Reactions of 3-nitro-2-trihalomethyl-2*H*-chromenes with indole, *N*-methylindole, and *N*-methylpyrrole. Stereoselective synthesis of 4-azolyl-3-nitro-2-trihalomethylchromanes

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Heating of 3-nitro-2-trifluoromethyl- and 3-nitro-2-trichloromethyl-2*H*-chromenes with indole, *N*-methylindole, and *N*-methylpyrrole under solvent-free conditions led with high stereoselectivity and in good yields to *cis*—*trans*-3-nitro-2-trifluoromethyl- or *trans*—*cis*-3-nitro-2-trichloromethylchromanes substituted by the indol-3-yl (pyrrol-2-yl) fragment in position 4.

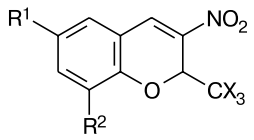
Key words: chromenes, chromanes, indoles, *N*-methylpyrrole, stereoselectivity, diastereomers, NMR spectroscopy.

2*H*-Chromene (2*H*-1-benzopyran) and its derivatives belong to an important class of oxygen-containing heterocyclic compounds that are common in the plant world[1] and exhibit a number of useful properties (*e.g.*, high biological activity).[2—5] In the last few years, considerable interest was aroused in the synthesis of partially fluorinated heterocycles, many of which have found use as agrochemical preparations and drugs.[6] However, data on the use of 2-trihalomethyl-2*H*-chromenes as substrates for organic synthesis are very scarce. Recently, we have described the synthesis of 3-nitro-2-trihalomethyl-2*H*-chromenes[7] and studied their reactions with a number of S-, N-, and C-nucleophiles.[8—11] We have found that base-catalyzed reactions follow the mechanism of conjugated nucleophilic addition to the C(4) atom to give mixtures of diastereomers or individual diastereomers of 2,3,4-trisubstituted chromanes; their stereochemistry was determined by NMR spectroscopy and X-ray diffraction analysis.

The present study was devoted to reactions of 3-nitro-2-trihalomethyl-2*H*-chromenes with indole, *N*-methylindole, and *N*-methylpyrrole, the heterocyclic systems of which are found in many biologically active natural molecules and medically important synthetic compounds.[12] In recent years, reactions of indoles and pyrroles with nitroalkenes, including the catalytic enantioselective Friedel—Crafts alkylation, have received much attention.[13—16] However, the sole relevant example in the 3-nitro-2*H*-chromene series is a reaction of 2-(4-chlorophenyl)-3-nitro-2*H*-chromene with indole in diethyl ether in the presence of iodine. This reaction occurs at the C(4) atom of the chromene system with low stereoselectivity to give a mixture of *cis*—*trans*- and *trans*—*cis*-2-(4-chlorophenyl)-4-(indol-3-yl)-3-nitrochromanes in the ratio 3 : 1, respectively.[17]

Results and Discussion

The starting 3-nitro-2-trihalomethyl-2*H*-chromenes **1a—g** (note that compound **1g** has not been described earlier) were synthesized by tandem condensation of appropriate salicylaldehydes with 3,3,3-trifluoro(trichloro)-1-nitropropenes in the presence of triethylamine.[7]



1a—g

1	a	b	c	d	e	f	g
X	F	F	F	Cl	Cl	Cl	Cl
R^1	H	Br	MeO	H	Br	NO_2	H
R^2	H	H	H	H	H	H	NO_2

Earlier, we have demonstrated that these compounds are highly reactive in reactions with various nucleophilic reagents (including β-dicarbonyl compounds) and developed a novel method for the synthesis of 4-pyrazolylchromanes.[10] Because some structurally similar compounds exhibit high pharmacological activity,[3—5] we attempted to extend the range of accessible chromanes with a heterocyclic substituent in position 4 and studied reactions of chromenes **1a—g** with indole, *N*-methylindole, and *N*-methylpyrrole.

