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PAPER

Reactions of 3-acylchromones with dimethyl 1,3-acetonedicarboxylate and 1,3-diphenylacetone: one-pot synthesis of functionalized 2-hydroxybenzophenones, 6*H*-benzo[*c*]chromenes and benzo[*c*]coumarins†

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Reactions of 3-methoxalyl-, 3-polyfluoroacyl- and 3-aroylchromones with dimethyl 1,3-acetonedicarboxylate and 1,3-diphenylacetone in the presence of DBU proceed at the C-2 atom of the chromone system with pyrone ring-opening and subsequent formal [3 + 3] cyclocondensation to functionalized 2-hydroxybenzophenones, 6*H*-benzo[*c*]chromenes and benzo[*c*]coumarins, depending on the substituent at the 3-position. An NMR study and X-ray crystallographic analysis are reported. The compounds synthesized can be considered as promising scaffolds for the design of the novel UV-A/B and UV-B filters.

Chromones (4*H*-1-benzopyran-4-ones, 4*H*-chromen-4-ones) are very attractive targets for combinatorial library synthesis due to their wide range of valuable biological activities.[1] Many natural and synthetic chromones have occupied an important place in drug research, as one of the so-called privileged drug scaffolds.[2] In addition, they are used as valuable synthetic intermediates in the preparation of new carbo- and heterocyclic systems.[3] The biological and industrial importance of chromones has led to a considerable amount of synthetic work in the field of 3-substituted chromones, especially 3-formylchromone and its derivatives.[4] These compounds have attracted attention long ago as highly reactive compounds, which can serve as the starting substances in the syntheses of a whole series of heterocycles with useful properties due to three strong electrophilic centers (C-2 and C-4 atoms of the chromone system and the carbonyl carbon of the 3-CHO group). In the chromone ring, the oxygen atom at the 1-position diminishes electron density on the adjacent C-2 atom and two carbonyl groups withdraw electrons through a double bond, hence the 2-position of 3-acylchromones is highly reactive toward the nucleophiles. That is why the reactions of these compounds with nucleophiles start predominantly from the attack of the unsubstituted C-2 atom (1,4-addition) and are accompanied by pyrone ring-opening to form the β-dicarbonyl intermediate capable of regioselective intramolecular cyclizations.[4,5] However, because such chromones possess three electrophilic centers, their interaction with dinucleophiles is sometimes difficult to predict.

We envisaged that introduction of powerful electron-withdrawing groups such as methoxalyl, polyfluoroacyl and aroyl into the 3-position of a chromone would increase its reactivity toward nucleophilic reagents and open up a broad synthetic scope of this important oxygen-containing heterocyclic system. Unlike 3-formylchromones,[4,5] 3-methoxalylchromones **1**,[6] 3-polyfluoroacylchromones **2**[7] and 3-aroylchromones **3**[8] (Fig. 1) have not received much attention despite their potential interest as building blocks in organic synthesis for the construction of 2-hydroxybenzophenones and benzo[*c*]coumarins *via* the reactions with 1,3-*C*,*C*-dinucleophiles.

The substituted 2-hydroxybenzophenone framework is ubiquitous in a wide variety of naturally occurring and synthetic compounds that exhibit important biological activities.[9] Recently, we have developed a domino Michael/retro-Michael/aldol process that takes place between 3-formylchromones and 1,3-bis(silyl enol ethers) in the presence of catalytic trimethylsilyl triflate to generate functionalized 2-hydroxybenzophenones.[10] 3-Formylchromones are also known to undergo Michael addition and cyclization reactions with dimethyl 1,3-acetonedicarboxylate under basic conditions to produce similarly functionalized 2-hydroxybenzophenones **I**.[11] Recently reported syntheses of benzo[*c*]coumarin skeleton **II**, which is present in a number of pharmacologically relevant natural products, such as autumnariol,[12] autumnariniol,[13] alternariol,[14] and altenuisol,[15] rely on

