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Cyclization of 1,3-diaryl-3-phenylsulfanyl-1-propanols to thiochromans with the participation of [1,3]-PhS shift

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Abstract—Optically active (3*R*,1*RS*)-3-aryl-1-phenyl-3-phenylsulfanyl-1-propanols were easily dehydrated forming mainly *rac-cis*-2-aryl-4-phenylthiochroman, and *rac-cis*-4-aryl-2-phenylthiochroman along with the corresponding *trans*-isomers. The observed reaction outcome (rearrangement and racemisation) apparently results from the S_EAr reaction involving the unusual 1,3-phenylsulfanyl group migration. This interpretation is supported by the results of theoretical studies (DFT) on the supposed intermediates.

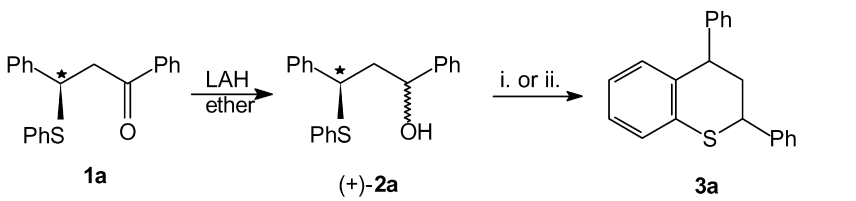
1. Introduction

The catalytic enantioselective Michael addition[1] of thiophenols to chalcones offers an easy access to the respective optically pure adducts and (+)-(*R*)-3-phenylsulfanyl-1,3-diphenylpropan-1-one, (+)-**1a** (over 95% e.e., 70% chem. yield), an interesting chiral building block is now available in the multigram quantity.[2] In order to elaborate their synthetic applications we studied possible transformations of the ketone functionality. Thus, its reduction gave the corresponding epimeric alcohol (+)-**2a**,[3] so we attempted an elimination to get the respective unsaturated enantiomeric sulfide. Unexpectedly, in both, acid and base-catalyzed elimination we obtained the cyclized product, namely 2,4-diphenylthiochroman (**3a**) (Scheme 1).[4]

When our work was underway, the similar observation on the acidic cyclization of *rac*-**2a** to **3a** was reported.[5] The heterocyclic system of **3** (3,4-dihydro-2*H*-1-benzothiopyran) has been known for its interesting properties, but it was regarded as an uneasily available one.[6] Under these circumstances and because our cyclization results differed in some respect from the reported one, we examined this reaction in more detail, finding that the rare 1,3-shift of phenylsulfanyl group takes place during the cyclization.

2. Results and discussion

When the racemic alcohol **2a** (d.m., 1:1) obtained from the racemic Michael adduct **1a** was heated with solid $KHSO_4$ (20 mol%) in toluene at 80°C, water elimination gave mainly *rac-cis*-**3a** (83%) along with *rac-trans*-**3a** (7%). Configuration of the major product (crystalline) was proved undoubtedly by 2D ^1H NMR (NOESY) and single crystal X-ray study. The presence of the earlier unnoticed[5] minor *trans*-isomer was observed running GC/MS analysis of the crude product, where two substances of the same



1a (+)-**2a** **3a**

For (*rac*)-**2a** i.: $KHSO_4$, toluene, 80°C, *cis* 83%, *trans* 7%
For (+)-**2a** ii.: MesCl/Et_3N, *cis* 81%, *trans* 17%

Scheme 1.

Keywords: cyclization; thiochromans; [1,3]-sulfanyl participation; X-ray structures; DFT calculations.

