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cis/trans-Isochromanones. DMAP induced cycloaddition of homophthalic anhydride and aldehydes

Milen G. Bogdanov and Mariana D. Palamareva*

Faculty of Chemistry, Sofia University, 1, J. Bouchier Ave., 1164 Sofia, Bulgaria

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Abstract—Homophthalic anhydride (**1**) reacts with wide variety of aromatic aldehydes, in the presence of chloroform and DMAP (*N*,*N*-dimethyl-4-amino-pyridine) at room temperature, to give in high yields *cis*- and *trans*-1-oxo-isochroman-4-carboxylic acids. Under these conditions, the *trans*-isomer is predominant and formation of Perkin-type products was not observed in contrast to the reaction carried out in the presence of pyridine. The unexpected *trans*-6-oxo-11-thiophen-2-yl-11,12-dihydro-6*H*-dibenzo[*c*,*h*]chromene-12-carboxylic acid methyl ester (**8**) was isolated when the reaction between **1** and thiophene-2-carbaldehyde was carried out in pyridine.

1. Introduction

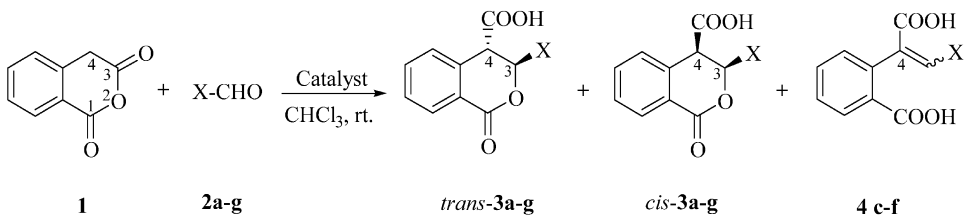
Until now, the reaction between homophthalic anhydride (**1**) and aldehydes has been performed under different reaction conditions[1–7] affording the corresponding thermodynamically controlled C-4 methylene condensed products of type **4** or the kinetically controlled cycloadducts *trans*-**3**[2] (Scheme 1). This reaction has been performed both in basic and acidic media (Table 1). The best results for benzaldehyde have been observed in the presence of strong base at low temperature[2] (entry 3). In contrast, under the same catalyst, but at room temperature[2] (entry 4), the reaction is considered as thermodynamically controlled yielding a mixture of acid *trans*-**3a** and the C-4 methylene condensed product **4a**, the latter being predominant. When the reaction is carried out in the presence of a Lewis acid ($BF_3{\cdot}Et_2O$ complex, entry 5),[3] the reaction gives the cycloadducts *cis*- and *trans*-**3a** and formation of **4a** is not observed. It is clear that there is some contradiction as to which is the thermodynamically favored diastereomer. In the analogous reaction between **1** and acyclic imines,[8,9] the *trans* is the thermodynamically preferred diastereomer.

Table 1. Ratios among products in the reaction of homophthalic anhydride (**1**) and benzaldehyde (**2a**) under different reaction conditions

Entry	Catalyst	Reaction conditions		Ratios (%)		
		t (°C)	Time (h)	*cis*-**3a**	*trans*-**3a**	**4a**
1	Na/liq. NH_3[1]	rt	14	—	61	—
2	Na_2CO_3[2]	rt	24	—	35[a]	43[a]
3	NaH[2]	0-rt	24	—	83[a]	—
4	NaH[2]	rt	33	—	5[a]	82[a]
5	$BF_3{\cdot}Et_2O$[3]	rt	5	38	43	—

[a] Isolated as a methyl esters after treatment of acidic residue with diazomethane.

4-Dimethylaminopyridine (DMAP) is known to be an excellent catalyst for a variety of synthetic transformations under mild conditions, such as alkylation, acylation, silylation, esterification, polymerisation and



1 **2a-g** *trans*-**3a-g** *cis*-**3a-g** **4 c-f**

X= Ar or HetAr (see Table 2)

Scheme 1.

Keywords: Homophthalic anhydride; Aldehydes; Cycloaddition; DMAP; Pyridine; Isochroman-4-carboxylic acids.
* Corresponding author. Tel.: +359-2-8161-221; fax: +359-2-962-54-38; e-mail address: mpalamareva@chem.uni-sofia.bg

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rearrangements.[10] This paper presents a study on the reaction of homophthalic anhydride (**1**) with different aromatic or heteroaromatic aldehydes in the presence of DMAP at mild conditions: room temperature and duration of 1.5–2.5 h. Thus, we demonstrated that under these conditions **1** reacted with benzaldehyde to give cycloadducts *cis*-**3a** and *trans*-**3a** only. This procedure gives excellent results and was extended to a wide variety of aromatic aldehydes. A comparison with the reaction in the presence of pyridine is done.