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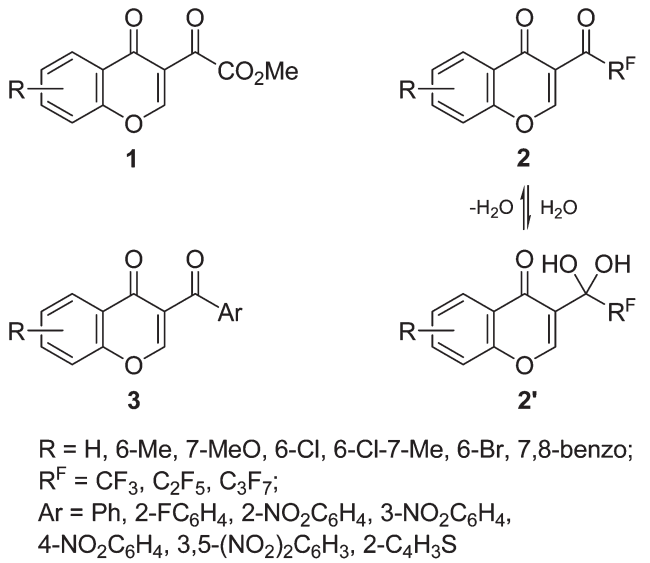
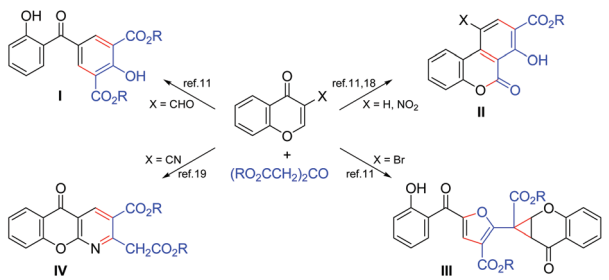


Fig. 1 3-Acylchromones **1–3** used for the reactions with 1,3-*C*,*C*-dinucleophiles.



Scheme 1 Reactions of 3-substituted chromones with dialkyl 1,3-acetonedicarboxylates.

sequential [3 + 3]-cycloaddition–Suzuki cross-coupling reactions,[16] Me_3SiOTf-mediated condensation of 1,3-bis(silyl enol ethers) with chromones followed by a domino retro-Michael–aldol–lactonization process,[17] and reactions of chromone and 3-nitrochromone with dialkyl acetonedicarboxylates.[11,18] It is interesting that the condensation of 3-bromochromones with dimethyl acetonedicarboxylate gave a highly unexpected product containing a cyclopropyl ring **III**,[11] whereas from 3-cyanochromones 5*H*-chromeno[2,3-*b*]pyridine **IV** was obtained (Scheme 1).[19]

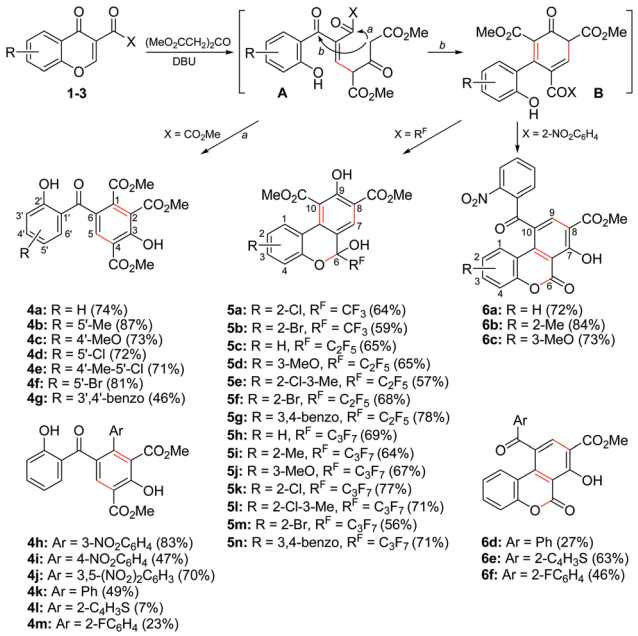
It should be noted that all these reactions with 3-substituted chromones, leading to various types of products **I–IV**, proceed *via* nucleophilic 1,4-addition at the 2-position followed by opening of the γ-pyrone ring. Although 3-substituted chromones (3-formyl-,[4,5] 3-trifluoroacetyl-,[7,20] 3-dichloroacetyl-,[21] 3-methoxalyl-,[6] 3-cyano-,[22] and 3-nitrochromones[23]) are widely used as valuable synthetic intermediates in the preparation of new heterocycles, examples of the participation of chromones **1–3** in any reactions with 1,3-*C*,*C*-dinucleophiles are lacking, a fact prompting us to investigate their reactions with dimethyl 1,3-acetonedicarboxylate and 1,3-diphenylacetone. We are reporting the straightforward synthesis of functionalized 2-hydroxybenzophenones, 6H-benzo[c]chromenes and benzo[c]coumarins from chromones **1–3** as 1,3-dielectrophiles and two mentioned active methylene compounds.