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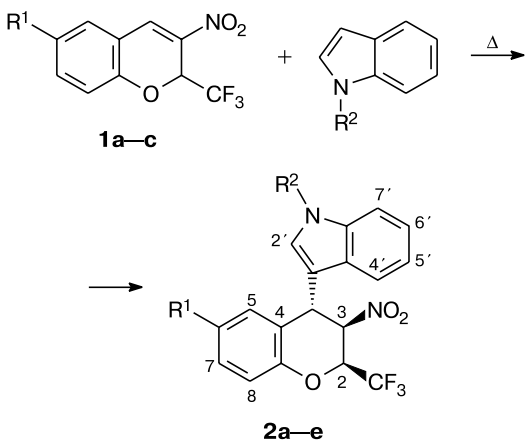
First, we investigated more reactive 2-CF_3-substituted chromenes **1a,c**: they reacted with indoles in boiling pyridine for 10—16 h (procedure ***A***) to give 4-(indol-3-yl)chromanes **2a,c,d** in 60—72% yields. With THF as a solvent and in the presence of catalytic amounts of iodine or DABCO, the yields of the products were substantially lower. In all respects (including ecological requirements which rose to prominence in the last few years[18]), the optimal reaction conditions were a threefold excess of indole and 80 °C (procedure ***B***). As the result, chromanes **2a—e** were obtained without any solvent or catalyst in higher yields (68—84%) and over a shorter period of time (5—8 h). Note that a reaction of 3,6-dinitro-2-trifluoromethyl-2*H*-chromene with indole in both pyridine and without any solvent resulted in resinification of the reaction mixture. The plausible reaction mechanisms involve nucleophilic 1,4-addition to the C(4) atom of 3-nitrochromenes (the Michael addition) or the Friedel—Crafts alkylation of π-abundant indoles at position 3[14] (Scheme 1).

Scheme 1

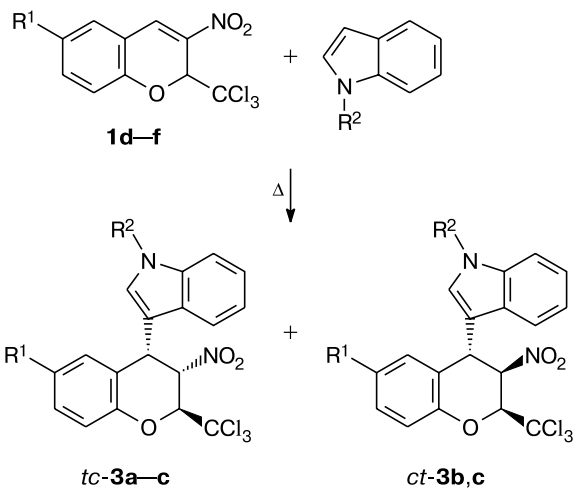


2	a	b	c	d	e
R^1	H	Br	MeO	H	Br
R^2	H	H	H	Me	Me

The reactions of 2-CF_3-chromenes **1a—c** with indoles were highly stereoselective according to both procedures ***A*** and ***B***. Recrystallization from dichloromethane—hexane gave 2,3,4-trisubstituted chromanes **2a—e** as one *cis—trans*-isomer (*ct*-isomer). The stereochemistry of the products obtained can be determined from low coupling constants ($J_{2,3} \approx J_{3,4}$ = 1.5—2.0 Hz) characteristic of *cis—trans*-diastereomers (Table 1). Earlier, $J_{2,3} \approx J_{3,4}$ = 1.2—1.8 Hz have been reported for *cis—trans*-adducts formed in reactions of thiols with chromenes **1** (see Ref. 9) and $J_{2,3} \approx J_{3,4}$ = 2.2 Hz, for *cis—trans*-2-(4-chlorophenyl)-4-(indol-3-yl)-3-nitrochromane (see Ref. 17); the structure of the latter was confirmed by X-ray diffraction analysis. Additional evidence for the *cis—trans*-configuration of chromanes **2a—e** can be the chemical shift (CS) in the narrow range δ 86.94—87.00 and the coupling constant of the doublet for the CF_3 group ($^3J_{CF_3,H(2)}$ = 5.8—6.1 Hz), which agrees well with the literature data[9] for *cis—trans*-adducts of chromenes **1a,b** with thiols. In attempted epimerization at the C(3) atom in boiling benzene in the presence of DABCO, chromane **2b** was isolated as the starting *ct*-isomer.

