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Efficient entry to trifluoromethyl substituted chromanes from oxidative aromatization of tetrahydro-2*H*-chromen-5(6*H*)-ones using iodine/alcohol with conventional and microwave methods

Helio G. Bonacorso *, Jussara Navarini, Carson W. Wiethan, Andrizia F. Junges, Susiane Cavinatto, Rosália Andrighetto, Marcos A.P. Martins, Nilo Zanatta

Núcleo de Química de Heterociclos (NUQUIMHE), Departamento de Química, Universidade Federal de Santa Maria, 97105-900 Santa Maria, RS, Brazil

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ABSTRACT

This paper describes the one-pot simple and efficient oxidative aromatization reaction employing an iodine/alcohol medium for the preparation of a series of 11 new 3-acyl-2-hydroxy-5-alkoxy-4-aryl-2-(trifluoromethyl)chromanes, where acyl = Ac, Bz, furan-2-oyl; aryl = Ph, 4-$NO_2C_6H_4$, 4-$OCH_3C_6H_4$ and alkoxy = OMe, O-Pr^n, EtO and OBn from the respective 3-acyl-4-aryl-2-(trifluoromethyl)-2-hydroxy-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-ones. Yields in the range of 50–89% were obtained when the oxidative reactions were performed using both conventional thermal heating (CTH) and microwave (MW) procedures. In general, the MW method produced similar yields with shorter reaction times and easier reaction workups. As an example, a representative X-ray diffraction ORTEP for 3-benzoyl-2-hydroxy-5-methoxy-4-methoxyphenyl-2-(trifluoromethyl)chromane is also shown.

1. Introduction

In recent years, the use of molecular iodine has received considerable attention. Molecular iodine is the simplest, least expensive, least toxic, most readily available oxidant for aromatization of cyclohexenone derivatives and their heterocyclic analogs that may possess some biological activity or serve as building blocks for the synthesis of derivatives with biological applications [1].

Iodine in methanol has been used as a novel reagent for the conversion of 2-cyclohexenones into the corresponding anisole derivatives. This methodology was reported first in 1980 by Tamura and Yoshimoto [2], who subjected a series of cyclohexenones to iodine in refluxing methanol to yield variously substituted anisole derivatives. Iodine in methanol was applied by Kotnis [3] to Hagemann's esters to afford substituted *p*-methoxybenzoates. Hedge et al. [4] have reported the aromatization of 2-cyclohexenone-4-carboxylates with iodine and sodium ethoxide. This methodology can also be used for the aromatization of 1,4-dihydropyridines into pyridines [5a] and tetrahydro-4-quinolines into 2-aryl-4-methoxyquinolines [5b].

On the other hand, the synthesis of fluoroorganic compounds is a challenging topic of the modern organic chemistry. Especially, the presence of trifluoromethyl moiety in the target molecule often results in significant changes of its physical, chemical and biological properties [6]. Design and synthesis of trifluoromethyl-containing compounds has received recently significant attention due to their application in various fields like pharmacy, medicine, agriculture and material science [7–9]. The trifluoromethyl group is a bulky and highly electron withdrawing group (electronegativity of 3.5 on the Pauling scale) that strongly affects the reactivity of the adjacent functional groups. The incorporation of a trifluoromethyl group into organic molecules generally increases their chemical stability owing to the high bond strength that can induce increased resistance to metabolic decomposition [10,6f].

Compounds in which a benzene ring and a pyran ring are fused together with various levels of saturation and oxidation are very common in nature. The 1-benzopyrans include structural skeletons such as chromane, 4*H*-chromene and 2*H*-chromene [11]. The class of compounds including the chromane (known as 3,4-dihydro-2*H*-1-benzopyran) is not itself found in nature, but the chromane unit is present in many natural products. Vitamin E (α-tocopherol) [12a,b], a substituted chromane, is found in plant oils and in the leaves of green vegetables as well as the antibiotic LLD253α [13] and the aromatase inhibitor pinostrobin [14]. Certain benzopyrans have also been highlighted because of their photochromic and thermochromic properties [11].