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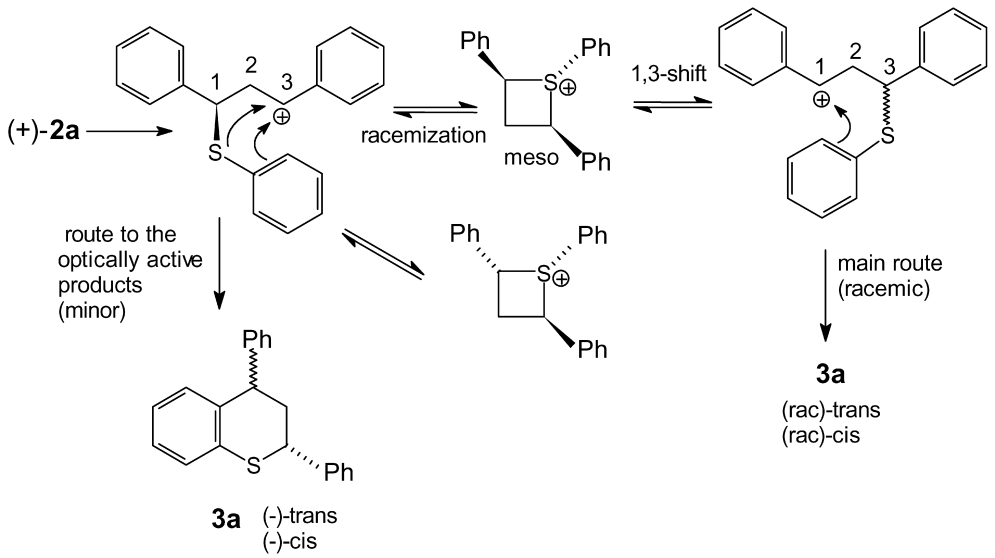


Scheme 2.

fragmentation but different retention times were detected. We were unable to isolate pure *trans*-**3a**, however, the crystallization and the removal of *cis*-**3a** led to the sample enriched in this isomer. Its ^{1}H and ^{13}C NMR spectra undoubtedly confirmed the structure of the minor isomer. Generally, a similar result was obtained in the same reaction with epimeric (+)-**2a**. Moreover, the milder elimination, avoiding acidic conditions (one-pot mesylation in the presence of excess of triethylamine followed by the amine-induced elimination of methanesulfonic acid) also led to a comparable outcome. Thus, (+)-**2a** gave mainly *cis*-**3a** (81%) along with *trans*-**3a** (17%) (Scheme 2). The direct cyclization of the benzylic cation formed from the epimeric alcohol (+)-**2a** should produce both cyclized products in the optically active forms. However, it was not the case. After recrystallization, we obtained over 57% of the isolated *cis*-**3a** as a racemate. This result suggests that the primarily formed benzylic carbocation with *R*-configuration at C-3 undergoes a racemisation, which probably involves a 1,3-shift of the phenylsulfanyl group. It seems that the rearranged/racemised cation cyclizes mainly to the most stable racemic *cis*-**3** with both phenyl groups at the pseudoequatorial positions (cf. ORTEP drawing, Fig. 1). On the other hand, the unrearranged cation may also cyclize and this reaction leaves the stereogenic center intact, so the formed products should be optically active. The isolated crystals of *cis*-**3**, being essentially racemic, (cf. elementary cell drawing, Fig. 2.) exhibited small, but measurable beyond the error, optical rotation (see Section 3). Unfortunately, we were unable to determine the ee of crude *cis*-**3a**. Anyhow, some of this product comes from the unrearranged cation.

In order to verify the hypothetical [1,3]-PhS shift we obtained (*R*)-(+)-3-(4-chlorophenyl)-1-phenyl-3-phenylsulfanylpropan-1-one (**1b**, 73% e.e.), reduced it to the corresponding epimeric alcohol (+)-**2b**, and submitted that product to the elimination ($MesCl/Et_3N$). This reaction delivered all four possible cyclic isomers, again containing small amounts of the unracemised products (Scheme 3). The main one was *rac-cis*-**3b**, accompanied by *rac-trans*-**3b** (the same MS spectra). The structure of *rac-cis*-**3b** was fully proved by a single crystal X-ray determination (Fig. 3). The presence of *cis*-**4** and *trans*-**4** resulting from the [1,3]-PhS shift was recorded as two GC peaks of the same MS fragmentation. Again, after the removal of the crystalline main isomer, ^{1}H and ^{13}C NMR of the remaining mixture allowed for the clear identification of the minor products. As expected, the ratios of *cis*/*trans* for both pairs of products as