2. Results and discussion

2.1. Small scale syntheses of 3-aryl-1-oxo-isochroman-4-carboxylic acids 3a–g

Scheme 1 shows that the reaction between **1** and aldehydes **2a–g**, including benzaldehyde (**2a**), lead always to cycloadducts **3**, while the C-4 methylene condensed by-products **4** are obtained in cases **c–f** only. To establish the ratios among *cis*-**3**, *trans*-**3** and **4** in the presence of DMAP, the reaction between **1** and aldehydes **2a–g** was performed on a small scale (by 0.54–0.77 mmol of **1**) under mild conditions (Table 2). The aprotic solvent used was chloroform. Such studies on the reaction of **1** with aldehydes are not known. The reaction is stereoselective towards the *trans*-isomer. The ratios among *cis*-**3**, *trans*-**3** and **4** were determined by ^{1}H NMR spectroscopy from the integrals of relevant protons. The signals for the protons at C-3 and C-4 were used[1–6] for any isomer of type **3**. In the case of products **4c–f**, the olefinic proton was taken into account. The results are summarized in Table 2. The configuration of each isomer was determined on the basis of $J_{3,4}$.[1–6] *trans* Configuration was as to the isomer with greater $J_{3,4}$ ($J_{3,4}>5.6$ Hz) and *cis* configuration as to the isomer with smaller $J_{3,4}$ ($J_{3,4}<4$ Hz). It is clear that the quantities of **3** (both isomers) vary from 70 to 100% when **1** is not present at the end of the reaction (TLC). When benzaldehyde or substituted benzaldehydes are used, the total yield of cycloadducts **3a–d,g** (both isomers) is 95%. In the cases when the aldehyde is substituted with a heterocyclic ring, such as furan-2-yl and thiophen-2-yl (**2e,f**), the C-4 methylene condensed products **4e,f** were detected in quantities 9–30%. It is known that the reaction of **1** with furfural in the presence of sodium carbonate[6] gives the C-4 methylene condensed product **4f** only. **4e** is known, but is prepared in another way.[11] It is clear that cycloaddition is the preferred reaction when DMAP is used as a base. The formation of the C-4 methylene condensed by-products **4** depends on the type of the aromatic or heteroaromatic substituent on the aldehyde. Formation of **4** is avoided if the substituent X does not deactivate or even activates the aldehyde group to nucleophilic addition (entries a, b, g). It is worth noting that the nitrogen atom in 9-methyl-carbazole-3-carbaldehyde (**2g**) influences slightly the aldehyde group. Thus, aldehyde **2g** behaves in a similar manner to **2a** in the reaction studied. The presence of electron-donating group in **2c–f** deactivates the aldehyde group and always leads to formation of **4** along with adducts **3**.

2.2. Large scale preparation of acids 3a–g

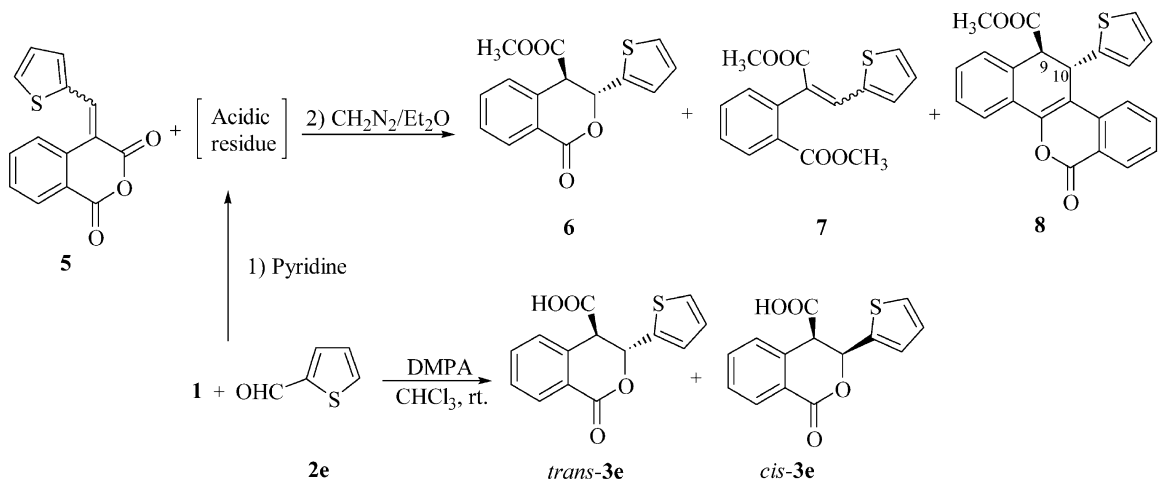
For the isolation and characterization of acids **3a–g**, we carried out the reactions between **1** and **2a–g**, on 2.7–3.9 mmol of substrate, in the presence of DMAP–chloroform. In all cases, both diastereomeric cycloadducts were formed. The diastereomers of **3a,b** were separated by fractional crystallization. In case **2d**, column chromatography lead to isolation of **4d** only, while *cis*- and *trans*-**3d** crystallized as a diastereomeric mixture. **3c,e,f** and **g** were isolated as *trans*-isomers only, since the quantity of the relevant *cis*-isomers was small. All isolated compounds gave the expected spectroscopic data (IR, ^{1}H NMR) and microanalyses.

