2 hydrogens in both isomers. The diagnostic signal for the olefinic proton in the *Z*-isomer, which appeared at 7.75 ppm, was shifted downfield in the *E*-isomer (8.23 ppm) due to the deshielding effect of the carbonyl group as indicated in the case of the reaction of 3-(polyfluoroacyl)chromones with indoles.[7] In addition, another characteristic feature of the ^{1}H NMR spectrum in DMSO-d_6 was the appearance of two doublets at 9.20 ppm and 7.95 ppm ($J_{H,NH} \approx 3.0$ Hz) for the indole H-2 proton of the *Z*- and *E*-isomers, respectively.

(Chromon-3-yl)bis(indol-3-yl)methanes **2** represent a new class of tris(heteroaryl)methanes, in which two different heterocycles with remarkably important biological and pharmaceutical activities are linked at the same carbon atom. In addition, in view of the easy functionalization of the chromone ring at the 2- and 4-positions by nucleophilic reagents, compounds **2** could serve as promising building blocks for novel three-dimensional molecules of structural and physicochemical interest.

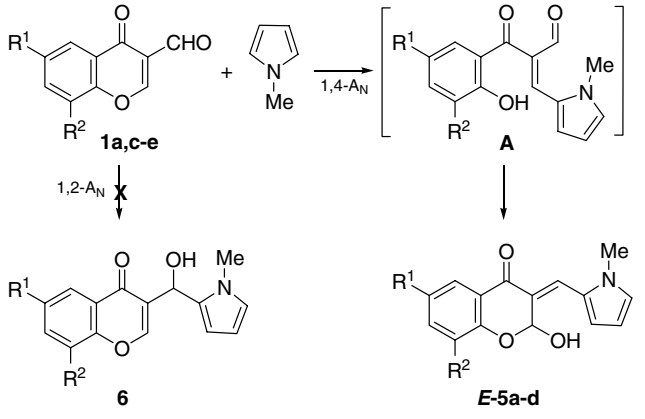
Next, taking into account the above results and that the pyrrole ring is an important structural fragment of many natural and biologically active substances,[9] it was of interest to evaluate the reactivity of *N*-methylpyrrole with compounds **1**. We anticipated that *N*-methylpyrrole might undergo similar bis-addition to give the corresponding bis-adducts. However, significantly different reactivity was observed in this case. Unlike indoles,



Scheme 2.

N-methylpyrrole reacted with **1a**,**c**–**e** under solvent-free conditions exclusively via 1,4-addition followed by recyclization to form *E*-2-hydroxy-3-(1-methylpyrrol-2-ylmethylene)chroman-4-ones **5a**–**d** in good yields.[10] The reactions were complete within 45 min and no bis-adducts of type **2** were observed even in the crude products. 3-Formyl-6-methylchromone **1b** did not react with *N*-methylpyrrole under these conditions. The formation of compounds **5**, in which the more nucleophilic C-2 atom of the pyrrole ring is involved, follows the reaction pathway described in Scheme 3.

The choice between structures **5** and **6** was made in favor of the former on the basis of spectral data. The ^{1}H NMR spectra of compounds **5a**–**d** in DMSO-d_6 consisted of a characteristic singlet due to the *exo*-methylene proton in the region of 7.72–7.83 ppm and two doublets due to the CH and OH protons at 6.39–6.54 and 7.79–8.22 ppm ($J = 6.0$–6.6 Hz), respectively. The main features of the ^{13}C NMR spectrum of product **5a** were resonances at 93.5 (C-2) and 179.6 ppm (C=O), no signal was observed at 153–155 ppm, where the C-2 atom of chromones usually appears. Comparison of these data with the ^{1}H and ^{13}C NMR spectra of carbinols of type **6**, which have recently been synthesized under Baylis–Hillman conditions by the reaction of chromone or 6-methylchromone with aromatic and heterocyclic aldehydes,[11] unambiguously proved the structures of **5**.



Chromone	R^1	R^2	Product	Yield (%)	Mp (°C)
1a	H	H	**5a**	58	190–191
1c	Cl	H	**5b**	68	193–194
1d	NO_2	H	**5c**	77	229–230
1e	Br	Br	**5d**	83	205–206

Scheme 3.

In conclusion, we have shown, for the first time, that the reaction of 3-formylchromones with indoles is a simple and practical method for the preparation of a new class of biologically interesting (chromon-3-yl)bis(indol-3-yl)methanes. The reaction with *N*-methylpyrrole proceeds via 1,4-addition followed by cyclization to *E*-2-hydroxy-3-(1-methylpyrrol-2-ylmethylene)chroman-4-ones. The resulting products are of considerable interest as reactive precursors for the synthesis of other useful organic materials. Further studies on the synthetic application of these compounds are in progress.