The diversity of properties of 3-acylchromones is due to the fact that, being actually highly reactive geminally activated push–pull alkenes with a good leaving group at the β-carbon atom, whose role is played by the phenolate anion, they acquire the ability to undergo additional transformations related to opening and recyclization of the γ-pyrone ring. Strangely enough, but these compounds have long remained out of sight of chemists engaged in organic synthesis, and their systematic study has started only in recent years. Nevertheless, it is already clear that chromones **1** and **2** are valuable substrates for the synthesis of diverse heterocycles with a potential biological activity.[6,20] 3-Aroylchromones **3** are less reactive than chromones **1** and **2** due to steric and electronic factors, however, their reactivity can be enhanced by introducing electron-withdrawing substituents, such as a nitro group and a fluorine atom, into the aroyl moiety. In the initial study we have prepared a series of substituted chromones **1–3** starting from easily accessible 3-dimethylamino-1-(2-hydroxyaryl)prop-2-en-1-ones by a one-pot acylation procedure.[6–8] Note that 3-polyfluoroacylchromones **2** were prone to the facile and reversible covalent hydrate formation as observed from their ^1H and ^{19}F NMR spectra, which contained two sets of signals (Fig. 1).[7]

Continuing our research program dedicated to the design and synthesis of novel heterocyclic compounds and in view of the unique biological properties displayed by many chromones and coumarin derivatives[1,24] Iaroshenko's laboratory started investigation in this area by the study of the reactions of chromones **1–3** with dimethyl 1,3-acetonedicarboxylate. It was found that the treatment of chromones **1** (X = CO_2Me) with dimethyl acetonedicarboxylate (1.1 equiv.) in dioxane at room temperature in the presence of DBU (1.3 equiv.)[11] resulted in the formation of functionalized 2-hydroxybenzophenones **4a–g** with an excellent regioselectivity and in good yields (46–87%). In most cases, the reaction was complete after 10–12 h and the products could be isolated by simple filtration of the precipitate formed or by column chromatography over silica gel. The progress of the reaction was monitored by TLC, and the results are summarized in Scheme 2.

While dimethyl acetonedicarboxylate reacts with chromones **1** at the methoxalyl group (route a) to produce compounds **4a–g**, its reactions with chromones **2** (X = R^F) under the same conditions took an entirely different course and gave a series of 6*H*-benzo[*c*]chromenes **5a–n** in 56–78% yields. This heterocyclic system certainly is the product of the primary 1,4-addition followed by the pyrone ring-opening, attack of the second CH_2 group on the carbonyl bound to the aromatic cycle, and ring-closure involving the phenolic hydroxyl and R^FCO group (route b). It is necessary to underline that in this case the attack of the CH_2 group is mainly directed to the carbonyl at the aromatic ring, due to which the R^FCO group remains free and can participate in the formation of cyclic semiketal form **5**. This result clearly shows that the present methodology could be applicable to various types of 3-polyfluoroacylchromones **2**, providing a rapid route to the synthesis of a wide range of the R^F-containing 6*H*-benzo[*c*]chromene derivatives **5** (Scheme 2).