2.2.1. Preparation of acid *trans*-3e and the methyl esters 6, 7 and 8. Comparison between two basic catalysts. The reaction between **1** and thiophene-2-carbaldehyde **2e** was performed also on larger scales (18–36 mmol of substrate) both in DMAP–chloroform and in pyridine. These experiments aimed to compare of DMAP with another basic catalyst. Significant differences were established, as shown in Scheme 2. When the reaction was carried out in pyridine, the unsaturated anhydride **5** was isolated in 27% yield. Compound **5** is known[11] but is prepared in another way. Having isolated **5**, the acidic residue was treated with diazomethane giving a mixture of compounds **6**, **7** and **8** (TLC) separated by column chromatography of the crude reaction mixture. The presence of **6** and **7** is well understood, but the presence of **8** is unexpected. There is no literature procedure for the preparation of compounds of this type in a reaction between **1** and carbonyl compounds. The structure of compound **8** was confirmed by spectral data

Table 2. Ratios among products in the reaction of homophthalic anhydride and aromatic aldehydes in the presence of DMAP at room temperature

2	X–CHO	Reaction time (h)[a]	Total yield (%)[b]	Ratio (%)[c]		
				3-*cis*	**3**-*trans*	**4**
2a	Benzaldehyde	2	100	30	70	—
2b	4-Nitro-benzaldehyde	2	98	23	77	—
2c	4-Methoxy-benzaldehyde	2.5	98	16	80	4
2d	Benzo[1,3]dioxole-5-carbaldehyde[d]	2	100	16	79	5
2e	Thiophene-2-carbaldehyde	1.5	100	9	82	9
2f	Furan-2-carbaldehyde	1.5	100	8	62	30
2g	9-Methyl-9*H*-carbazole-3-carbaldehyde	2	80	9	91	—

[a] The complete consumption of **1** was determined by TLC.
[b] Yields of the obtained acidic residue before recrystallization.
[c] The ratio was determined by ^{1}H NMR integrals of the obtained acidic residue (see text).
[d] Pipperonal.



Scheme 2.

(^{1}H, ^{13}C NMR, MS, IR) and microanalysis. In general, the lower value of $J_{9,10}$ (J=1.3 Hz) in ^{1}H NMR spectrum suggests the *cis*-configuration of **8** and a conformation with equatorial thiophenyl and axial methoxycarbonyl group,[1] but X-ray crystallography of **8**[12] showed the configuration to be *trans* and that the substituents at C-9 and C-10 are diaxial. The torsion angle H9–C9–C10–H10 is 78°. (Fig. 1). This angle agrees with the smaller value of the coupling constant $J_{9,10}$. The presence of the parent acid of **8** can be rationalized by lactam ring opening in *trans*-**3e** and subsequent interaction with an equimolar quantity of homophthalic anhydride.

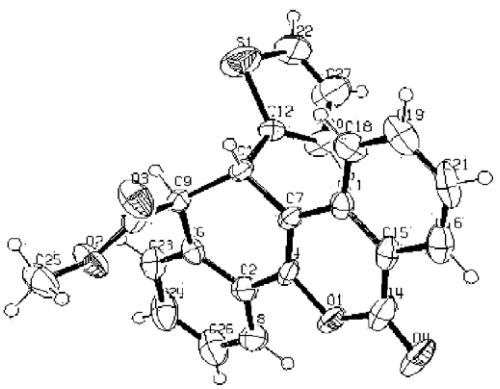


Figure 1. Configuration and conformation of *trans*-**8**.

The reaction between **1** and thiophene-2-carbaldehyde **2e** in the presence of DMAP on larger scale proceeded similarly to the smaller-scale cases and by-products **5** (Perkin-type) and **8** were not observed. Under these conditions, we were able to isolate also acid *cis*-**3e**. The conversion of *trans*-**3e** to the methyl ester was accomplished by treatment with diazomethane in diethylether solution. The direct esterification of acid **3e** or its treatment with iodomethane in the presence of potassium carbonate leads to α,β-unsaturated product **7**.

3. Conclusions

We have presented an optimized method for synthesis of 1-oxo-isochroman-4-carboxylic acid derivatives by the cyclo-addition reaction of homophthalic anhydride with aldehydes, catalyzed by DMAP. The reaction occurs under mild conditions and has been extended to a wide variety of aldehydes. The reaction is highly stereoselective towards the *trans*-cycloadducts in cases **3a–g**. This method has been compared with the analogous reaction in pyridine and has proved to be preferable.