Earlier, 2-CCl_3-chromenes have been reported to be less reactive than 2-CF_3-chromenes; however, their reactivities can be enhanced by introducing electron-withdrawing substituents into the benzene ring.[9] Indeed, under the conditions of procedure ***B*** (solvent-free conditions), 2-CCl_3-chromenes **1d—f** reacted with *N*-methylindole and indole for 10—20 h to give chromanes **3a—c** in 30—70% yields (Scheme 2). The lowest yield (30%) after the longest reaction time (20 h) was obtained from chromene **1d** having no substituents in the benzene ring; this is in full agreement with the lowered reactivity[9] of the double bond in 3-nitro-2-trichloromethyl-2*H*-chromene **1d** compared to fluorinated analog **1a**.

Scheme 2



3	a	b	c
R^1	H	Br	NO_2
R^2	Me	Me	H

In contrast to 2-CF_3-chromanes **2a—e** obtained as the *ct*-isomer only, 2-CCl_3-chromane **3a** exists in the *trans—cis*-configuration (*tc*-isomer), which is evident from the experimental coupling constants $J_{2,3}$ = 6.7 Hz and $J_{3,4}$ = 5.7 Hz. They correlate well with literature data: $J_{2,3}$ = 6.1—7.6 Hz and $J_{3,4}$ = 4.8—5.5 Hz for *trans—cis*-adducts of thiols with chromenes **1** (see Ref. 9) and $J_{2,3}$ = 9.3 Hz and $J_{3,4}$ = 5.6 Hz for *trans—cis*-2-(4-chlorophenyl)-4-(indol-3-yl)-3-nitrochromane (see Ref. 17),

Table 1. ^{1}H and ^{19}F NMR and IR spectra of 4-azolylchromanes **2a—e**, **3a—c**, and **4a—d**