Thus, the most important step in determining the structure of a product is intramolecular cyclization of intermediate **A** (route a or b). From this point of view, it clearly appears that the more reactive methoxalyl group has a proclivity to the formation of



Scheme 2 Synthesis of compounds **4–6**.

2-hydroxybenzophenone derivatives **4**, while a partially hydrated polyfluoroacyl group of chromones **2** would be responsible for their observed different reactivity.

It is important that similar reactions of 3-(2-nitrobenzoyl)chromone **3** (X = 2-$NO_2C_6H_4$) afforded benzo[*c*]coumarins **6a–c** (route b), due to the fact that in this case intramolecular cyclization took place with the participation of the OH and CO_2Me groups. On the other hand, polyfunctionalized 2-hydroxybenzophenones **4h–j** were obtained in 47–83% yields from 3-aroylchromones **3** (X = 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 3,5-$(NO_2)_2C_6H_3$) and dimethyl acetonedicarboxylate (route a, Scheme 2). When 3-benzoyl-, 3-(2-thenoyl)- and 3-(2-fluorobenzoyl)chromones **3** (X = Ph, 2-C_4H_3S, 2-FC_6H_4) were used, the reaction also proceeded smoothly to give, however, mixtures **4k** + **6d**, **4l** + **6e** and **4m** + **6f**, from which 2-hydroxybenzophenones **4k–m** and benzo[*c*]coumarins **6d–f** were isolated by column chromatography in a pure form. The reaction includes the nucleophilic 1,4-addition of the first CH_2 group with concomitant opening of the pyrone ring and subsequent intramolecular cyclization with the participation of the second CH_2 group and the ArCO moiety to give compounds **4h–m**; for intramolecular attack of the salicyloyl radical the reaction would result in the benzo[*c*]coumarins **6a–f**.

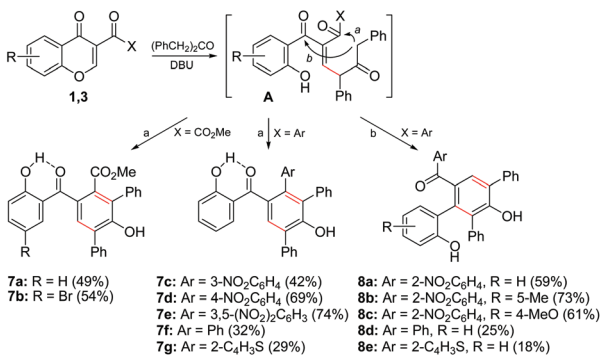
Thus, higher reactivity of the carbonyl group connected to the 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$ and 3,5-$(NO_2)_2C_6H_3$ than 2-HOC_6H_4 of intermediate **A** toward the CH_2 group was shown. Clearly the electron-withdrawing NO_2 group enhances the electrophilicity of the ArCO and encourages nucleophilic addition at this carbonyl group. Unexpectedly lower reactivity of 2-$O_2NC_6H_4CO$ appeared to be a result of the steric effect of the *ortho*-substituted nitro group. These results show the interplay of electronic and steric factors on the course of the reaction with dimethyl acetonedicarboxylate and make it very useful for a combinatorial approach to the synthesis of novel benzene derivatives with potential biological activity and useful physical properties.

The regiochemistry of compounds **4b,c,k,m**, **5h** and **6a,d** was unambiguously confirmed by X-ray single crystal analyses (Fig. S1–S7, see the ESI†).[25] In addition, the HMBC spectrum of **6d** displayed cross-peaks between the resonances of the *ortho*-H-2′, H-6′ (δ 7.85 ppm, 2H) and H-9 (δ 8.08 ppm) and the benzoyl carbonyl (δ 196.4 ppm); for **4i** the most informative were the cross-peaks between the salicyloyl carbonyl (δ 196.1 ppm) and the hydrogen atoms H-3′, H-5′ (δ 6.79–6.83 ppm), H-4′, H-6′ (δ 7.31–7.41 ppm) and H-5 (δ 7.99 ppm).