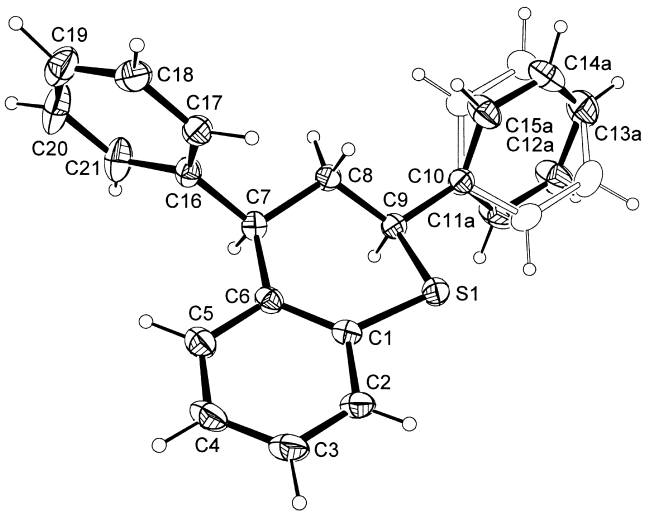


Figure 1. An Ortep view of the molecule *cis*-**3a**.

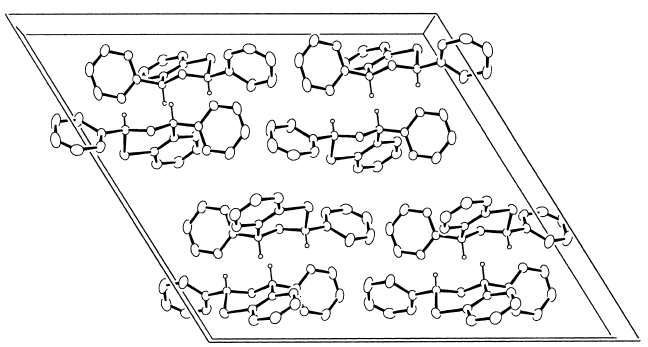
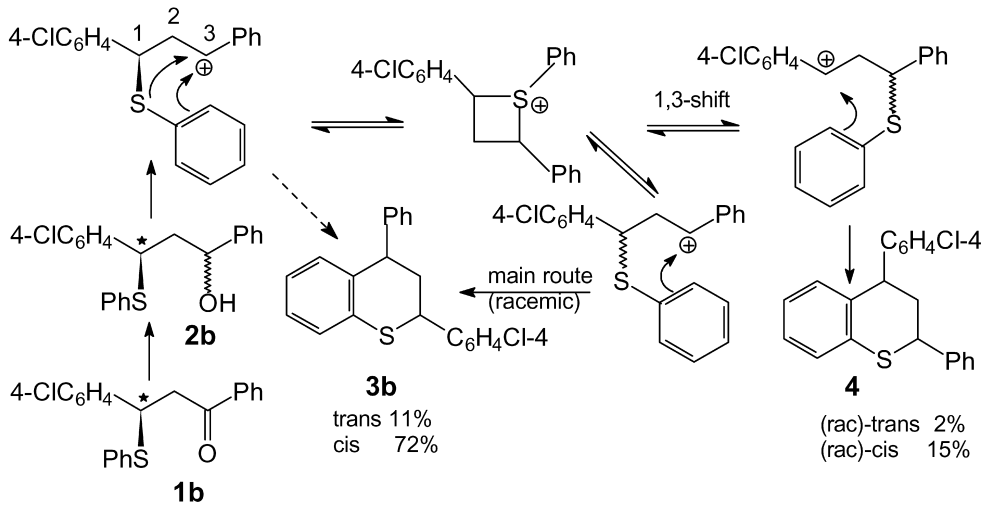


Figure 2. Elementary cell drawing for *rac-cis*-**3a** (single crystal X-ray).



Scheme 3.

well as for the pair from the previous reaction are nearly the same (ca. 7/1).

[1,3]-*SR* Participation of a sulfur atom via a four-membered sulfonium ion intermediate has already been observed but it is a rare phenomenon.[7] Contrary to the respective [1,2]- and [1,4]-SPh shifts, which are widely observed,[8] four-membered rings form slowly, the products are significantly strained and their occurrence requires special facilitating effects, e.g. the Thorpe–Ingold effect. It seemed that in our case the presence of 1,3-diaryl substituents could be responsible for such facilitation. To examine this we performed theoretical DFT calculations (for the details, see Section 3) optimizing energy for all of the possible cationic species formed from (+)-**2a**. The obtained results are presented in Figure 4.

