# A short and efficient construction of the dibenzo[*c*,*h*]chromen-6-one skeleton

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**Abstract**

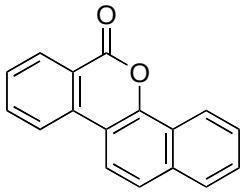
We hereby report a major revision of the synthetic methodology for construction of the dibenzochromenone skeleton. Homophthalic acid derivatives were reacted with thionylchloride/DMF in the presence of $NaN_3$. As the main product, dibenzochromenone derivatives were obtained. When the reaction was performed in the absence of $NaN_3$, only isochromenones were formed. The mechanism of the formation of these products is discussed.

**Keywords***:* Homophthalic acid, acyl azide, isocoumarin, dibenzochromenone, arnottin I.

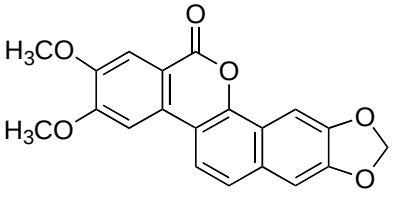
## Introduction

Dibenzo[c,*h*]chromen-6-one **1** motifs are of considerable interest due to their biological activity and structural intricacies. They exhibit a wide range of biological activities.[1]

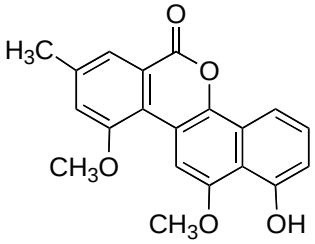
 



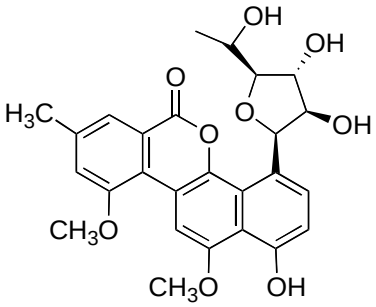
**1** Dibenzo[*c,h*]chromen-6-one



**2** arnottin I



**3** defucogilvocarcin M



**4** gilvocarcin M

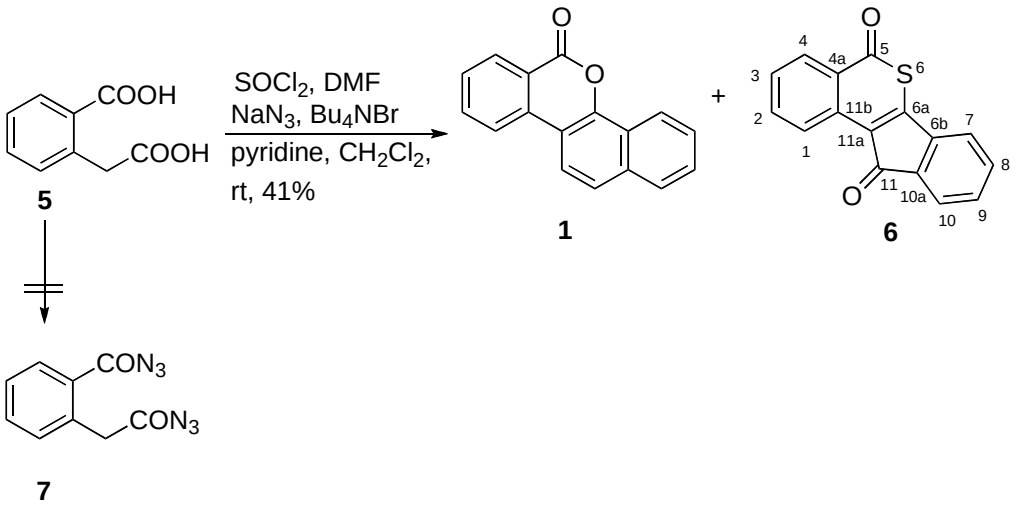
Arnottin I **2**, a dibenzo[c,*h*]chromen-6-one derivative was first isolated by Ishikawa and co-workers in 1977, as a minor constituent from the bark of *Xanthoxylum arnottianum*.[2] However, the structure of this compound was not determined until 1993 since the producing plant yielded only small quantities of the material.[3] Gilvocarcins **3**, **4**,[4] a relatively small family of natural antibiotics having the dibenzo[c,*h*]chromenone skeleton, also exhibit diverse biological activity.[5] The key step in syntheses of these compounds has been mainly metal-catalyzed aryl-aryl coupling reactions of the suitable substituted starting materials which were synthesized by multi-step procedures. James and Snieckus used mainly Negishi/Suzuki cross coupling followed by a remote metallation (DreM)-carbamoyl migration strategy.[5] Ishikawa *et al.* used palladium-catalyzed coupling of *o*-bromobenzoates and 1-tetralones to construct the dibenzo[c,*h*]chromenone structure.[6] Suzuki *et al.* used a three component system for the synthesis of defucogilvocarcin M **3**.[7] Nickel-catalyzed synthesis of benzocoumarin derivatives and its application to the total synthesis of arnottin I **2** was achieved by Madan and Cheng.[8] In this paper, we describe a concise procedure leading directly to the core skeleton of dibenzo[c,*h*]chromenone structure with some substituents resembling the arnottin I structure **2**. Furthermore, the position of the substituents in the products should provide information about the mechanism of formation of the products.