Chromane	^{1}H NMR ($CDCl_3$), δ (*J*/Hz)						IR, ν/cm^{-1}
	H(2)	H(3)	H(4)[a]	H(5)—H(8)	H(2′), H(4′)—H(7′) of indole or H(3′)—H(5′) of pyrrole	NH (br.s) or Me (s)	
ct-**2a**[b]	4.62 (qd, *J* = 5.8, *J* = 1.5)	5.40 (t, *J* = 1.5)	5.02 (br.s)	7.05 (t, H(6), *J* = 7.5); 7.13 (d, H(8), *J* = 8.2); 7.18 (d, H(5), *J* = 7.6); 7.23—7.35 (m, 1 H, H(7))	6.63 (d, H(2′), *J* = 2.0); 7.23–7.35 (m, H(5′), H(6′)); 7.44 (d, H(7′), *J* = 8.2); 7.64 (d, H(4′), *J* = 7.7)	8.17 (NH)	3399, 1588, 1556, 1488, 1460, 1366
ct-**2b**[c]	4.60 (qd, *J* = 6.0, *J* = 1.9)	5.36 (t, *J* = 2.0)	4.98 (br.s)	7.03 (d, H(8), *J* = 8.8); 7.31—7.35 (m, H(5)); 7.42 (dd, H(7), *J* = 8.8, *J* = 2.4)	6.65 (d, H(2′), *J* = 2.0); 7.26 (td, H(5′), *J* = 7.5, *J* = 1.0); 7.31—7.35 (m, H(6′)); 7.45 (d, H(7′), *J* = 8.2); 7.62 (d, H(4′), *J* = 7.8)	8.22 (NH)	3396, 1557, 1478, 1460, 1366
ct-**2c**[d]	4.58 (qd, *J* = 6.1, *J* = 1.8)	5.35 (t, *J* = 1.8)	4.98 (br.s)	6.68 (d, H(5), *J* = 2.9); 6.88 (dd, H(7), *J* = 9.0, *J* = 2.9); 7.05 (d, H(8), *J* = 9.0)	6.67 (d, H(2′), *J* = 2.5); 7.25 (t, H(5′), *J* = 7.5); 7.32 (ddd, H(6′), *J* = 8.2, *J* = 7.2, *J* = 1.0); 7.44 (d, H(7′), *J* = 8.1); 7.64 (d, H(4′), *J* = 7.9)	3.71 (s, MeO); 8.19 (NH)	3403, 1555, 1498, 1461, 1367
ct-**2d**[e]	4.62 (qd, *J* = 6.1, *J* = 1.8)	5.37 (t, *J* = 1.9)	5.00 (br.s)	7.05 (td, H(6), *J* = 7.5, *J* = 1.0); 7.13 (d, H(8), *J* = 8.2); 7.18 (dd, H(5), *J* = 7.6, *J* = 1.0); 7.29—7.38 (m, H(7))	6.44 (s, H(2′)); 7.24 (ddd, H(5′), *J* = 8.2, *J* = 7.0, *J* = 1.6); 7.29—7.38 (m, H(6′), H(7′)); 7.62 (d, H(4′), *J* = 7.9)	3.71 (Me)	1590, 1558, 1487, 1459, 1368
ct-**2e**[f]	4.60 (qd, *J* = 6.0, *J* = 2.0)	5.34 (t, *J* = 2.0)	4.96 (br.s)	7.03 (d, H(8), *J* = 8.8); 7.32 (d, H(5), *J* = 2.4); 7.42 (dd, H(7), *J* = 8.8, *J* = 2.4)	6.46 (d, H(2′), *J* = 0.7); 7.25 (ddd, H(5′), *J* = 8.0, *J* = 6.5, *J* = 1.6); 7.33—7.40 (m, H(6′), H(7′)); 7.60 (dt, H(4′), *J* = 7.9, *J* = 0.9)	3.74 (Me)	1556, 1478, 1467, 1364
tc-**3a**	5.58 (d, *J* = 6.7)	5.43 (dd, *J* = 6.7, *J* = 5.7)	5.26 (d, *J* = 5.7)	7.04 (td, H(6), *J* = 7.5, *J* = 1.1); 7.20 (d, H(8), *J* = 8.0); 7.22—7.34 (m, H(5), H(7))	6.88 (s, H(2′)); 7.15 (ddd, H(5′), *J* = 8.0, *J* = 6.9, *J* = 1.2); 7.22—7.34 (m, H(6′), H(7′)); 7.55 (d, H(4′), *J* = 8.0)	3.73 (Me)	1591, 1561, 1488, 1370, 1360
ct-**3b**	4.57 (dd, *J* = 1.5, *J* = 0.6)	5.85 (t, *J* = 1.5)	4.93 (br.s)	7.11 (d, H(8), *J* = 8.8); 7.33—7.39 (m, H(5)); 7.45 (dd, H(7), *J* = 8.8, *J* = 2.4)	6.45 (d, H(2′), *J* = 0.8); 7.24—7.28 (m, H(5′)); 7.33—7.39 (m, H(6′), H(7′)); 7.66 (dt, H(4′), *J* = 7.9, *J* = 0.9)	3.75 (Me)	1561, 1541, 1478, 1367
tc-**3b**	5.52 (d, *J* = 6.2)	5.43 (t, *J* = 6.0)	5.21 (d, *J* = 5.8)	7.09 (d, H(8), *J* = 8.5); 7.38 (d, H(5), *J* = 2.4); 7.42 (dd, H(7), *J* = 8.5, *J* = 2.4)	6.88 (s, H(2′)); 7.16 (ddd, H(5′), *J* = 7.9, *J* = 6.7, *J* = 1.0); 7.27 (ddd, H(6′), *J* = 8.2, *J* = 6.7, *J* = 0.9); 7.32 (d, H(7′), *J* = 8.2); 7.52 (d, H(4′), *J* = 8.0)	3.76 (Me)	—
tc-**3c** (87%)	5.51 (d, *J* = 4.7)	5.62 (dd, *J* = 5.8, *J* = 4.7)	5.35 (d, *J* = 5.8)	7.27—7.36 (m, H(8)); 8.22—8.26 (m, H(5), H(7))	7.07 (d, H(2′), *J* = 2.5); 7.21 (t, H(5′), *J* = 7.5); 7.27—7.36 (m, H(6′)); 7.45 (d, H(7′), *J* = 8.0); 7.53 (d, H(4′), *J* = 8.1)	8.34 (NH)	3425, 1589, 1561, 1515, 1480, 1347
ct-**3c** (13%)	4.66 (d, *J* = 1.5)	5.94 (t, *J* = 1.5)	5.05 (br.s)	7.30—7.37 (m, H(8)); 8.20—8.28 (m, H(5), H(7))	6.59 (d, H(2′), *J* = 2.0); 7.48 (d, H(7′), *J* = 8.0); 7.69 (d, H(4′), *J* = 8.0)	8.34 (NH)	—
tc-**4a**[g]	5.50 (d, *J* = 6.4)	5.31 (t, *J* = 6.1)	4.88 (d, *J* = 5.8)	7.05 (d, H(8), *J* = 8.6); 7.33 (d, H(5), *J* = 2.3); 7.41 (dd, H(7), *J* = 8.6, *J* = 2.3)	6.07—6.12 (m, H(5′), H(4′)); 6.60 (dd, H(3′), *J* = 2.4, *J* = 1.9)	3.61 (Me)	1564, 1478, 1448, 1359