Thus five local energy minimums were found. The highest energy value corresponds to the open-chain benzylic cation A and this energy was taken as a reference level. The lowest energy structure (10.1 kcal/mol less than A) represents the *meso-cis*-sulfonium ion M. The observed racemisation can be accounted for the reversible formation of this species.

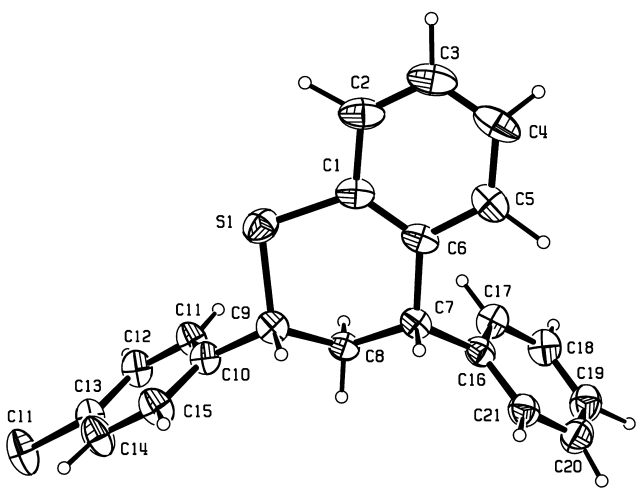


Figure 3. An Ortep view of the molecule *rac-cis*-**3b**.

The second lowest energy *trans*-sulfonium ion N (8.0 kcal/mol less than A) leads here to the degenerate rearrangement. However, in the case of different aryl moieties (as formed from **2b**) this equilibrium should also produce a rearranged product. Two other cations are the expected Wheland-type intermediates X and Y (7.2 kcal/mol less than the benzylic cation A for *cis* and 6.4 kcal/mol less for *trans*, respectively), which deprotonate to the corresponding neutral molecule of *cis*-**3a** and *trans*-**3a**. These products differ in energy by 1.8 kcal/mol, while their precursor-intermediates differ by 0.8 kcal/mol. The observed *cis*/*trans* selectivity of cyclization (7:1, i.e. 87% d.e.) is in a reasonable agreement with the selectivities resulting from both energy differences

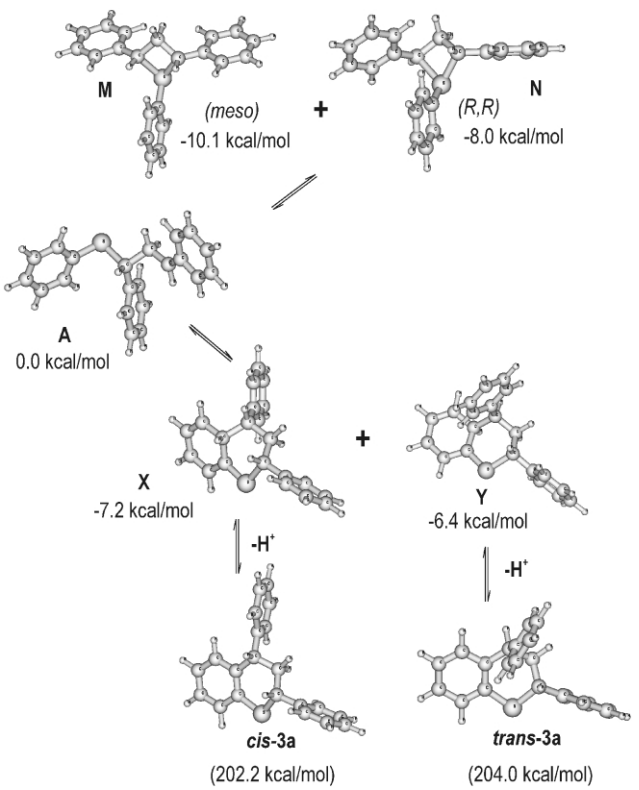


Figure 4. The DFT structures of intermediates and products. Relative energies are given in kcal/mol.