## Results and Discussion

Recently, we have treated homophthalic acid **5** with thionyl chloride, DMF, and sodium azide in the presence of tetrabutylammonium bromide as a catalyst. Unfortunately, the expected diazide **7** was not formed. The dibenzo[c,*h*]chromenone **1** was formed in 41% yield.[9,10] In order to test the

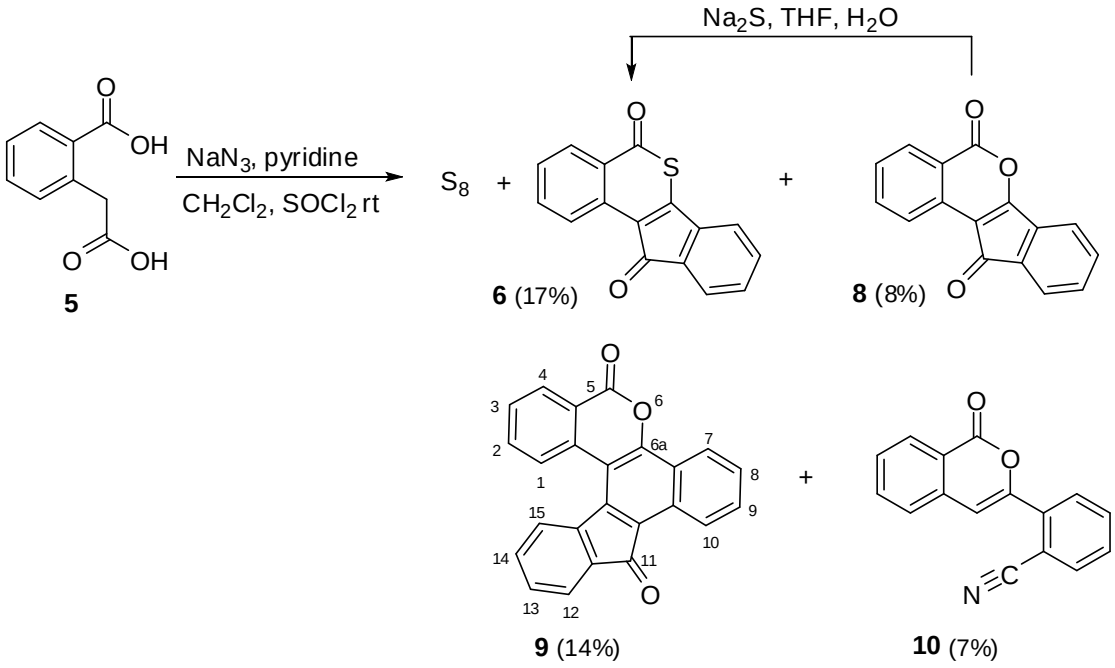
general applicability of this reaction for the formation of substituted dibenzo[c,*h*]chromenones, substituted homophthalic acids were used. First, the original reaction was reinvestigated.

*N*,*N*-Dimethyl(chlorosulfinyloxy)methaniminium chloride formed from thionyl chloride and dimethyl formamide is an efficient reagent for the synthesis of acyl azides from carboxylic acids.[10] Therefore, homophthalic acid **5** was reacted with thionyl chloride, DMF, and sodium azide, in the presence of tetrabutylammonium bromide as a catalyst in methylene chloride, anticipating formation of the diazide **7**. However, the desired diazide **7** was not formed. Besides the major product, 6*H*-dibenzo[*c*,*h*]chromen-6-one **1**, an thioisocoumarin derivative **6** was isolated in 4% yield (Scheme 1).[11,12]




**Scheme 1**

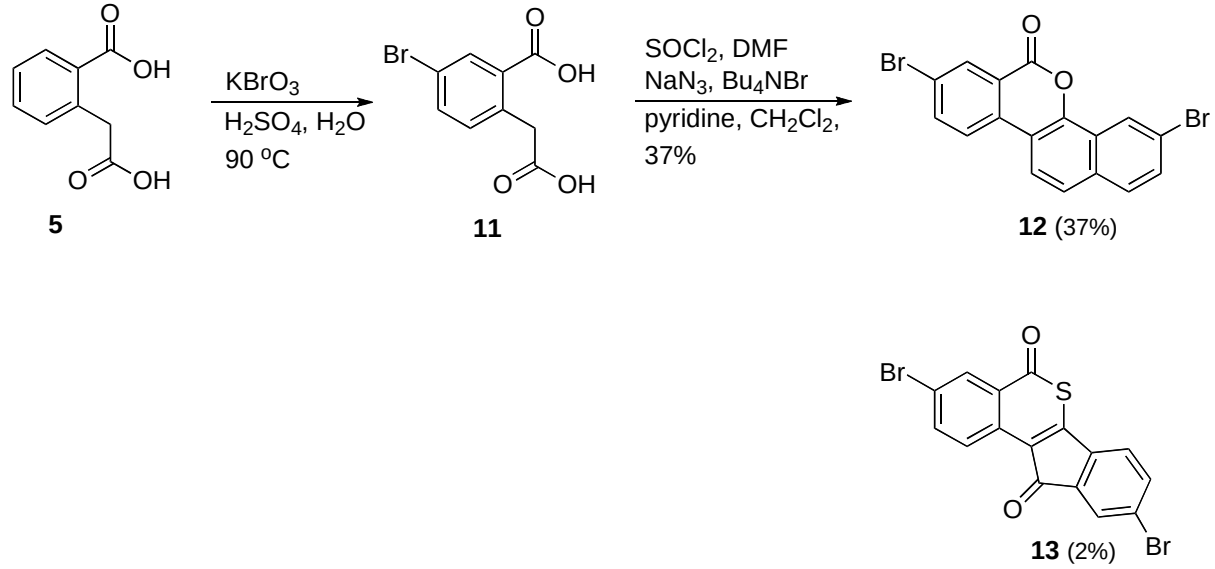
COSY, HMQC, and HMBC experiments were conducted to confirm the the assignment of the structure of **6**. Two carbonyl carbons appeared at 191.3 and 183.1 ppm, the high field resonance being that for the five-membered ring carbonyl carbon. With the help a of COSY-spectrum we were able to distinguish between the aromatic protons of two benzene rings. The HMBC specrum showed that the carbonyl carbon resonance at 183.1 (C-5) correlates with the doublet (H-4) resonating at 8.17 ppm. On the other hand, the carbonyl carbon resonance at 191.3 (C-11) correlated with the doublet at 7.5 ppm (H-10). These observations clearly show that the carbonyl groups are directly connected to different benzene rings. The quaternary carbon atom C-6a correlated with the doublet resonating at 7.17 (H-7) whereas the carbon atom C-11a correlated with the doublet at 8.95 ppm (H-1). Those findings support the proposed structure. The incorporation of a sulfur atom into the molecule was determined by elemental analysis as well as by its mass spectrum. With the isolation of this new isothiocoumarin derivative **6**, the focus of the research was directed to the increase of its yield.