4. 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 and Bruker Avance DRX-250 spectrometer at 250.13 MHz. The ^{13}C NMR spectra were obtained on a Bruker AM300 NMR spectrometer at 75 MHz in $CDCl_3$. The chemical shift is given in ppm (δ) 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%. Mass spectra were recorded on a Hewlett Packard MS 5973 using electron impact of 30 eV. The microanalyses were done in the relevant laboratories at the Faculty of Chemistry, University of Sofia. TLC was done on precoated 0.2 mm Merck silica gel 60F_{254} plates. Merck silica gel 60 (0.040–0.063 mm) was used for chromatographic filtration and column chromatography.

4.1. General procedure for determination of the ratios of the products obtained from 1 and aldehydes 2a–g in the small scale experiments

To a mixture of **1** (0.54–0.77 mmol) and 1.1 equiv. of corresponding aldehyde (see Table 2) in dry chloroform (1 ml), DMAP (1 equiv.) was added. The reaction mixture was stirred at room temperature for 1.5–2.5 h. At the end of the reaction, presence of **1** was not established (TLC). The obtained carboxylic acids were extracted with 10% sodium hydrogen carbonate and the aqueous layer was acidified (pH=3) with 10% hydrochloric acid and extracted with ethyl acetate. The organic layer was dried (sodium sulfate), filtered and the solvent was then evaporated. The ratios of

all products (*cis*-**3**/*trans*-**3**/**4**) were determined, as described above, by ^{1}H NMR (300 MHz) integrations. The data obtained are summarized in Table 2.

4.2. General procedure for synthesis of 1-oxo-isochroman-4-carboxylic acids on large scales

To a mixture of **1** (2.69–3.87 mmol) and 1.1 equiv. of corresponding aldehyde **2** in dry chloroform (5 ml) DMAP (1 equiv.) was added. The reaction mixture was stirred at room temperature for 1.5–2.5 h. At the end of the reaction, when **1** was shown to have been consumed (TLC), the obtained carboxylic acids were extracted with 10% sodium hydrogen carbonate. The aqueous layer was acidified (pH=3) with 10% hydrochloric acid and extracted with ethyl acetate. The organic layer was dried (sodium sulfate), filtered and the solvent was then evaporated under reduced pressure. The products were obtained by precipitation or fractional crystallization of the residue.

4.2.1. 3-Phenyl-1-oxo-isochroman-4-carboxylic acids (3a). *cis-Diastereomer*. The residue was treated with dichloromethane until precipitation. Yield: 0.14 g (14%), mp 179–180 °C, (lit.[3] mp 189–190 °C); IR (Nujol): (CO) 1735, 1710 cm^{-1}; ^{1}H NMR (250 MHz, dimethyl sulfoxide-d_6): δ=4.14 (1H, d, J=3.5 Hz, *H*-4), 5.80 (1H, d, J=3.5 Hz, *H*-3), 7.38–7.46 (4H, m, phenyl protons), 7.53–7.59 (3H, m, phenyl protons), 7.65 (1H, dt, J=1.5, 7.5 Hz, phenyl proton), 8.18 (1H, dd, J=1.4, 7.8 Hz, phenyl proton), 13.01 (1H, s, COOH). Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.64%; H, 4.51%; Found: C, 71.36%; H, 4.32%.

trans-Diastereomer. The dichloromethane filtrate was distilled under reduced pressure and the product was recrystallized from ethyl acetate giving colorless prisms. Yield: 0.61 g (61%), mp 169–170 °C, (lit.[3] mp 180–181 °C); IR (Nujol): (CO) 1735, 1715 cm^{-1}; ^{1}H NMR (250 MHz, dimethyl sulfoxide-d_6): δ=4.36 (1H, d, J=7.5 Hz, *H*-4), 5.92 (1H, d, J=7.5 Hz, *H*-3), 7.29–7.39 (6H, m, phenyl protons), 7.50 (1H, t, J=7.5 Hz, phenyl proton), 7.62 (1H, dt, J=1.5, 7.5 Hz, phenyl proton), 8.18 (1H, dd, J=1.5, 7.8 Hz, phenyl proton), 12.75 (1H, s, COOH). Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.64%; H, 4.51%; Found: C, 71.88%; H, 4.11%.