(95% based on energies of products and 78% based on energies of intermediates). Also the calculated energy required for the deprotonation of the Wheland-type intermediates (ca. 210 kcal/mol) agree with the typical value of proton affinities.[9]

In conclusion, the results of theoretical studies are in agreement with the experimental ones and both support the [1,3]-PhS shift participation in the observed conversion of 1,3-diaryl-3-phenylsulfanyl-1-propanols to thiochromans.

3. Experimental

3.1. General

Melting points were determined using a Boetius hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1600 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker CPX (300 MHz) spectrometer using TMS as an internal standard. GC/MS spectra were determined on a Hewlett–Packard 5890 II gas chromatograph (25 m capillary column) with a Hewlett–Packard mass spectrometer 5971A operating on the electron impact mode (70 eV). Optical rotations at 578 nm were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter. Separations of products by chromatography were performed on silica gel 60 (230–400 mesh) purchased from Merck. TLC analyses were performed using silica gel 60 precoated plates (Merck).

3.2. X-Ray crystallographic data

Colorless crystals of **3a**,**b** suitable for X-ray diffraction studies were grown by dissolving the compound in ethanol, and then by the slow evaporation at room temperature. The crystals were examined on a Kuma KM4CCD diffractometer equipped with a CCD camera (λ=0.71073 Å, θ_{max}=26°) at 293(2) K. Precise shell constants were determined by the least-squares method on the ground of the most of the data collection reflections. The data were corrected for the Lorentz-polarization effect.[10] The structures were solved by direct methods from SHELXS-97[11] and refined by SHELXL-97.[12] All non-hydrogen atoms were treated anisotropically. Hydrogen atoms were found from a ΔF map and refined without constraints.

3.2.1. Compound 3a. Monoclinic, C2/*c*, a=22.203(2), b=8.3995(5), c=19.9649(19) Å, β=121.179(13)°, D_x=1.261 mg m^{-3}, V=3185.5(5) Å^3, Z=8, μ=0.20 mm^{-1}, F(000)=1280, CCD camera, 8925 reflections collected, 3134 unique reflections, 2778 observed unique reflections, R_{int}=0.031, R_1=0.060 and wR_2=0.163 for $I>2\sigma(I)$, R_1=0.066 and wR_2=0.168 for all data, S=1.08, ρ_{max}=0.27, ρ_{min}=−0.27 e Å^{-3}.

3.2.2. Compound 3b. Triclinic, $P1_1$, a=8.4836(9), b=9.9211(13), c=11.1661(13) Å, α=68.686(12), β=80.763(9), γ=83.817(10)°, D_x=1.296 mg m^{-3}, V=862.93(18) Å^3, Z=2, μ=0.339 mm^{-1}, F(000)=352, CCD camera, 4614 reflections collected, 3109 unique reflections, 2270 observed unique reflections, R_{int}=0.062, R_1=0.070 and wR_2=0.202 for $I>2\sigma(I)$, R_1=0.088 and wR_2=0.226 for all data, S=1.09, ρ_{max}=0.44, ρ_{min}=−0.45 e Å^{-3}.

Crystallographic data (excluding structure factors) for the structures in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 188981 for **3a** and 188982 for **3b**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

3.3. Preparation of the chiral Michael adducts

The addition was carried out as reported before.[2] The products were further enantioenriched by recrystallization from hexane/methylene chloride. For both Michael adducts the enantiomeric forms were isolated from the mother liquors and had lower mps than the corresponding racemic crystals.

3.3.1. (*R*)-(+)-1,3-Diphenyl-3-phenylsulfanylpropan-1-one 1a. Prepared on 10 mmol scale as described earlier,[2] 70% yield after recrystallization, mp 96–97°C; $[\alpha]_D^{20}$=+136 (1.02, CH_2Cl_2), >95% e.e. All data are in agreement with those reported earlier.[2]