**Scheme 2**

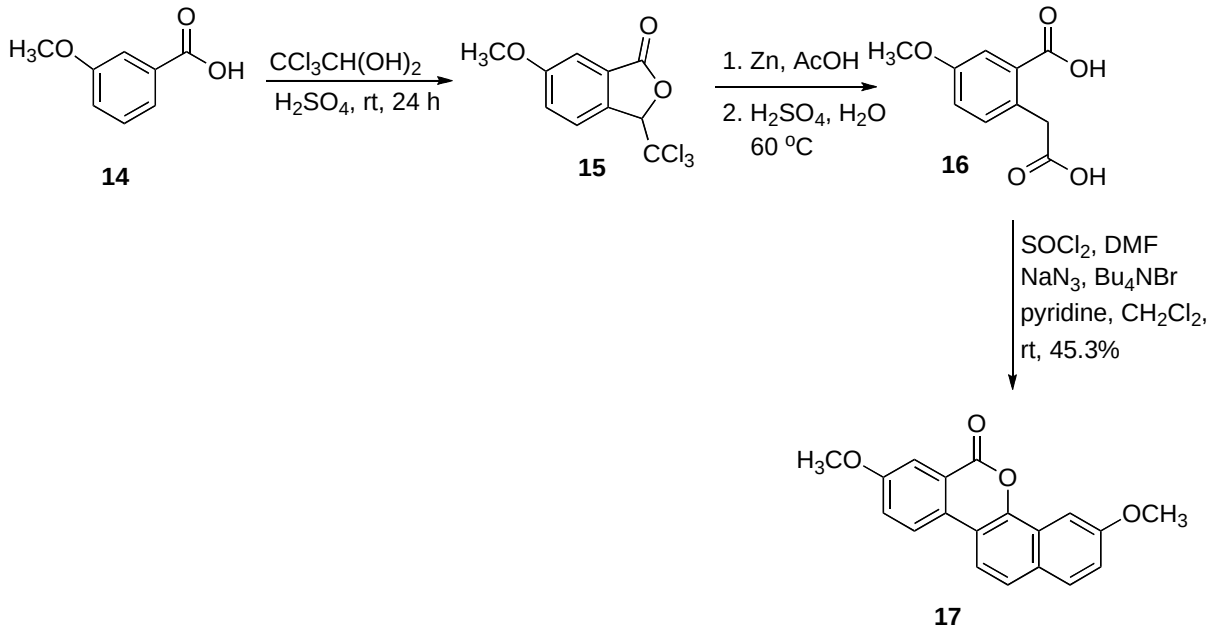
The same reaction was carried out but in the absence of DMF. This procedure increased the yield of the isothiocoumarin derivative **6** from 4% to 17%. On the other hand, elemental sulfur and new condensation products such as **8**, **9** and **10** were isolated in 8, 14, and 7% yields, respectively (Scheme 2). Interestingly, the major product **1**, which was formed when the reaction was carried out in the presence of DMF, was not detected. This observation shows that DMF is involved in the formation of 6*H*-dibenzo[*c*,*h*]chromen-6-one **1**. The spectral data of **8** was in agreement with those reported in the literature.[13] The presence of three benzene rings in **9** was easily established by analysis of the $^{1}$H-NMR spectrum. The $^{13}$C-NMR spectrum had 22 lines for aromatic carbons. The carbonyl resonances observed at 191.8, 158.0 ppm are in agreement with the proposed structures. COSY, HMQC, and HMBC spectra also support the structure. Again with the help of the COSY spectrum, the connection of the aromatic protons was easily determined. The HMBC spectrum showed correlation of the carbonyl resonance at 191.8 (C-11) ppm with the doublet resonating at 7.59 (H-12) ppm. The other carbonyl carbon at 160.4 (C-5) correlated with the doublet at 8.30 (H-4) ppm. Furthermore, the carbon atom at 151.2 (C-6a) correlated with the doublet at 8.25 (H-7) ppm. Additionaly, the coupling constants between the protons H-7 and H-8 ($J_{7,8}$ = 8.4 Hz) and H-8 and H-9 ($J_{8,9}$ = 6.9 Hz) clearly showed the presence of a naphthalene unit in the proposed structure. The high resolution mass spectrum and the $^{1}$H-NMR spectrum of **10** clearly indicated the presence of a nitrogen atom in the molecule. Nine proton resonances between 7.2-8.3 ppm, where one of them resonates as singlet, support the structure. Furthermore, an IR absorption band at 2225 cm$^{-1}$ demonstrated the presence of a nitrile group. Two dimensional NMR spectra were also in agreement with the proposed structure **10**.