4.2.2. 3-(4-Nitro-phenyl)-1-oxo-isochroman-4-carboxylic acids (3b). *cis-Diastereomer*. The residue was treated with dichloromethane until precipitation. Yield: 0.18 g (18%), mp 199–201 °C; IR (Nujol): (CO) 1740, 1710 cm^{-1}; ^{1}H NMR (250 MHz, dimethyl sulfoxide-d_6): δ=4.48 (1H, d, J=3.5 Hz, *H*-4), 6.19 (1H, d, J=3.5 Hz, *H*-3), 7.53–7.62 (2H, m, phenyl protons), 7.74 (1H, dt, J=1.5, 7.5 Hz, phenyl proton), 7.83 (2H, d, J=8.5 Hz, phenyl protons), 8.06 (1H, dd, J=1.3, 7.8 Hz, phenyl proton), 8.32–8.36 (2H, m, phenyl protons), 12.86 (1H, s, COOH). Anal. Calcd for $C_{16}H_{11}NO_6$: C, 61.35%; H, 3.54%; Found: C, 61.41%; H, 3.44%.

trans-Diastereomer. After isolation of the *cis*-isomer, the solvent was removed under reduced pressure and the product was crystallized from ethanol–water (1:1) as colorless prisms. Yield: 0.70 g (70%), mp 163–165 °C; IR (Nujol): (CO) 1740, 1715 cm^{-1}; ^{1}H NMR (250 MHz, dimethyl sulfoxide-d_6): δ=4.35 (1H, d, J=7.5 Hz, *H*-4), 6.06 (1H, d, J=7.5 Hz, *H*-3), 7.38 (1H, d, J=7.8 Hz, phenyl proton), 7.50 (1H, t, J=7.5 Hz, phenyl proton), 7.61–7.69 (3H, m, phenyl protons), 8.11 (1H, dd, J=1.3, 7.8 Hz, phenyl proton), 8.19–8.23 (2H, m, phenyl protons), 13.21 (1H, s, COOH). Anal. Calcd for $C_{16}H_{11}NO_6$: C, 61.35%; H, 3.54%; Found: C, 61.51%; H, 3.54%.

4.2.3. 3-(4-Methoxy-phenyl)-1-oxo-isochroman-4-carboxylic acid (3c). *trans-Diastereomer*. The residue crystallized as white crystals (from ethyl acetate). Yield: 0.60 g (60%), mp 149–151 °C; IR (Nujol): (CO) 1740, 1715 cm^{-1}; ^{1}H NMR (250 MHz, dimethyl sulfoxide-d_6): δ=3.73 (3H, s, OCH_3), 4.61 (1H, d, J=7.2 Hz, *H*-4), 5.86 (1H, d, J=7.2 Hz, *H*-3), 6.89–6.95 (2H, m, phenyl protons), 7.32–7.39 (3H, m, phenyl protons), 7.51 (1H, dt, J=1.0, 7.5 Hz, phenyl proton), 7.69 (1H, dt, J=1.5, 7.5 Hz, phenyl proton), 7.97 (1H, dd, J=1.3, 7.8 Hz, phenyl proton), 13.22 (1H, s, COOH). Anal. Calcd for $C_{17}H_{14}O_5$: C, 68.45%; H, 4.73%; Found: C, 68.68%; H, 4.68%.

4.2.4. 3-Benzo[1,3]dioxol-5-yl-1-oxo-isochroman-4-carboxylic acids (3d) and 2-(2-benzo[1,3]dioxol-5-yl-1-carboxyvinyl)-benzoic acid (4d). A precipitate being a mixture of *cis*- and *trans*-diastereomers **3d** (from ethyl acetate, after column chromatography) was obtained. Yield: 0.76 g (76%), mp 139–141 °C; IR (Nujol): (CO) 1740, 1700 cm^{-1}; ^{1}H NMR (250 MHz, dimethyl sulfoxide-d_6).

cis-Diastereomer. δ=4.08 (1H, d, J=3.6 Hz, *H*-4), 5.69 (1H, d, J=3.6 Hz, *H*-3).

trans-Diastereomer. δ=4.30 (1H, d, J=8.0 Hz, *H*-4), 5.77 (1H, d, J=8.0 Hz, *H*-3), other signals for both diastereomers: δ=5.95 (2H, s, $-OCH_2O-$), 6.73 (1H, d, J=8.0 Hz, phenyl proton), 6.80–6.89 (2H, m, phenyl protons), 7.29 (1H, d, J=8 Hz, phenyl proton), 7.45 (1H, t, J=7.4 Hz, phenyl proton), 7.61 (1H, dt, J=1.5, 7.6 Hz, phenyl proton), 8.17 (1H, dd, J=1.3, 7.6 Hz, phenyl proton). Anal. Calcd for $C_{17}H_{12}O_6$: C, 65.39%; H, 3.87%; Found: C, 64.98%; H, 4.05%.

By-product **4d** was obtained from the filtrate of **3d** as colorless prisms (from ethyl acetate, after column chromatography). Yield: 0.04 g (4%), mp 177–179 °C; IR (Nujol): (CO) 1745, 1715 cm^{-1}; ^{1}H NMR (250 MHz, dimethyl sulfoxide-d_6): δ=5.94 (2H, s, $-OCH_2O-$), 6.24 (1H, d, J=1.5 Hz, phenyl proton), 6.69 (1H, dd, J=1.8, 8.3 Hz, phenyl proton), 6.79 (1H, d, J=8.0 Hz, phenyl proton), 7.09 (1H, dd, J=1.8, 7.0 Hz, phenyl proton), 7.45–7.57 (2H, m, phenyl protons), 7.56 (1H, s, H-olefinic), 8.01 (1H, dd, J=2.0, 7.0 Hz, phenyl proton), 12.57 (2H, s, COOH).