(*to be continued*)

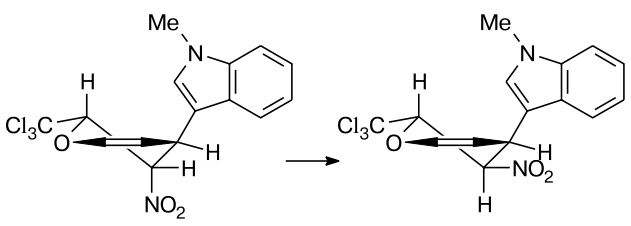
Table 1 (*continued*)

Chromane	^{1}H NMR ($CDCl_3$), δ (*J*/Hz)						IR, ν/cm^{-1}
	H(2)	H(3)	H(4)[a]	H(5)—H(8)	H(2′), H(4′)—H(7′) of indole or H(3′)—H(5′) of pyrrole	NH (br.s) or Me (s)	
tc-**4b** (96%)	5.59 (d, *J* = 5.9)	5.39 (t, *J* = 5.9)	5.02 (d, *J* = 5.7)	7.29 (d, H(8), *J* = 8.9); 8.17 (dd, H(5), *J* = 2.7, *J* = 0.5); 8.22 (dd, H(7), *J* = 8.9, *J* = 2.7)	6.03 (dd, H(5′), *J* = 3.8, *J* = 1.7); 6.12 (dd, H(4′), *J* = 3.8, *J* = 2.8); 6.64 (dd, H(3′), *J* = 2.8, *J* = 1.7)	3.65 (Me)	1588, 1564, 1521, 1487, 1343
ct-**4b** (4%)	4.71 (d, *J* = 1.5)	5.50 (t, *J* = 1.5)	4.71 (br.s)	7.30 (d, H(8), *J* = 8.9); 8.13 (d, H(5), *J* = 2.7); 8.23 (m, H(7))	5.48 (m, H(5′); 6.05 (m, H(4′); 6.75 (m, H(3′))	3.81 (Me)	—
tc-**4c** (87%)	5.57 (d, *J* = 5.9)	5.42 (t, *J* = 5.8)	4.96 (d, *J* = 5.6)	7.18 (t, H(6), *J* = 8.0); 7.49 (ddd, H(5), *J* = 7.8, *J* = 1.5, *J* = 0.7); 7.93 (dd, H(7), *J* = 8.2, *J* = 1.5)	6.11 (dd, H(5′), *J* = 3.8, *J* = 1.7); 6.14 (dd, H(4′), *J* = 3.8, *J* = 2.7); 6.65 (dd, H(3′), *J* = 2.7, *J* = 1.7)	3.63 (Me)	1588, 1558, 1526, 1492, 1459, 1364, 1346
ct-**4c** (13%)	4.73 (d, *J* = 1.5)	5.50 (t, *J* = 1.5)	4.71 (br.s)	7.15 (t, H(6), *J* = 8.0); 7.41 (dd, H(5), *J* = 7.8, *J* = 1.5); 7.98 (dd, H(7), *J* = 8.2, *J* = 1.5)	5.52 (dd, H(5′), *J* = 3.5, *J* = 1.8); 6.06 (dd, H(4′), *J* = 3.5, *J* = 2.9); 6.74 (dd, H(3′), *J* = 2.9, *J* = 1.8)	3.80 (Me)	—
ct-**4d**[h]	4.65 (qd, *J* = 6.3, *J* = 2.0)	4.98 (t, *J* = 2.0)	4.64 (br.s)	6.99 (d, H(8), *J* = 8.8); 7.24 (d, H(5), *J* = 2.4); 7.40 (dd, H(7), *J* = 8.8, *J* = 2.4)	5.54 (ddd, H(5′), *J* = 3.7, *J* = 1.8, *J* = 0.7); 6.05 (dd, H(4′), *J* = 3.7, *J* = 2.8); 6.71 (dd, H(3′), *J* = 2.8, *J* = 1.8)	3.76 (Me)	1556, 1494, 1480, 1365