The sulfur containing product, indeno[1,2-*c*]isothiochromenone-5,11-dione **6** was synthesized independently, in quantitative yield, by reacting **8** with $Na_2S$ in THF and water (1:1). Therefore, we assume that sulfide anion formed under the reaction conditions by reduction of $SOCl_2$ by $NaN_3$,[14] substitutes oxygen atom in **8** to give **6**. Sulfide anions formed under reaction conditions can undergo further reaction with excess $SOCl_2$ present in the reaction media and produce elemental sulfur. In a separate reaction we successfully demonstrated that reaction of $Na_2S$ with $SOCl_2$ in dichloromethane produces sulfur in a very fast process.



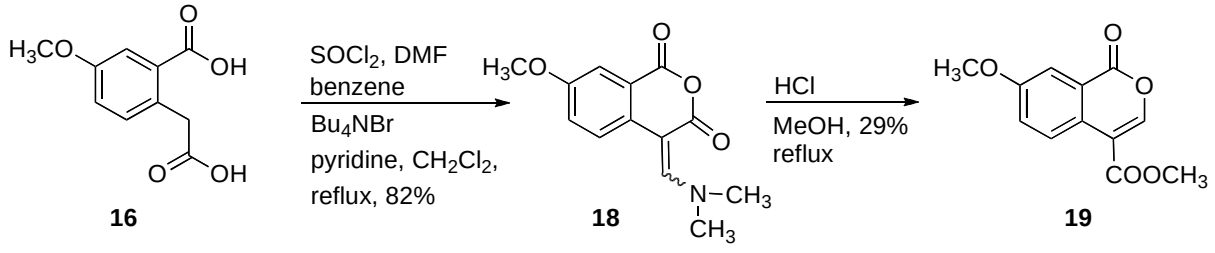

**Scheme 3**

In order to test the scope of the procedure shown in Scheme 1, the reaction was carried out with two substituted homophthalic acids**.** Bromohomophthalic acid **11** was synthesized by direct bromination of homophthalic acid. It is well known that the bromination of aromatic compounds containing electron-withdrawing groups has been an area of concern. Homophthalic acid **5** was reacted with potassium bromate[15,16] in sulfuric acid to give the desired brominated diacid **11** in 44% yield. Bromohomophthalic acid **11** was reacted with thionyl chloride, DMF and sodium azide, under the same reaction conditions as described in Scheme 1, to give dibromodibenzochromenone derivative **12** in 37% yield. The $^1$H-NMR spectrum was consistent with the proposed structure. In contrast to **1**, this dibromo derivative **11** was found to be poorly soluble in organic solvents so that a $^{13}$C-NMR spectrum could not be recorded. Additionally, a minor compound **13** (2%) was isolated. The structure was easily determined by comparison of the spectral data of **13** with those of **6**.




**Scheme 4**

For the synthesis of 4-methoxyhomophthalic acid **16**, a modified literature procedure was applied.[17] Methoxybenzoic acid **14** was condensed with chloral hydrate to obtain the lactone **15**, which was then reduced by zinc in acetic acid followed by hydrolysis to produce the methoxy-diacid **16** (Scheme 4). With the synthesis of diacid **16**, we were now able to assess its use for rapid and efficient generation of a dibenzochromenone skeleton, but with methoxyl substituents. Treatment of diacid **16** with thionyl chloride, DMF and sodium azide under the same reaction condition as reported for the synthesis of **12**, resulted in the formation of the corresponding dimethoxydibenzochromenone derivative **17** in 45% (Scheme 4). The structure and especially the exact positions of the methoxyl groups were determined with the help of COSY, HSQC and HMBC experiments.



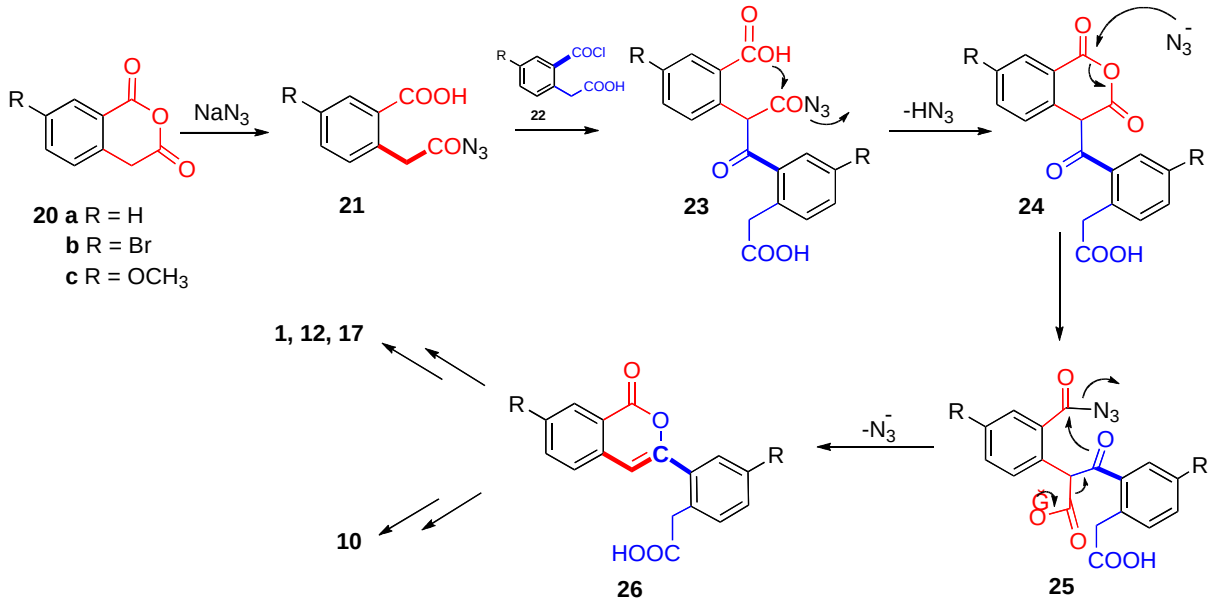

**Scheme 5**

During these reactions a nitrogen atom, arising from azide anion used in the reaction, was not incorporated in the products **12**, **13** as well as **17**. To determine the function of azide anion, the