3.3.2. (*R*)-(+)-3-(4-Chlorophenyl)-1-phenyl-3-phenylsulfanylpropan-1-one 1b. Yield 61%, recrystallized three times, mp 74–75°C; ^{1}H NMR (300 MHz, $CDCl_3$): 3.44–3.58 (m, 2H, CH_2), 4.83 (t, J=7.1 Hz, 1H, *CH), 7.11–7.25 (m, 9H, ArH), 7.36 (t,† J=7.5 Hz, 2H, ArH), 7.48 (t, J=7.2 Hz, 1H, ArH), 7.79 (d, J=7.5 Hz, 2H, ArH); IR (KBr): 3064, 1727, 1687, 1581, 1450, 1224, 1090, 813, 744, 685 cm^{-1}; ^{1}H NMR (CCl_4, Eu(hfc)$_3$): *CH, $\Delta\delta$ 0.123 ppm, $[\alpha]_D^{20}$=+167 (1.00, CH_2Cl_2), 73% e.e.

3.4. Preparation of the alcohols

The reduction with LAH was carried out as described before.[3]

3.4.1. (3*R*)-1,3-Diphenyl-3-phenylsulfanylpropan-1-ol 2a. Diastereomeric ratio 50:50. Yield 98%. All spectral data were reported in the literature.[3]

rac-**2a**. Yield 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 1.88 (s, 1H,OH), 2.16–2.25 and 2.27–2.41 (two m, 2H, CH_2), 4.18 and 4.35 (t, J=7.4 Hz, dd, J_1=9.7 Hz, J_2=5.7 Hz, 1H, S–CH), 4.48 and 4.82 (dd, J_1=9.4 Hz, J_2=3.8 Hz, dd, J_1=7.9 Hz, J_2=5.7 Hz, 1H, CH), 7.10–7.30 (m, 15H, ArH); IR and MS spectra are in agreement with the literature data.[5]

3.4.2. (3*R*)-3-(4-Chlorophenyl)-1-phenyl-3-phenylsulfanylpropan-1-ol 2b. Diastereomeric ratio 50:50. Yield 95%. ^{1}H NMR (300 MHz, $CDCl_3$): 1.80 (br s,1H, OH), 2.22–2.36 and 2.39–2.50 (two m, 2H, CH_2), 4.23 and 4.38 (dd, J_1=8.1 Hz, J_2=6.7 Hz, dd, J_1=9.8 Hz, J_2=5.6 Hz, 1H, S–CH), 4.51 and 4.91 (dd, J_1=9.6 Hz, J_2=3.8 Hz, dd,

† The reported J values are those observed from the splitting patterns in the spectrum and may not reflect true coupling constant values.

J_1=7.9 Hz, J_2=5.6 Hz, 1H, CH), 7.11 (d, J=8.4 Hz, 1H. ArH), 7.17–7.38 (m, 13H, ArH); IR (film): 3396, 3061, 1584, 1490, 1438, 1091, 1056, 1025, 827, 751, 701 cm^{-1}; MS (EI, 70 eV): m/z (%)=354 (1) [M^+], 244 (15), 110 (51), 107 (100), 79 (46), 77 (32), 65 (8), 51 (9); $[\alpha]_D^{20}$=+144 (1.02, CH_2Cl_2); R_f=0.35 (*tert*-BuOMe/$CHCl_3$/hexane, 2.0:2.0:12.0).

3.5. Cyclization under acidic conditions

A solution of alcohol **2a** (0.285 g, 0.89 mmol) in dry toluene (30 mL) with a catalytic amount of $KHSO_4$ (0.024 g, 20 mol%) was placed in a rotatory evaporator equipped with a catch-drop. This mixture was heated at 75–80°C under slightly reduced pressure for 1.5 h, until a half amount of toluene was distilling off. The reaction color turned from light-yellow to brown during that time. Next the reaction mixture was allowed to cool to room temperature, $KHSO_4$ was filtered off, and then the solvent was evaporated under the reduced pressure. The crude product was purified by crystallization from hexane/methylene chloride. The analysis of both, the crystals and filtrate by ^{1}H NMR and GC/MS indicated that thiochroman **3a** was obtained in a crude yield of 90% and that it contained a mixture of two diastereomers: *cis*-**3a** (83% yield) and *trans*-**3a** (7% yield).