Acknowledgments

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8. *Preparation of* **2a–d**. A solution of 3-formylchromone **1** (2.5 mmol) in an excess of indole or *N*-methylindole (7.5 mmol) was heated at 85–90 °C for 5 h. Completion of the reaction was determined by the appearance of the solid reaction mixture. The precipitate, obtained from the hot solution, was twice recrystallized from *n*-butanol/*p*-xylene (4:1), washed with ethanol, and dried at 90 °C for 1 day to give compounds **2** as colorless crystals.
3-[Bis(indol-3-yl)methyl]chromone **2a**: IR (KBr) 3389, 1633, 1614, 1572, 1465 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.05 (d, 1H, CH, $^4J = 0.8$ Hz), 6.91 (ddd, 2H, 2H-5′, $^3J = 7.9$, 7.1 Hz, $^4J = 1.0$ Hz), 6.98 (d, 2H, 2H-2′, $J = 1.8$ Hz), 7.06 (ddd, 2H, 2H-6′, $^3J = 8.2$, 7.1 Hz, $^4J = 1.0$ Hz), 7.36 (dd, 4H, 2H-4′, 2H-7′, $^3J = 8.1$ Hz, $^4J = 1.0$ Hz), 7.49 (ddd, 1H, H-6, $^3J = 8.1$, 7.2 Hz, $^4J = 1.0$ Hz), 7.60 (dd, 1H, H-8, $^3J = 8.5$ Hz, $^4J = 1.0$ Hz), 7.78 (ddd, 1H, H-7, $^3J = 8.5$, 7.2 Hz, $^4J = 1.7$ Hz), 7.91 (d, 1H, H-2, $^4J = 0.7$ Hz), 8.10 (dd, 1H, H-5, $^3J = 8.0$ Hz, $^4J = 1.5$ Hz), 10.86 (d, 1H, NH, $J = 1.9$ Hz). Anal. Calcd for $C_{26}H_{18}N_2O_2$: C, 79.98; H, 4.65; N, 7.17. Found: C, 79.66; H, 4.47; N, 6.99.
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10. *Preparation of* **5a–d**. A solution of 3-formylchromone **1** (1.0 mmol) in an excess of *N*-methylpyrrole (3.0 mmol) was heated at 85–90 °C for 45 min. Completion of the reaction was determined by the appearance of the solid reaction mixture. The precipitate, obtained from the hot solution, was cooled and treated with hexane (5 mL). The residue was filtered, washed with hexane, recrystallized from *n*-butanol/dioxane (3:1), and washed with ethanol to give compounds **5** as yellow crystals.
E-2-Hydroxy-3-(1-methylpyrrol-2-ylmethylene)chroman-4-one **5a**: IR (KBr) 3376, 3277, 1645, 1608, 1585, 1557, 1485 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.77 (s, 3H, Me), 6.29 (dd, 1H, H-4′, $J = 4.0$, 2.5 Hz), 6.39 (d, 1H, H-2, $J = 6.3$ Hz), 6.75 (dd, 1H, H-5′, $J = 4.1$, 1.2 Hz), 7.04 (d, 1H, H-8, $^3J = 8.0$ Hz), 7.12 (ddd, 1H, H-6, $^3J = 7.8$, 7.3 Hz, $^4J = 0.9$ Hz), 7.24 (t, 1H, H-3′, $J = 1.8$ Hz), 7.58 (ddd, 1H, H-7, $^3J = 8.0$, 7.3 Hz, $^4J = 1.7$ Hz), 7.72 (s, 1H, =CH), 7.79 (d, 1H, OH, $J = 6.3$ Hz), 7.86 (dd, 1H, H-5, $^3J = 7.8$ Hz, $^4J = 1.7$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 33.97 (qd, Me, $J = 139.7$, 2.4 Hz), 93.52 (ddd, C-2, $J = 169.7$, 10.6, 3.4 Hz), 110.07 (ddd, C-4′, $J = 172.9$, 7.8, 3.4 Hz), 116.78 (dm, C-3′, $J = 172.2$ Hz), 118.50 (dd, C-8, $J = 162.8$, 7.5 Hz), 121.57 (ddd, C-3, $J = 7.8$, 4.5, 1.3 Hz), 121.67 (dd, C-5, $J = 163.3$, 7.9 Hz), 125.85 (t, C-4a, $J = 4.9$ Hz), 126.52 (d, =CH, $J = 153.7$ Hz), 126.53 (ddd, C-6, $J = 161.8$, 8.4, 1.3 Hz), 127.09 (qd, C-2′, $J = 6.7$, 1.8 Hz), 129.74 (d.quint.d, C-5′, $J = 186.4$, 8.0, 3.6 Hz), 135.53 (ddd, C-7, $J = 160.6$, 9.2, 2.0 Hz), 157.22 (m, C-8a), 179.64 (dtd, C-4, $J = 6.2$, 4.1, 1.7 Hz). Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.38; H, 5.14; N, 5.41.
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