reaction with **16** was run in the absence of $NaN_3$. Instead of the formation of a dibenzochromenone **17**, an aminomethylene compound **18** was formed, which was converted to the isocoumarin derivative **19**[18] by reaction with methanol saturated with hydrogen chloride (Scheme 5).

## Conclusions

The reactions performed in our work show that the dibenzochromenone structure **1** can be easily generated, even with the substituted homophthalic acid derivatives, in 37-45% yields in a one-pot reaction. Furthermore, the attempted azidination reactions of homophthalic acid derivatives **5**, **11**, and **16** show that $NaN_3$ plays an important role in determination the mode of the reaction. In the absence of $NaN_3$, isocoumarin derivative **19** was formed from the reaction of **16** instead of the dibenzocoumarin derivative **17**. The mechanism we propose is shown in Scheme 6.

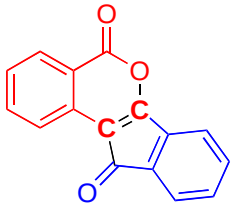



**Scheme 6**

We suggest that the first step is the formation of the anhydride **20**, which could then be regiospecifically opened up by the azide anion to the corresponding monoazide **21**. Formation of an acyl azide activates the methylenic protons for further reaction. Intermolecular acylation of **21** with acyl chloride **22** followed by ring-closure would result in the formation of **24**. This anhydride might undergo again ring-opening by azide anion attack to form β-keto-acid carboxylate **25**. Decarboxylation of **25** would lead to cyclization to form the key intermediate **26**, which could easily be converted in the dibenzochromenone derivatives **1**, **12**, and **17** as well as into the nitrile **10**. Recently, Threadgill *et al.*[19] obtained relevant information about the

mechanism of the acylation of isocoumarin derivatives which strongly support our suggestion. Furthermore, the exact determination of the positions of the substituents in **12** and **17** supports our proposed mechanism.

The formation of the compounds having cyclopentadienone structures such **6**, **8**, **13** as well as **9**, however, cannot be explained via this mechanism. As one can easily recognize from the position of the substituents in **13**, for the construction of this skeleton requires a C–C connection of methylene groups of two homophthalic acid units.



**8**

Before such a C–C connection between the two methylene groups can take place, one of these groups should contain a good leaving group. We therefore assume, that firstly a chlorination on one of the methylene goups[20] takes place under the reaction conditions, followed by attack of the enol form of the second methylene group. Decarboxylation and cyclization can then lead to the compounds **8** and **13**.

## Experimental Section

**General.** Melting points were determined on a Thomas-Hoover capillary melting point apparatus. IR spectra were recorded on a Perkin Elmer 980 spectrometer. NMR spectra were recorded on a Bruker-Avance instrument at 400 MHz for $^{1}$H and 100 MHz for $^{13}$C NMR. Apparent splitting is given in all cases. Mass spectra were recorded on an Agilent 5975C spectrometer operating at an ionization potential of 70 eV. Column chromatography was performed on silica gel (60-mesh, Merck). TLC was carried out on Merck 0.2 mm silica gel 60 $F_{254}$ analytical aluminum plates.

**Synthesis of 6*H*-dibenzo[*c*,*h*]chromen-6-one (1).** In a 25 mL dropping funnel, benzene (7 mL), dimethyl formamide (2,8 mL) and thionyl chloride (2.3 mL) were consecutively added. The formed solution was allowed to form two separate layers. The lower layer was added to a suspension of the homophthalic acid **5** (2.5 g, 13.9 mmol), sodium azide (2.6 g, 44 mmol), tetrabutylammonium bromide (0.6 g, 2.3 mmol), and pyridine (3.2 mL) in dichloromethane (100 mL). The mixture was then stirred at room temperature overnight and washed with saturated aqueous sodium bicarbonate solution (3 x 50 mL), with 1.0 M HCl solution (3 x 50) three times and finally with water (2 x 25 mL). The organic phase was dried over magnesium sulfate and

concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 40 g, $CH_2Cl_2$) to give colorless crystals **1** (0.7 g, mp, 182-183 ºC[9], Lit. mp. 179-180 ºC[11]) in 41% yield. The product was recrystallized from ethyl acetate. The NMR spectra were in agreement with those reported in the literature.[9,11] As the second fraction indeno[1,2-*c*]isothiochromene-5,11-dione **6** was isolated.