4.2.5. 3-Thiophen-2-yl-1-oxo-isochroman-4-carboxylic acid (3e). *trans-Diastereomer*. This compound was obtained as colorless prisms (from ethyl acetate). Yield: 0.75 g (75%), mp 122–124 °C; IR (Nujol): (CO) 1740, 1685 cm^{-1}; ^{1}H NMR (250 MHz, dimethyl sulfoxide-d_6) δ=4.28 (1H, d, J=5.7 Hz, *H*-4), 6.23 (1H, d, J=5.7 Hz, *H*-3), 6.92 (1H, dd, J=3.6, 5.0 Hz, thienyl proton), 7.03–7.09 (1H, m, thienyl proton), 7.25 (1H, dd, J=3.6, 5.0 Hz, thienyl proton), 7.40–7.45 (1H, m, phenyl proton), 7.48–7.52 (1H, m, phenyl proton), 7.63 (1H, dt, J=1.6,

7.7 Hz, phenyl proton), 8.12 (1H, dd, *J*=1.5, 7.8 Hz, H-8). Anal. Calcd for $C_{14}H_{10}O_4S$: C, 61.30%; H, 3.67%; Found: C, 61.50%; H, 3.51%.

4.2.6. 3-Furan-2-yl-1-oxo-isochroman-4-carboxylic acid (3f). *trans-Diastereomer*. This compound was obtained as white crystals (from ethyl acetate). Yield: 0.54 g (54%), mp 152–154 °C; IR (Nujol): (CO) 1730, 1710 cm^{-1}; ^1H NMR (250 MHz, dimethyl sulfoxide-d_6): δ=4.59 (1H, d, *J*=4.8 Hz, *H*-4), 6.07 (1H, d, *J*=4.8 Hz, *H*-3), 6.31 (1H, d, *J*=3.3 Hz, furyl proton), 6.40 (1H, dd, *J*=2.0, 3.5 Hz, furyl proton), 7.49–7.55 (2H, m, phenyl protons), 7.64 (1H, dd, *J*=0.8, 2.0 Hz, furyl proton), 7.72 (1H, dt, *J*=1.5, 7.8 Hz, phenyl proton), 7.95 (1H, d, *J*=7.8 Hz, phenyl proton), 13.40 (1H, s, COOH). Anal. Calcd for $C_{14}H_{10}O_5$: C, 65.12%; H, 3.90%; Found: C, 64.97%; H, 3.88%.

4.2.7. 3-(9-Methyl-9*H*-carbazol-3-yl)-1-oxo-isochroman-4-carboxylic acid (3g). *trans-Diastereomer*. This compound was precipitated in water, purified by recrystallization and isolated as white crystals (from DMF). Yield: 0.78 g (78%), mp 206–208 °C; IR (Nujol): (CO) 1740, 1715 cm^{-1}; ^1H NMR (250 MHz, dimethyl sulfoxide-d_6): δ=3.87 (3H, s, $-NCH_3$), 4.79 (1H, d, *J*=8.0 Hz, *H*-4), 6.07 (1H, d, *J*=8.0 Hz, *H*-3), 7.22 (1H, t, *J*=7 Hz, phenyl proton), 7.39–7.62 (6H, m, phenyl protons), 7.71 (1H, dt, *J*=1.5, 7.8 Hz, phenyl proton), 8.03 (1H, dd, *J*=1.0, 7.5 Hz, phenyl proton), 8.13 (1H, d, *J*=7.8 Hz, phenyl proton), 8.26 (1H, s, phenyl proton), 13.26 (1H, s, COOH). Anal. Calcd for $C_{23}H_{17}NO_4$: C, 74.38%; H, 4.61%; Found: C, 73.99%; H, 4.52%.

4.3. Reaction between homophthalic anhydride and thiophene-2-carbaldehide (2e) performed on larger scales and subsequent transformations

4.3.1. Reaction in DMAP–chloroform. 1-Oxo-3-thiophen-2-yl-isochroman-4-carboxylic acid (**3e**). To a stirring mixture of 3.00 g (18.52 mmol) homophthalic anhydride and 1.7 ml (18.25 mmol) 2-thiophene carbaldehyde in dry chloroform (20 ml) was added DMAP 3.34 g (27.37 mmol). After stirring for 1.5 h. at room temperature, TLC analysis showed the absence of homophthalic anhydride. The reaction mixture was then extracted with 10% sodium hydrogen carbonate three times. The hydrogen carbonate layers were washed once with ethyl acetate, acidified with 10% hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and dried (sodium sulfate). The solvent was removed under reduced pressure. Crystallization of the residue gave:

trans-Diastereomer. This compound was obtained as colorless prisms (from hexane–ethyl acetate). Yield: 3.74 g (74%), mp 122–124 °C (see Section 4.2.5).