3.6. Cyclization under basic conditions

Freshly distilled methanesulfonyl chloride (0.151 mL, 1.95 mmol) was added dropwise to a magnetically stirred solution of the appropriate alcohol **2** (1.5 mmol) and Et_3N (1.672 mL, 12 mmol) in dry toluene (10 mL) cooled to −10°C. This mixture was stirred for 0.5 h at this temperature and then kept overnight at −20°C. Finally, the reaction mixture was slowly warmed to 50°C. After cooling to room temperature the reaction mixture was quenched with 1N HCl, and extracted with Et_2O (2×10 mL). The combined extracts were washed with satd. aq. $NaHCO_3$, water and brine before drying with Na_2SO_4 and concentrating in vacuo. The crude product was purified by column chromatography on silica gel using as eluent *tert*-BuOMe/$CHCl_3$/hexane (2.5:2.0:10 for **3a** and 2.5:2.0:14 for **3b** and **4**).

3.6.1. 2,4-Diphenylthiochroman *cis*-3a. Yield 81%. Mp 129.5–130°C (hexane, CH_2Cl_2), lit.[5] mp 129–132°C; ^{1}H NMR (300 MHz, $CDCl_3$): 2.45–2.54 (m, 2H, CH_2), 4.19 (dd, J_1=10.4 Hz, J_2=6.1 Hz, 1H, CH), 4.57 (dd, J_1=10.4 Hz, J_2=4.4 Hz, 1H, S–CH), 6.66 (d, J=7.8 Hz, 1H, ArH), 6.83 (t, J=7.5 Hz, 1H, ArH), 7.00 (t, J=7.5 Hz, 1H, ArH), 7.08 (d, J=7.9 Hz, 1H, ArH), 7.15–7.37 (m, 10H, ArH); ^{13}C NMR (75 MHz): 41.6 (C-3), 46.1 (C-2), 47.8 (C-4), 124.2, 126.1, 126.6, 126.8, 127.6, 127.8, 128.7, 130.0, 134.7, 136.8, 141.2, 145.0 (aromatic moiety); IR (KBr): 3057, 2913, 1601, 1585, 1492, 1452, 1051, 763, 700 cm^{-1}. GC retention time: 20.7 min (from 140 to 290°C, 8°C/min); MS (EI, 70 eV): m/z (%)=302 (88) [M^+], 211 (66), 210 (95), 197 (100), 165 (33), 91 (18), 77 (12), 51 (7); $[\alpha]_D^{20}$=−2.0 (1.52, CH_2Cl_2).

3.6.2. *trans*-3a. Yield 17%. ^{1}H NMR (300 MHz, $CDCl_3$): 2.31–2.41 (m, 2H, CH_2), 3.95 (t, J=7.6 Hz, 1H, CH), 4.34 (t, J=3.9 Hz, 1H, S–CH), 6.66–7.36 (m, 14H, ArH); ^{13}C NMR (75 MHz): 42.1 (C-3), 44.8 (C-2), 50.4 (C-4), 124.1, 125.8, 126.5, 127.1, 127.2, 127.8, 128.7, 7, 131.4, 134.4, 135.1, 140.3, 144.9 (aromatic moiety). GC retention time: 20.4 min (from 140 to 290°C, 8°C/min); MS (EI, 70 eV):m/z (%)=302 (87) [M^+], 211 (65), 210 (93), 197 (100), 165 (37), 91 (17), 77 (12), 51 (8).

3.6.3. 2-(4-Chlorophenyl)-4-phenylthiochroman *cis*-3b. Yield 72%. Mp 146.5–147°C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): 2.47–2.58 (m, 2H, CH_2), 4.24 (dd, J_1=10.9 Hz, J_2=5.1 Hz, 1H, CH), 4.60 (dd, J_1=11.0 Hz, J_2=3.5 Hz, 1H, S–CH), 6.72 (d, J=8.0 Hz, 1H, ArH), 6.90 (t, J=7.4 Hz, 1H, ArH), 7.07 (t, J=7.5 Hz, 1H, ArH), 7.14 (d, J=7.6 Hz, 1H, ArH), 7.18–7.42 (m, 9H, ArH); ^{13}C NMR (75 MHz): 41.5 (C-3), 45.4 (C-2), 47.6 (C-4), 124.4, 126.1, 126.7, 126.9, 128.7, 128.8, 128.9, 129.0, 130.1, 133.5, 134.2, 136.8, 139.8, 144.8 (aromatic moiety); IR (KBr): 3060, 3027, 1586, 1490, 1453, 1434, 1089, 1014, 833, 749, 701 cm^{-1}. GC retention time: 23.1 min (from 150 to 290°C, 7.5°C/min); MS (EI, 70 eV): m/z (%)=336 (35) [M^+], 244 (20), 211 (54), 210 (74), 197 (100), 165 (33), 152 (13), 125 (10), 91 (12), 77 (15), 51 (9); $[\alpha]_D^{20}$=−3.0 (0.98, CH_2Cl_2). Anal. calcd for $C_{21}H_{17}ClS$ (336.88): C, 74.87; H, 5.09; Cl, 10.52; S, 9.52. Found: C, 74.59; H, 5.41; Cl, 10.86; S, 9.09.