* Corresponding author. Fax: +55 55 3220 8031.
E-mail address: heliogb@base.ufsm.br (H.G. Bonacorso).

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In addition, chromenones are not only important biologically active compounds and natural products but also valuable substrates for the synthesis of related pharmacologically interesting compounds. In this context, we decided to study the oxidative aromatization of a series of trifluoromethyl-substituted chromenones, which we had been previously synthesized in our laboratory [15]. These heterocyclic compounds, besides having a cyclohexenone ring, also include a 3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one. The 3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one structure is the core of the complex structure with four main attached substituents, viz., a hydroxyl and a trifluoromethyl group at the C2-position and an acyl and an aryl substituent at the C3- and C4-positions, respectively. Although the study of the oxidative aromatization of some chromenones is described in the literature [16,17], the specific oxidative aromatization reactions of tetra-substituted chromenone **1**, which contains functional groups amenable to oxidative processes, have not been studied.

We are particularly interested in the transformation of chromenones to chromanes as the product of aromatization reactions that potentially provide an efficient and interesting intermediate for synthesis of the other trifluoromethylated derivative compounds in this class.

Considering the importance of the heterocyclic precursors **1** and product **2** and according to the previously published work [16,17], the aim of this work is to report the synthesis of a new series of high substituted chromane derivatives (**2**) from the 2-trifluoromethyl-2*H*-chromenones (**1**) employing iodine/alcohol as an efficient and selective oxidative medium with the conventional thermal heating (CTH) and microwave (MW) irradiation procedures.

2. Results and discussion

The 2-trifluoromethyl-2*H*-chromenones **1** were readily prepared using a multicomponent reaction (MCR) methodology from 4-methoxy-4-alkyl(aryl/heteroaryl)-1,1,1-trifluoroalken-3-en-2-ones, aryl aldehydes and 1,3-cyclohexanedione in the presence of a catalytic amount of triethylamine, as described by us previously [15].

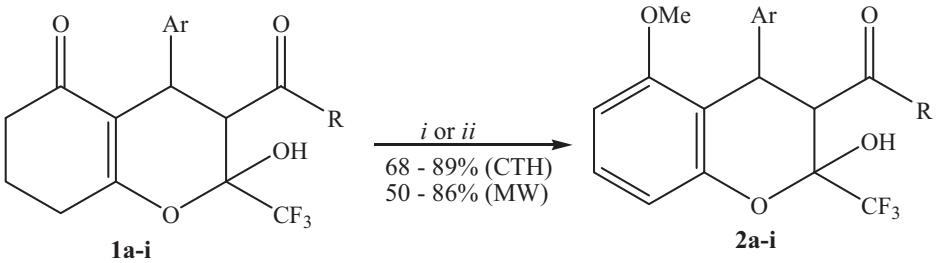
We first performed the oxidative aromatization reaction of the 3-acetyl-2-hydroxy-4-phenyl-2-trifluoromethyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (**1a**) based on the methodology described by Mphahlele and Moekwa [16]. According to this author, 1 mmol of substrate and 2 mmol of iodine in methanol (5 mL/mmol of **1a**) were used under reflux for 2 h. However, under these reaction conditions, it was not possible to obtain the compound **2a**, and only the starting material was recovered.

To investigate better reaction conditions, the reaction was carried out under different conditions such as varying the reaction time from 6 to 16 h and varying the volume of solvent from 5 to 20 mL because the amount of methanol used was very important for dissolving the chromenone precursor **1a**. The best results were obtained when the reaction conditions were 16 h of reflux in 20 mL of solvent. The product **2a** was obtained as oil, with a yield of 89%. The oil was identified by ^{1}H NMR experiments and GC/MS.