[a] In the *trans*—*cis*-isomers, the doublet for H(4) is broadened because of additional splitting at the H(5) and H(7) protons.
[b] ^{19}F NMR, δ: 86.95 (d, CF_3, *J* = 5.8 Hz).
[c] ^{19}F NMR, δ: 87.00 (d, CF_3, *J* = 6.0 Hz).
[d] ^{19}F NMR, δ: 86.95 (d, CF_3, *J* = 6.1 Hz).
[e] ^{19}F NMR, δ: 86.95 (d, CF_3, *J* = 6.1 Hz).
[f] ^{19}F NMR, δ: 86.94 (d, CF_3, *J* = 6.0 Hz).
[g] The content of the *ct*-isomer in the sample is ~2%.
[h] ^{19}F NMR, δ: 87.05 (d, CF_3, *J* = 6.3 Hz).

whose structure was confirmed by X-ray diffraction analysis. Interestingly, the reaction of chromene **1e** with *N*-methylindole followed by treatment with hexane gave a mixture of *ct*-**3b** and *tc*-**3b** in the ratio 91 : 9. On recrystallization of this mixture from dichloromethane—hexane, the ratio of the isomers changed to *ct*-**3b** : *tc*-**3b** = 15 : 85. This is associated with epimerization at the C(3) atom and indicates a higher thermodynamic stability of the *trans*—*cis*-isomer of 2-CCl_3-chromanes (Scheme 3).

Scheme 3



ct-**3b** *tc*-**3b**

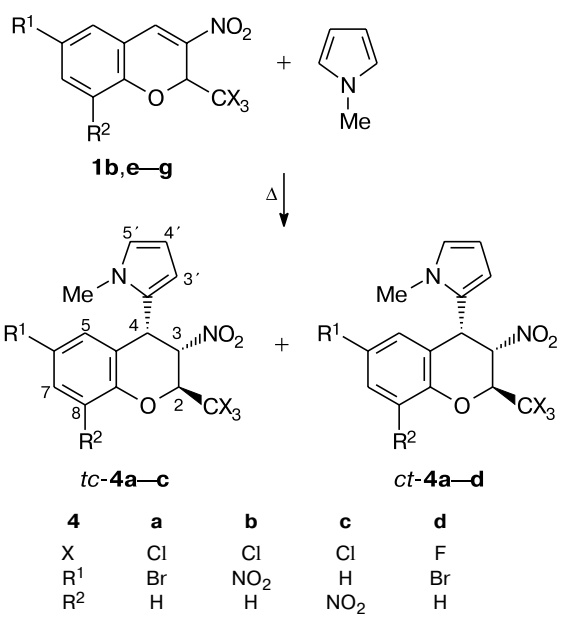
A reaction of chromene **1f** with indole gave, both prior to and after recrystallization, a mixture of *trans*—*cis*- and *cis*-*trans*-chromanes **3c**, the former being substantially dominant (87—92%). When moving from *ct*- to *tc*-isomers **3b,c**, the CS of the H(2) proton shifts downfield by ~0.9 ppm (see Table 1). This is due to the deshielding effect of the NO_2 group, which is *cis* to H(2) in the *tc*-isomer; the H(4) proton is deshielded by ~0.3 ppm, while the H(3) proton is shielded by ~0.4 ppm. It should also be noted that the ^{1}H NMR spectra of CF_3-containing *cis*—*trans*-isomers **2a**—**e** show narrow signals for the H(2), H(3), and H(4) protons at δ 4.58—4.62, 5.34—5.40, and 4.96—5.02, respectively. In the series of the *ct*-isomers, passing from CF_3- to CCl_3-chromanes (*e.g.*, *ct*-**2e** → *ct*-**3b**) is accompanied by a downfield shift (by ~0.5 ppm) of only the signal for the H(3) proton, while the CS of the H(2) and H(4) atoms remain virtually unchanged. We have observed a similar pattern earlier,[9] which confirms our correct assignment of the configuration.