3.6.4. *trans*-3b. Yield 11%. ^{1}H NMR (300 MHz, $CDCl_3$): 2.43–2.58 (m, 2H, CH_2), 4.17 (dd, J_1=10.1 Hz, J_2=4.7 Hz, 1H, CH), 4.39 (dd, J_1=9.1 Hz, J_2=4.2 Hz, 1H, S–CH), 6.70–7.42 (m, 13H, ArH); ^{13}C NMR (75 MHz): 42.0 (C-3), 44.7 (C-2), 49.9 (C-4), 125.7, 126.5, 127.2, 127.4, 127.8, 128.6, 128.7, 128.8, 129.8, 131.3, 134.0, 134.7, 139.1, 144.7 (aromatic moiety). GC retention time: 21.2 min (from 150 to 290°C, 7.5°C/min); MS (EI, 70 eV):m/z (%)=336 (48) [M^+], 244 (21), 211 (53), 210 (76), 197 (100), 165 (32), 152 (11), 125 (10), 91 (11), 77 (16), 51 (10).

3.6.5. 2-Phenyl-4-(4-chlorophenyl)thiochroman *cis*-4. Yield 15%. ^{1}H NMR (300 MHz, $CDCl_3$): 2.27–2.31 (m, 2H, CH_2), 3.97 (dd, J_1=9.3 Hz, J_2=5.9 Hz, 1H, CH), 4.21–4.27 (m, 1H, S–CH), 6.73–7.44 (m, 13H, ArH); ^{13}C NMR (75 MHz): 41.6 (C-3), 46.0 (C-2), 47.2 (C-4), 124.3, 126.3, 126.8, 127.6, 127.9, 128.7, 128.9, 129.0, 129.9, 132.5, 134.7, 136.2, 141.0, 143.6 (aromatic moiety); this spectrum was subtracted from that of the mixture with **3b**, see above. GC retention time: 33.1 min (from 150 to 290°C, 7.5°C/min); MS (EI, 70 eV): m/z (%)=336 (5) [M^+], 235 (17), 233 (39), 199 (100), 165 (11), 151 (8), 135 (10), 115 (17), 109 (23), 91 (21), 77 (8), 65 (10), 51 (4).

3.6.6. *trans*-4. Yield 2%. GC retention time: 32.1 min (from 150 to 290°C, 7.5°C/min); MS (EI, 70 eV): m/z (%)=336 (3) [M^+], 235 (16), 233 (41), 199 (100), 165 (17), 151 (3), 135 (6), 115 (22), 109 (21), 91 (16), 77 (13), 65 (15), 51 (7).

3.7. Details of the theoretical treatment

The theoretical studies supporting the search for the reaction mechanism were performed applying the density functional theory (DFT) method. The DFT approach utilized Backe's three-parameter functional[13] with the local correlation part of Vosco et al.[14] and the non-local part of Lee et al.[15] (abbreviated as B3LYP). The calculation were performed in the standard 6-13G* atomic basis set.[16] The enthalpy

differences between studied moieties taking part in the proposed reaction scheme were calculated for the theoretically optimized structures. The results reported here were obtained using the GAUSSIAN-98 code.[17]

Additional information including MS fragmentation schemes for **3a**,**b**, and **4** as well as the Cartesian coordinates for the optimized structures (Fig. 4) are available from the corresponding author upon request.

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