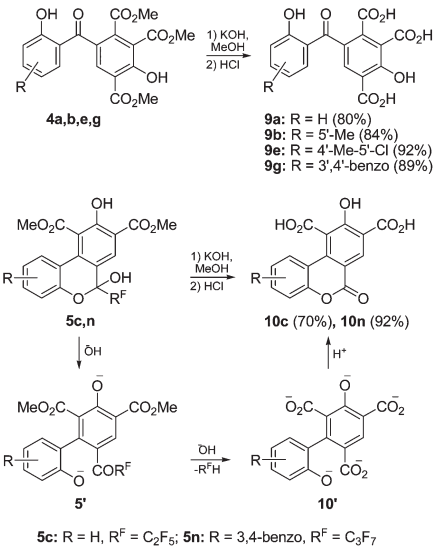
The reaction of chromones **1** and **3** with 1,3-diphenylacetone as a 1,3-*C*,*C*-dinucleophile was also investigated. It was expected that the nucleophilic C atom of 1,3-diphenylacetone would cleave the pyrone ring to give *via* intermediate **A** the required substituted benzenes. In fact, we found that this condensation, under the same reaction conditions at reflux, affords target products **7a–g** and **8a–e**, molecules of which consist of four or five aromatic ring fragments (Scheme 3). In this case, intramolecular attack of the methylene group on the more reactive methoxalyl or nitrobenzoyl carbonyls (except for 2-nitrobenzoyl) leads to the 2-hydroxybenzophenone derivatives **7a–e** in 42–74% yields (route a), whereas the reaction of 3-(2-nitrobenzoyl)chromones **3** proceeds at the salicyloyl carbonyl group to give compounds **8a–c** in 59–73% yields (route b). As expected, both carbonyl groups of 3-benzoyl- and 3-(2-thenoyl)chromones **3** reacted with 1,3-diphenylacetone to give mixtures **7f** + **8d** and **7g** + **8e** (routes a and b), from which compounds **7f,g** and **8d,e** were isolated by column chromatography in a pure state.

In the NMR spectra of **7a–g** in DMSO-d_6, the phenolic OH groups appeared as two singlets at δ 8.6–9.3 and 10.5–11.6 ppm (intramolecular O–H···O=C hydrogen bond); in contrast, in compounds **8a–e** they were observed at δ 8.4–8.7 and 8.9–9.2 ppm. Moreover, the HMBC spectrum of **7e** displayed cross-peaks between the salicyloyl carbonyl (δ 197.9 ppm) and the hydrogen atoms H-3′, H-5′ (δ 6.74–6.81 ppm) and H-4′, H-6′ (δ 7.36–7.41 ppm). The exact structure of **7d,f,g** and **8c,e** was established by X-ray single crystal analysis (Fig. S8–S12, see the ESI†).[25]

It is necessary to mention that not all 3-substituted chromones reacted with 1,3-diphenylacetone and dimethyl acetonedicarboxylate with the formation of the corresponding benzenes; in the case of 3-(2-phenylethynyl)chromone, prepared for this study, the reaction led to the mixture of inseparable regioisomers, low soluble in common organic solvents. We also hoped to spread



Scheme 3 Synthesis of compounds **7** and **8**.



Scheme 4 Hydrolysis of compounds **4** and **5**.

the scope on the unsymmetrical 1,3,5-tricarbonyls, however, these attempts experienced a failure.

Further experiments were conducted to study the base-mediated hydrolysis of the products obtained. We found that compounds **4a,b,e,g**, when treated with potassium hydroxide in refluxing methanol, underwent conversion into tricarboxylic acids **9a,b,e,g** (80–92% yields, Scheme 4). The parent 3-methoxybenzene-1,2,4-tricarboxylic acid was first obtained as the minor product of the oxidation of gladiolic acid.[26]

Next, taking into account the above results and that the benzo[*c*]coumarin ring is an important structural fragment of many natural and biologically active substances,[12–15] it was of interest to evaluate the behavior of 6*H*-benzo[*c*]chromenes **5c,n** in their reactions with potassium hydroxide with the purpose of the preparation of novel benzo[*c*]coumarin derivatives. We found that these compounds react with potassium hydroxide to produce **10c,n** in 70 and 92% yields, respectively (Scheme 4). The formation of **10** can be rationalized by assuming that the initially formed salt **5′** undergoes a haloform reaction followed by subsequent protonation and cyclization. Interestingly, although the chemistry of the benzo[*c*]coumarin system has been well documented,[11,16–18,27] compounds **10** are hitherto unreported.