Reactions of *N*-methylpyrrole with 2-CCl_3-chromenes **1e**—**g** containing electron-withdrawing substituents in po-

sitions 6 and 8 gave, under solvent-free conditions of procedure ***B***, *trans—cis*-chromanes **4a—c** in 52—75% yield (the content of the *ct*-isomer varied from 2 to 13%). A reaction of *N*-methylpyrrole with 2-CF_3-chromene **1b** afforded individual *cis—trans*-chromane **4d** in 70% yield, which resisted epimerization into the *tc*-isomer in boiling methanol in the presence of K_2CO_3. In this case, the coupling constants for the *tc*-isomers are $J_{2,3}$ = 5.9—6.4 Hz and $J_{3,4}$ = 5.6—5.8 Hz and those for the *ct*-isomers are $J_{2,3} \approx J_{3,4}$ = 1.5—2.0 Hz (Scheme 4, see Table 1).

Hence, we can conclude that the nature of the CX_3 group is decisive for the stereoselectivity of reactions with indoles and *N*-methylpyrrole: for X = F, the only product is the *ct*-isomer with the *cis*-arranged CF_3 and NO_2 groups, while for X = Cl, the major isomer exists in the *tc*-configuration, in which the bulkier CCl_3 group is *trans* to the NO_2 group. Out of four possible diastereomers (*trans—trans*, *cis—cis*, *trans—cis*, and *cis—trans*), the indolyl (pyrrolyl) fragment and trihalomethyl substituent are *trans* to each other only in the last two isomers, which probably has control over the stereochemistry of this reaction. It should also be noted that addition of indoles and pyrrole to chromenes **1** is not accompanied by elimination of nitrous acid observed earlier in reactions of 3-nitro-2*H*-chromenes with dialkyl phosphites[19] and acetylacetone.[10]

Scheme 4



4	a	b	c	d
X	Cl	Cl	Cl	F
R^1	Br	NO_2	H	Br
R^2	H	H	NO_2	H

Table 2. Yields, physicochemical characteristics, and elemental analysis data for 4-azolylchromanes **2a—e**, **3a—c**, and **4a—d**

Chromane	Yield (%), (τ/h)*	M.p. /°C	Found / Calculated (%)			Molecular formula
			C	H	N	
2a	68 (6), ***A***	182—183	59.51	3.52	7.69	$C_{18}H_{13}F_3N_2O_3$
	60 (16), ***B***		59.67	3.62	7.73	
2b	84 (8), ***B***	223—224	49.09	2.65	6.34	$C_{18}H_{12}BrF_3N_2O_3$
			49.00	2.74	6.35	
2c	73 (8), ***B***	189—190	58.16	3.69	7.17	$C_{19}H_{15}F_3N_2O_4$
	72 (15), ***A***		58.17	3.85	7.14	
2d	68 (5), ***B***	164—165	60.48	3.78	7.34	$C_{19}H_{15}F_3N_2O_3$
	62 (10), ***A***		60.64	4.02	7.44	
2e	68 (5), ***B***	207—208	50.26	3.07	6.10	$C_{19}H_{11}BrF_3N_2O_3$
			50.13	3.10	6.15	
3a	30 (20), ***B***	135—136	53.58	3.45	6.50	$C_{19}H_{15}Cl_3N_2O_3$
			53.61	3.55	6.58	
3b	61 (15), ***B***	219—220	45.28	2.63	5.61	$C_{19}H_{14}BrCl_3N_2O_3$
			45.23	2.80	5.55	
3c	70 (10), ***B***	199—200	47.23	2.57	9.12	$C_{18}H_{12}Cl_3N_3O_5$
			47.34	2.65	9.20	
4a	65 (10), ***B***	117—118	39.67	2.57	6.12	$C_{15}H_{12}BrCl_3N_2O_3$
			26.64	2.66	6.16	
4b	52 (6), ***B***	175—176	42.83	2.68	9.98	$C_{15}H_{12}Cl_3N_3O_5$
			42.83	2.88	9.99	
4c	75 (8), ***B***	157—158	42.56	2.70	9.71	$C_{15}H_{12}Cl_3N_3O_5$
			42.83	2.88	9.99	
4d	72 (6), ***B***	153—154	44.56	2.94	6.84	$C_{15}H_{12}BrF_3N_2O_3$
			44.47	2.99	6.91	

* The reaction time and the procedure used.