cis-Diastereomer. This compound was obtained as colorless needless (from ethyl acetate) after isolation of the *trans*-diastereomer. Yield: 0.35 g (7%), mp 160–162 °C; IR (Nujol): (CO) 1740, 1690 cm^{-1}; ^1H NMR (300 MHz, dimethyl sulfoxide-d_6): δ=4.37 (1H, d, *J*=3.5 Hz, *H*-4), 6.23 (1H, d, *J*=3.5 Hz, *H*-3), 7.09 (1H, dd, *J*=3.5, 5.0 Hz, thienyl proton), 7.24 (1H, d, *J*=3.5 Hz, thienyl proton), 7.52–7.60 (3H, m, thienyl and phenyl protons), 7.72 (1H, dt, *J*=1.5, 7.5 Hz, phenyl proton), 8.03 (1H, dd, *J*=1.5, 7.7 Hz, phenyl proton), 12.95 (1H, s, COOH). Anal. Calcd for $C_{14}H_{10}O_4S$: C, 61.30%; H, 3.67%; Found: C, 61.28%; H, 3.67%.

4.3.2. Reaction in pyridine. 4-Thiophen-2-yl-methylene-isochroman-1,3-dione (**5**), *trans*-1-oxo-3-thiophen-2-yl-isochroman-4-carboxylic acid methyl ester (**6**), 2-(1-methoxycarbonyl-2-thiophen-2-yl-vinyl)-benzoic acid methyl ester (**7**) and *trans*-6-oxo-11-thiophen-2-yl-11,12-dihydro-6*H*-dibenzo [*c*,*h*]chromene-12-carboxylic acid methyl ester (**8**)

To a mixture of 5.91 g (36.5 mmol) homophthalic anhydride and 5 ml (57.74 mmol) 2-thiophene carbaldehyde, 35 ml pyridine was added. After stirring for 5 h. at room temperature, the reaction mixture was filtered to give orange crystals of **5** (2.67 g) in 27% yield. The filtrate was diluted with water and extracted with chloroform. The chloroform layer was washed with diluted hydrochloric acid once and extracted with 10% sodium hydrogen carbonate. The hydrogen carbonate extract was washed once with ethyl acetate, acidified (pH=3) with 10% hydrochloric acid and extracted three times with ethyl acetate (100 ml). The organic layers were washed with water, dried (sodium sulfate) and the solvent was removed under reduced pressure to give 6.74 g an oil. The residue, containing acidic compounds was diluted with chloroform and treated with diazomethane. The mixture was stirred at room temperature for 2 h. The excess diazomethane and chloroform was removed under reduced pressure giving an oil (6.80 g). The residue was purified by column chromatography on silica gel to give the esterified products *trans*-**6** (2.34 g, 34%), *trans*-**8** (1.00 g, 15%) along with 1.70 g (25%) of **7**.

Compound **5** was obtained as orange needles (from pyridine). Yield: 2.67 g (27%). After recrystallization from DMF: mp 232 °C, (lit.[11] mp 232 °C); IR: (CO–O–CO) 1755, 1715 cm^{-1}; ^1H NMR (250 MHz, TFA): δ=7.25 (1H, t, *J*=4 Hz, thienyl proton), 7.53 (1H, t, *J*=7.5 Hz, phenyl proton), 7.80–7.96 (4H, m, thienyl and phenyl protons), 8.27 (1H, d, *J*=8 Hz, phenyl proton), 8.60 (1H, s, H-olefinic). Anal. Calcd for $C_{14}H_8O_3S$: C, 65.61%; H, 3.15%; Found: C, 65.59%; H, 3.15%.

Compound **6** was obtained as colorless prisms after column chromatography (from hexane–ethyl acetate). Yield: 2.34 g (34%), mp 126–128 °C; IR: (CO) 1750, 1730 cm^{-1}; ^1H NMR (300 MHz, deuteriochloroform): δ=3.75 (3H, s, OCH_3), 4.34 (1H, d, *J*=6.3 Hz, *H*-4), 6.18 (1H, d, *J*=6.3 Hz, *H*-3), 6.23 (1H, dd, *J*=3.6, 5.0 Hz, thienyl proton), 7.04–7.07 (1H, m, thienyl proton), 7.26 (1H, dd, *J*=1.5, 5.1 Hz, thienyl proton), 7.29 (1H, dm, *J*=7.6 Hz, phenyl proton), 7.49 (1H, t, *J*=7.6 Hz, phenyl proton), 7.63 (1H, dt, *J*=1.5, 7.6 Hz, phenyl proton), 8.15 (1H, dd, *J*=1.5, 7.8 Hz, phenyl proton); ^{13}C NMR (75 MHz): δ=169.71, 163.28, 139.62, 135.45, 134.40, 130.65, 129.07, 127.67, 127.20, 126.79, 126.66, 124.74, 76.32, 52.93, 50.41; MS *m*/*z*: 288 (molecular ion), 229 $(M-COOCH_3)^+$. Anal. Calcd for $C_{15}H_{12}O_4S$: C, 62.49%; H, 4.20%; Found: C, 62.18%; H, 3.80%.