Red crystals (73 mg, 4%) from methylene chloride, mp 235-236 ºC (Found: C, 71.32; H, 3.09; S, 12.34% $C_{16}H_8O_2S$ requires **:** C, 72.71; H, 3.05; S, 12.13% IR $\nu_{max}$ (KBr)/$cm^{-1}$ 2989, 1699, 1654, 1275, 1262, 764, 750; $^1$H-NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 8.1 Hz, H-1), 8.17 (d, *J* = 8.0 Hz, H-4), 7.72 (t, *J* = 7. 5 Hz, H-2), 7.50 (d, *J* = 7.1 Hz, H-10), 7.47 (t, *J* = 7.7 Hz, H-3), 7.40 (t, *J* = 7.4, H-8), 7.31 (t, *J* = 7.4 Hz, H-9), 7.17 (d, *J* = 7.3 Hz, H-7). $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 191.3 (C-11), 183.1 (C-5), 156.2 (C-6a), 140.6 (C-6b), 135.0 (C-2), 134.1 (C-8), 133.8 (C-11b), 133.3 (C-9), 131.1 (C-10a), 128.6 (C-3), 127.0 (C-4), 126.5 (C-11a), 126.3 (C-1), 123.1 (C-10), 119.9 (C-4a), 119.7 (C-7). MS, *m*/*z* 264 ($M^+$, 100%), 236 ($M^+$-CO, 81%), 208 ($M^+$-2CO, 27%), 176 ($M^+$-2CO, -S, 10%), 163 (35%), 104 (22%).

**Reaction of homophthalic acid with thionyl chloride and sodium azide in the absence of dimethyl formamide**

To a suspension of homophthalic acid (5.0 g, 27.8 mmol), $NaN_3$ (7.2 g, 111 mmol), tetrabutylammonium bromide (0.75 g, 2.3 mmol), and pyridine (9 mL) in dichloromethane (100mL), thionyl chloride (4.6 mL, 63.4 mL) was added dropwise under a nitrogen atmosphere and the mixture was stirred at room temperature for 10 h. The inorganic salts were separated by filtration. The filtrate was washed with 1.0 M HCl solution three times, followed by water extraction. The organic phase was dried ($MgSO_4$) and solvent removed under reduced pressure. The residue was purified by chromatography over silica gel (60 g) eluting with methylene chloride.

Sulfur (340 mg, 10.6 mmol) was isolated as the first fraction. The compound **6** (623 mg, 17%) was isolated as the second fraction. The third fraction was characterized as **8**. **Indeno[1,2-*c*]isochromene-5,11-dione (8).** Yellow solid (275 mg, 8%), m.p. 257-258 ºC (Lit. 258-259 ˚C[13b]) 403 mg, 8% , yellow solid; $^1$H-NMR ($CDCl_3$, TMS) δ 8.31 (d, *J* = 7. 9 Hz, H-1), 8.23 (d, *J* = 8.0 Hz, H-4), 7.74 (t, *J* = 7.6 Hz, H-2), 7.52 (d, *J* = 7.1, H-10), 7.48 (d, *J* = 7.4 Hz, H-3), 7.45-7.39 (m, 2H, H-7 and H-8), 7.34 (dt, *J* = 6.8 and 1.8 Hz, H-9). $^{13}$C-NMR (400 MHz, $CDCl_3$) δ 189.9 (C-11), 170.6 (C-5), 160.8 (C-6a), 136.4 (C-6b), 136.0 (C-2), 133.6 (C-8), 132.8 (C-10 or C-11b), 132.8 (C-10 or C-11b), 131.6 (C-8), 130.9 (C-4), 128.4 (C-3), 123.3 (C-1), 123.1 (C-10), 119.9 (C-7), 119.0 (C-4a), 107.7 (C-11a). MS *m*/*z* ($C_{16}H_8O_3$) 248 ($M^+$, 100%), 220 ($M^+$-CO, 19), 163 (30).

**Dibenzo[*c*,*h*]indeno[2,1-*f*]chromene-5,11-dione (9)** was isolated as the fourth fraction. Yellow solid, m.p. 212-213 ºC (451 mg, 14%); HRMS calcd for $C_{24}H_{12}O_3$ ($M^+$ + H) 349.0865; found 349.0871; IR $\nu_{max}$/$cm^{-1}$ 2955, 2922 2852, 1727, 1706, 1286, 1259, 1103, 742; $^1$H-NMR (400 MHz, benzene-$d_6$) δ 9.33 (d, *J* = 8.4 Hz, 1H, H-10), 8.30 (dd, *J* = 7.8 and 1.3 Hz, 1H, H-4), 8.25 (d, *J* = 8.4 Hz, 1H, H-7), 7.89 (d, *J* = 7.6 Hz, 1H, H-1), 7.59 (dd, *J* = 7.0 and 1.0 Hz, 1H, H-12),

7.40 (d, *J* = 7.5 Hz, 1H, H-15), 7.26 (ddd, *J* = 8.4, 6.9 and 1.2 Hz, 1H, H-9), 7.09 (ddd, *J* = 8.4, 6.9 and 1.2 Hz, 1H, H-8), 7.05 (ddd, *J* = 7.8, 7.4 and 1.5 Hz, 1H, H-2), 6.98 (d, *J* = 7.8 and 1.5 Hz, 1H, H-3), 6.87 (dd, *J* = 7.5 and 1.3 Hz, 1H, H-14), 6.80 (d, *J* = 7.5 and 0.9 Hz, 1H, H-13). $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 191.8 158.0, 151.2, 142.3, 141.7, 133.8, 132.3, 131.6, 131.4, 129.4, 129.1, 128.7, 128.0, 127.4, 126.2, 125.5, 124.3,123.0, 122.7, 122.4, 122.1,121.4, 121.0, 109.5. MS *m*/*z* 348 ($M^+$, 1%), 296 (100), 268 (17), 240( 45), 195 (18), 120 (36).