UV-study

Very recently we have communicated the synthesis of a series of benzophenones as novel UV-filters with the intensive absorption in the A and B UV-range.[28] Inspired by our recent study and taking into account the structural similarities of the compounds synthesized here with presently known UV-filters used industrially for the production of sunlight protective materials, we have undertaken the study of the UV-activity of the library of compounds synthesized. As is shown in the ESI,† benzophenones **4** and **7** have shown the intensive absorption resulting in three λ_{max} at 230 nm (UVC), 240–290 nm (UVC) and 315–380 nm (UVA/UVB) with the absorption coefficients ε = 45 000–89 000 cm^{-1} mol^{-1} L. As expected, the high absorption has been shown for compounds **5**, where due to the rigidity of the structure the maximal overlapping between the orbitals of two benzene rings is realized; in this case, the absorption coefficients were ε = 29 000–84 000 cm^{-1} mol^{-1} L. For compound **5f** we have observed the highest absorption coefficient of ε = 84 000 cm^{-1} mol^{-1} L in this series. In general, absorptions observed in the current study for the scaffolds **4**, **5** and **7** are significantly higher compared with other known UVA/UVB filters[29] and with the UV-filters we have prepared in our recent study.[28]

One of the strong requirements for suncream-additives is an increased water solubility which ensures the good miscibility of the components in the emulsion. This was achieved by the above-mentioned hydrolysis of the ester derivatives to the corresponding salts and subsequent transformation into the acids **9**. The water solubility of these compounds is prominent even at room temperature and lies in a range of 10–20 g L^{-1}. Moreover, the potassium salts, which were isolated in many cases as intermediates of the hydrolysis process, have increased solubility of about 20–40 g L^{-1}.

In conclusion, we have developed a simple and convenient method for the synthesis of functionalized 2-hydroxybenzophenones, 6*H*-benzo[*c*]chromenes and benzo[*c*]coumarins by formal [3 + 3] cyclocondensations of 3-acylchromones with dimethyl-1,3-acetonedicarboxylate and 1,3-diphenylacetone. The products constitute an important structural subunit of a variety of biologically active compounds, which are not readily available by other methods. The biological evaluation of the synthesized compounds is currently being studied in our laboratories. Nevertheless, due to the strong UV-absorption properties of many of the representatives the libraries synthesized here can also find a use in the preparation of the sun-protective materials and creams.

Experimental

General procedure for the synthesis of compounds 4–8

To a stirred reaction mixture of the corresponding chromone (1.0 mmol) and 1,3-*C*,*C*-dinucleophile (1.1 mmol) in dioxane (6–7 mL), DBU (0.20 mL, 1.3 mmol) was added slowly *via* a syringe at room temperature. Stirring at room temperature (for dimethyl acetonedicarboxylate) or at reflux (for 1,3-diphenylacetone) was continued until chromone was consumed completely (followed by TLC, approximately 10–12 h). The reaction mixture was quenched with an aqueous solution of 10% NH_4Cl and extracted with chloroform, dried (Na_2SO_4), the solvent was distilled off under reduced pressure, and the resulting residue was subjected to column chromatography on silica gel using heptane–ethylacetate (5 : 1) as an eluent, slowly increasing the polarity up to 3 : 1 to give the isolated products.

General procedures for the synthesis of compounds 9 and 10

To a stirred reaction mixture of the corresponding compound **4** or **5** (1.0 mmol) in methanol (6–7 mL) potassium hydroxide (8.0 mmol) was added. The reaction mixture was heated under reflux. Stirring and heating were continued until the reagent was consumed completely (followed by TLC, approximately 2 days). The solvent was distilled off in a vacuum and the resulting residue was quenched with water, then neutralized with an

aqueous solution of HCl (30%). The resulting residue was filtered and dried.

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