In conclusion, indole, *N*-methylindole, and *N*-methylpyrrole add to the activated double bond of 3-nitro-2-trihalomethyl-2*H*-chromenes to give *cis—trans*-2-CF_3- and *trans-cis*-2-CCl_3-4-azolylchromanes, which are of biological interest.

Experimental

IR spectra were recorded on a Perkin-Elmer Spectrum BX-II instrument (KBr pellets). ^{1}H and ^{19}F NMR spectra were recorded on a Bruker DRX-400 spectrometer (400.1 (^{1}H) and 376.5 MHz (^{19}F)) in $CDCl_3$ with Me_4Si and C_6F_6 as the internal standards, respectively.

The starting chromenes **1a—g** were prepared according to a known procedure.[7]

3,8-Dinitro-2-trichloromethyl-2*H*-chromene (1g). Yield 53%, m.p. 126—127 °C (from ethanol), a yellow powder. Found (%): C, 35.33; H, 1.31; N, 8.14. $C_{11}H_8Cl_3NO_4$. Calculated (%): C, 35.18; H 1.48; N, 8.25. IR, ν/cm^{-1}: 3071, 1649, 1613, 1575, 1530, 1453, 1375, 1357, 1329. ^{1}H NMR, δ: 6.49 (s, 1 H, H(2)); 7.24 (t, 1 H, H(6), J = 7.9 Hz); 7.64 (dd, 1 H, H(5), J = 7.6 Hz, J = 1.5 Hz); 8.07 (dd, 1 H, H(7), J = 8.3 Hz, J = 1.5 Hz); 8.14 (s, 1 H, H(4)).

Reactions of 3-nitrochromenes 1a—g with indoles and *N*-methylpyrrole (general procedure *A*). A mixture of an appropriate nitrochromene (1.0 mmol) and indole or *N*-methylindole (1.3 mmol) in dry pyridine (5 mL) was refluxed for a specified time (Table 2, monitoring by TLC). On cooling to ~20 °C, 30% AcOH (20 mL) was added. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from dichloromethane—hexane (1 : 1).

B. A mixture of an appropriate nitrochromene (1.0 mmol) and indole, *N*-methylindole, or *N*-methylpyrrole (3.0 mmol) was kept at 80 °C for a specified time (see Table 2) until crystallization began. Then the product was recrystallized from dichloromethane—hexane (1 : 1) to give compounds **2a—e**, **3a—c**, and **4a—d** as colorless powders: **4-(indol-3-yl)-3-nitro-2-trifluoromethylchromane (2a)**, **6-bromo-4-(indol-3-yl)-3-nitro-2-trifluoromethylchromane (2b)**, **4-(indol-3-yl)-6-methoxy-3-nitro-2-trifluoromethylchromane (2c)**, **4-(1-methylindol-3-yl)-3-nitro-2-trifluoromethylchromane (2d)**, **6-bromo-4-(1-methylindol-3-yl)-3-nitro-2-trifluoromethylchromane (2e)**, **4-(1-methylindol-3-yl)-3-nitro-2-trichloromethylchromane (3a)**, **6-bromo-4-(1-methylindol-3-yl)-3-nitro-2-trichloromethylchromane (3b)**, **4-(indol-3-yl)-3,6-dinitro-2-trichloromethylchromane (3c)**, **6-bromo-4-(1-methylpyrrol-2-yl)-3-nitro-2-trichloromethylchromane (4a)**, **4-(1-methylpyrrol-2-yl)-3,6-dinitro-2-trichloromethylchromane (4b)**, **4-(1-methylpyrrol-2-yl)-3,8-dinitro-2-trichloromethylchromane (4c)**, and **6-bromo-4-(1-methylpyrrol-2-yl)-3-nitro-2-trifluoromethylchromane (4d)**.

The ^{1}H and ^{19}F NMR and IR spectra of chromanes **2a—e**, **3a—c**, and **4a—d** are given in Table 1. Their yields, melting points, and elemental analysis data are presented in Table 2.

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