**2-(1-Oxo-1*H*-isochromen-3-yl)benzonitrile (10)** was isolated as the fifth fraction. M.p. 201-202 ºC, (225 mg, 7%); HRMS calcd for $C_{13}H_{13}NO_4$ $(M + K)^+$ 286.0270; found 286.0260; IR $\nu_{max}$(KBr)/$cm^{-1}$ 2962, 2921, 2851, 2225, 1732, 1645, 1606, 1458, 1259, 1232, 1033, 1008, 794; $^1$H-NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.4 Hz, 1H, H-8), 7.99 (dd, *J* = 8.0 Hz, 1H, H-6'), 7.80 (dd, *J* = 7.8 and 1.1 Hz, 1H, H-3'), 7.76 (ddd, *J* = 7.8, 7.3 and 1.3 Hz, 1H, H-6), 7.71 (dd, *J* = 7.95 and 1.37 Hz, 1H, H-5'), 7.58 (dd, *J* = 7.3 and 1.5 Hz, 1H, H-5), 7.57 (dd, *J* = 8.4 and 7.8 Hz, 1H, H-7), 7.52 (dd, *J* = 7.6 and 1.2 Hz, 1H, H-4'), 7.32 (s, 1H, H-4); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 160.0, 148.2, 134.9, 133.6, 133.5, 132.8, 131.4, 128.09, 128.06, 127.7, 127.1, 125.1, 119.3, 116.4, 107.8, 105.5; MS (70 eV) 247 ($M^+$ 100%), 219 (39), 190 (51), 164 (11), 130 (13), 89 (32).

**5-Bromo-2-(carboxymethyl)benzoic acid (11).** Homophthalic acid **5** (5.0 g, 27 mmol) and potassium bromate (6.58 g, 40 mmol) were mixed in water (30 mL) and the mixture was heated at 90 °C. A mixture of sulfuric acid (24 ml, 95%) and water (40 mL) was added dropwise to the resulting mixture at 90 °C over a period of 30 min. After completion of addition the mixture was stirred 2 h at the same temperature. Then the mixture was cooled to the room temperature and the product was filtered off and washed with water (3 x 50 mL) to give **11** (3.2 g, 44%). The product was recrystallized from EtOAc/hexane (4/1), m.p. 216-217, m.p. 215[16]). $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7.99 (d, $J_{6,2}$ = 2.4 Hz, 1H, H-6), 7.71 (dd, $J_{2,3}$= 8.0 Hz, $J_{2,6}$ = 2.4 Hz, 1H, H-2 ), 7.31 (d, $J_{3,2}$= 8.0 Hz, 1H, H-3 ), 3.92 (s, 2H, -$CH_2$) ; $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ 172.0, 166.9, 135.9, 134.5, 134.4, 132.7, 132.6, 119.7, 39.2.

**3,8-Dibromo-6*H*-dibenzo[*c*,*h*]chromen-6-one (12).** 5-Bromo-2-(carboxymethyl)-benzoic acid (**11**) (1.45 g, 5.6 mmol), $NaN_3$ (1.45 g, 43 mmol), tetrabutylammonium bromide (0.3 g, 1.15 mmol) and pyridine (1.8 mL) were added to 100 mL of $CH_2Cl_2$. In a dropping funnel, 2.0 mL of dry benzene, 1.2 mL of *N*,*N*-dimethylformamide and 0.92 mL $SOCl_2$ were mixed and the solution was left to form two separate layers. After 10 min, the bottom phase was added dropwise to the mixture prepared above. The resulting mixture was stirred for 18 h. Inorganic non-reacted starting materials were removed by filtration. The filtrate was washed with 0.1 M HCl (3 x 50 mL) followed by water (3 x 100 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the crude product, which was purified by chromatography on silica gel (40 g) eluting with $CH_2Cl_2$. As the first fraction the thioisocoumarin derivative **13**, which could not be purified, was isolated, 24 mg (orange solid), 2%, purity about 85% according to the $^1$H-NMR.

**3,8-Dibromoindeno[1,2-*c*]thioisochromene-5,11-dione (13).** Orange solid. $^1$H-NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 8.7 Hz, H-1), 8.30 (d, *J* = 2.0 Hz, H-4), 7.8 (dd, *J* = 8.7 and 2.0 Hz,

H-2), 7.64 (d, *J* = 1.7 Hz, H-10), 7.57 (dd. *J* = 7.7 and 1.7 Hz, H-8), 7.06 (d, *J* = 7.7 Hz, H-7). MS *m*/*z* ($C_{16}H_6Br_2O_2S$) 420/422/424 ($M^+$, 32, 65, 33%), 394/396/398 ($M^+$-CO 32%), 316/318 ($M^+$-Br and -CO, 10%), 211 (100%), 167 (58%), 109 (51%).

The second fraction was identified as dibromobenzochromenone **12**. 433 mg (37%) as a white solid, m.p. 312-323 ºC. (Found: C, 50.11; H, 2.00% $C_{17}H_8Br_2O_2$ requires C, 50.53; H, 2.00%); IR $\nu_{max}$(KBr)/$cm^{-1}$ 3079, 2919, 1711, 1482, 1262, 1230, 1185, 827; $^1$H-NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 1.9 Hz, H-4), 8.60 (d, *J* = 2.1 Hz, H-7), 8.05 (d, *J* = 8.6 Hz, H-10), 8.02 (d, *J* = 8.9 Hz, H-11), 7.96 (dd, *J* = 8.6 and 2.1 Hz, H-9), 7.74 (2d, *J* = 8.4 Hz, H-1 and H-12) 7.68 (dd, *J* = 8.7 and 1.9 Hz, H-2). $^{13}$C-NMR spectrum could not be taken due to the poor solubility of the compound. MS Spectrum: 70 eV, m/z; 402/404/406 ($M^+$, 52, 100, 49%), 295/297 ($M^+$-Br, 17%), 267/269 ($M^+$-Br, and -CO, 11%), 216 (9%), 187 (41%).