Compound **7** was obtained as colorless prisms after column

chromatography (from hexane–ethyl acetate). Yield: 1.70 g (25%), mp 90–92 °C, (lit.[11] mp 90 °C); IR: (CO) 1730, 1710 cm^{-1}; ^1H NMR (300 MHz, deuteriochloroform): δ=3.75 (3H, s, -OCH_3), 3.78 (3H, s, -OCH_3), 6.88 (1H, dd, *J*=3.6, 8.8 Hz, thienyl proton), 7.06–7.08 (1H, m, thienyl proton), 7.15–7.19 (1H, m, phenyl proton), 7.30 (1H, dd, *J*=1.4, 8.8 Hz, thienyl proton), 7.51–7.62 (2H, m, phenyl protons), 7.98 (1H, s, H-olefinic), 8.16 (1H, dd, *J*=1.5, 7.7 Hz, phenyl proton); ^{13}C NMR (75 MHz): δ=167.59, 166.55, 138.61, 137.05, 133.16, 132.87, 131.98, 131.33, 131.31, 130.38, 130.06, 129.95, 128.81, 126.76, 52.21, 52.03; MS *m*/*z*: 302 (molecular ion), 243 $(M-COOCH_3)^+$. Anal. Calcd for $C_{16}H_{14}O_4S$: C, 63.56%; H, 4.67%; Found: C, 63.27%; H, 4.93%.

Compound **8** was obtained as colorless prisms after column chromatography (from hexane–ethyl acetate). Yield: 1.00 g (15%), mp 220–222 °C; IR: (CO) 1740, 1730 cm^{-1}; ^1H NMR (300 MHz, deuteriochloroform) δ=3.61 (3H, s, OCH_3), 4.12 (1H, d, *J*=1.3 Hz, *H*-4), 5.33 (1H, d, *J*=1.3 Hz, *H*-3), 6.73–6.79 (2H, m, thienyl protons), 7.01 (1H, dd, *J*=1.5, 4.8 Hz, thienyl proton), 7.29 (1H, dd, *J*=1.7, 7.4 Hz, thienyl proton), 7.35 (1H, dt, *J*=1.3, 7.4 Hz, phenyl proton), 7.41–7.51 (2H, m, phenyl protons), 7.65–7.75 (2H, m, phenyl protons), 7.99 (1H, dd, *J*=1.3, 7.6 Hz, phenyl proton), 8.36 (1H, dm, *J*=7.6 Hz, phenyl proton); ^{13}C NMR (75 MHz): δ=171.59, 161.64, 147.78, 143.32, 136.33, 135.10, 130.97, 130.74, 130.36, 129.93, 128.73, 128.09, 127.83, 126.85, 125.19, 124.47, 123.31, 122.57, 121.37, 111.31, 52.80, 52.18, 35.86; MS *m*/*z*: 388 (molecular ion), 329 $(M-COOCH_3)^+$. Anal. Calcd for $C_{23}H_{16}O_4S$: C, 71.12%; H, 4.15%; Found: C, 71.02%; H, 4.07%.

4.4. Methyl ester 6 of acid *trans*-3e

The reaction was attempted in three modes.

(1) To a stirring solution of *trans*-**3e** (0.71 g, 2.59 mmol) in 3.5 ml methanol, H_2SO_4 (0.2 ml, 3.8 mmol) was added dropwise. The reaction mixture was refluxed for 3 h. and left over night. The colorless crystals were filtered and washed with water/methanol yielding 0.55 g (74%) of **7**, mp 90–92 °C.

(2) To a mixture of potassium carbonate (0.24 g, 1.74 mmol) and acid *trans*-**3e** (0.48 g, 1.74 mmol) in DMF (3 ml), iodomethane (0.2 ml, 3.47 mmol) was added dropwise. The reaction mixture was stirred for 3 h. added to water and extracted with ethyl acetate. The organic layer was washed with water, dried (sodium sulfate) and evaporated giving an oil. The later afforded **7** as colorless crystals (from ethyl acetate) in yield 76% (0.38 g), mp 90–92 °C.

(3) A stirring solution of trans-**3e** (1.00 g, 3.65 mmol) in 5 ml chloroform was treated with diazomethane. The mixture was stirred at room temperature for 2 h. The excess diazomethane and chloroform was removed under reduced pressure giving an oil. The later afforded *trans*-**6** as colorless crystals (from ethyl acetate) in yield 85% (0.85 g), mp 126–128 °C.

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