**3,8-Dimethoxyindeno[1,2-*c*]isochromene-5,11-dione (17).** 2-(Carboxymethyl)-5-methoxybenzoic acid (1.275 g, 6.07 mmol) $NaN_3$ (1.574 g, 46.7 mmol), tetrabutylammonium bromide (0.32 g, 1.23 mmol) and 2.0 mL pyridine, 1.2 mL of *N*,*N*-dimethylformamide and 0.92 mL $SOCl_2$ were reacted as described above. After the normal work-up procedure, the residue was purified by chromatography on silica gel (40 g) eluting with $CH_2Cl_2$. 3,8-Dimethoxy-6*H*-dibenzo[*c*,*h*]chromen-6-one (**17**) was isolated as white solid (0.48 g, 45%), m.p. 244-245 ºC; (Found: C, 73.98; H, 4.71%; $C_{19}H_{14}O_4$ requires C, 74.50; H, 4.61%); IR $\nu_{max}$(KBr)/$cm^{-1}$ 3075, 2945, 2840, 1712, 1609, 1498, 1223, 1061, 1020, 8228; $^1$H-NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.9 Hz, H-10), 7.74 (d, *J* = 2.8 Hz, H-7), 7.75 (d, *J* =8.7 Hz, H-12), 7.69 (d, *J* = 2.4 Hz, H-1), 7.65 d, *J* = 8.9 Hz, H-4), 7.57 (d, *J* = 8.7 Hz, H-11), 7.34 (dd, *J* = 8.9 and 2.8 Hz, H-9), /.12 (dd, *J* = 8.9 and 2.5 Hz, H-3), 3.95 (s, 3H), 3.92 (s, 3H). $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 161.5 (C-6), 159.8 (C-8), 158.7 (C-2), 145.3 (C-4b), 129.3 (C-4), 129.1 (C-10a), 129.0 (C-4a), 125.0 (C-9), 124.5 (C-3), 124.2 (C-12a), 123.9 (C-10), 122.3 (C-6a), 120.3 (C-3), 116.5 (C-11), 113.7 (c-10b), 100.1 (C-1), 55.84 ($OCH_3$), 55.78 ($OCH_3$). MS *m*/*z* 306 ($M^+$, 100%), 263 (21%), 220 (10), 192 (9), 163 (12),

**(*Z*)-4-[(Dimethylamino)methylene]-7-methoxyisochroman-1,3-dione (18).** 2-(Carboxymethyl)-5-methoxybenzoic acid (**16**) (130 mg, 0.62 mmol) tetrabutylammonium bromide (32 mg g, 0.12 mmol) and pyridine (0.3 mL), benzene (0.4 mL) *N*,*N*-dimethylformamide 0.15 mL) and $SOCl_2$ (0.12 mL) in 40 mL of $CH_2Cl_2$ were reacted as described above. The resulting mixture was stirred overnight. Inorganic non-reacted starting materials were removed. The filtrate was washed with 0.3 M HCl solution three times. The organic phase was dried over $MgSO_4$. Removal of the solvent gave the crude product, which was purified by chromatography on silica gel (10 g) eluting with ethyl acetate to give a yellow solid 123 mg, 82%). $^1$H-NMR (400 MHz, $CDCl_3$) δ 7.78 (bs, H-5), 7.49 (t, *J* = 1.6 Hz, H-8), 7.09 (dd, *J* = 7.2 and 2.4 Hz, H-6), 3.87 (s, 3H, -$OCH_3$), 3.24 (bs, 6H, -$NCH_3$). $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 163.2 , 156.6, 156.2, 132.9, 124.2, 120.4, 117.5, 111.4 , 88.2, 55.6, 47.5, 45.0 MS *m*/*z*, ($C_{13}H_{13}NO_4$) 247 ($M^+$, 100%), 204.0 (85), 188.1 (18), 160.1 (19), 132.1 (61).

**Methyl 7-methoxy-1-oxo-1*H*-isochromene-4-carboxylate (19).** (*Z*)-4-((dimethylamino)-methylene)-7-methoxyisochroman-1,3-dione (**18**) (65 mg, 0.26 mmol) was dissolved in methanol (20 mL). Dry HCl gas produced from sulfuric acid and sodium chloride was passed slowly through this solution. After the saturation was completed, it was refluxed for 2 h. The solvent was removed under reduced pressure, water was added to the residue which was then extracted with chloroform (3x10 mL). The combined extracts were dried (MgSO4) and the solvent was removed at reduced pressure. The residue was purified by chromatography on silica gel eluting with ethyl acetate/hexane (3:2) to yield 17.5 mg 29% (isolated yield) of methyl 7-methoxy-1-oxo-1H-isochromene-4-carboxylate (**19**), as a white solid (m.p. 121-123 $^{o}$C, 124-125 $^{o}$C[18] ); $^{1}$H-NMR (400 MHz, $CDCl_3$,) δ 8.57 (d, *J* = 9.1 Hz , H-5), 8.10 (s, H-3), 7.71 (d, *J* =2.9 Hz, H-8), 7.37 (dd, *J* = 9.1 and 2.9 Hz, H-6), 3.90 (s, 3H, -$OCH_3$), 3.89 (s, 3H, -$OCH_3$). $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 164.7, 161.0, 159.9 , 150.5, 127.3, 127.0 , 124.5, 121.91 (C- ), 110.7), 109.9), 55.7, 52.1. MS *m*/*z*, ($C_{12}H_{10}O_5$) 234.1/235.1 ($M^+$, 8/1), 203.0 ($M^+$ -$OCH_3$), 202.0 (-H), 174.1 (-CO), 163.1.

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