With the optimal reaction conditions using CTH in hand, it was extended to all. Thus, we carried out the synthesis of a series of 5-methoxy-chromanes (**2a–i**) from other chromenone derivatives **1** with yields of 68–89% (Scheme 1). Unfortunately, due to the low solubility of **1f**, the optimal conditions failed to obtain chromane **2f** (R = 2-furyl, R^1 = Me and Ar = 4-$NO_2C_6H_4$). Using a high dilution (up to 50 mL/mol of **1f**) and longer reaction times (up to 24 h) did not change this unsatisfactory result.

The compounds **2** were obtained as solids or oils, and the structures were fully confirmed by ^{1}H NMR, ^{13}C NMR, GC/MS, and X-ray diffraction. The purity was confirmed by CHN elemental analysis. The ^{1}H NMR spectra showed an important feature, the absence of methylene proton signals from the cyclohexenone ring in the region δ 2.62–1.93 ppm and the presence of a singlet for the OMe group in the region δ 3.34 ppm. ^{13}C NMR also showed important features such as the absence of the signal for the carbonyl carbon C-5, which showed NMR signals in the range of δ 194.9 ppm for the **1** series, with signals now appearing in the region of δ 157.6 ppm. Due to the presence of the CF_3 group, the C-2 carbon presented a characteristic quartet at δ 93.9 ppm with $^2J_{CF}$ = 33 Hz. Additionally, the CF_3 group showed a typical quartet at δ 122.3 ppm with $^1J_{CF}$ = 286 Hz. The new methoxy group of the anisole structure showed an NMR signal in the region of δ 55.1 ppm.

The X-ray diffraction measurement was carried out for compound **2h** (Fig. 1) [18], proving that H3 and H4 are situated *trans* to each other, as are the aryl and acyl substituents attached to these carbons. The X-ray data clearly demonstrate the presence of an anisole unit fused to the pyran ring at C4a–C8a, confirming that the oxidative aromatization reaction on the chromen-5-one precursor has occurred.



i = I_2 (2 equiv.), MeOH (20 - 50mL), 16 h, reflux (CTH)
ii = I_2 (2 equiv.), MeOH (3mL), 0.5 h, 100 ºC (MW)

1,2	a	b	c	d	e	f	g	h	i
Ar	Ph	Ph	Ph	4-NO_2Ph	4-NO_2Ph	4-NO_2Ph	4-MeOPh	4-MeOPh	4-MeOPh
R	CH_3	Ph	2-Furyl	CH_3	Ph	2-Furyl	CH_3	Ph	2-Furyl

Scheme 1. Synthesis of 5-methoxychromane derivatives (**2a–i**).

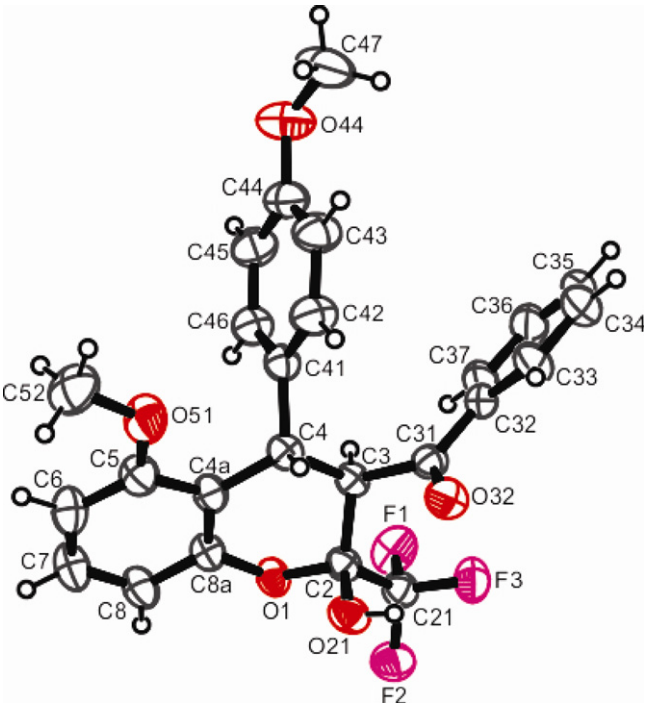


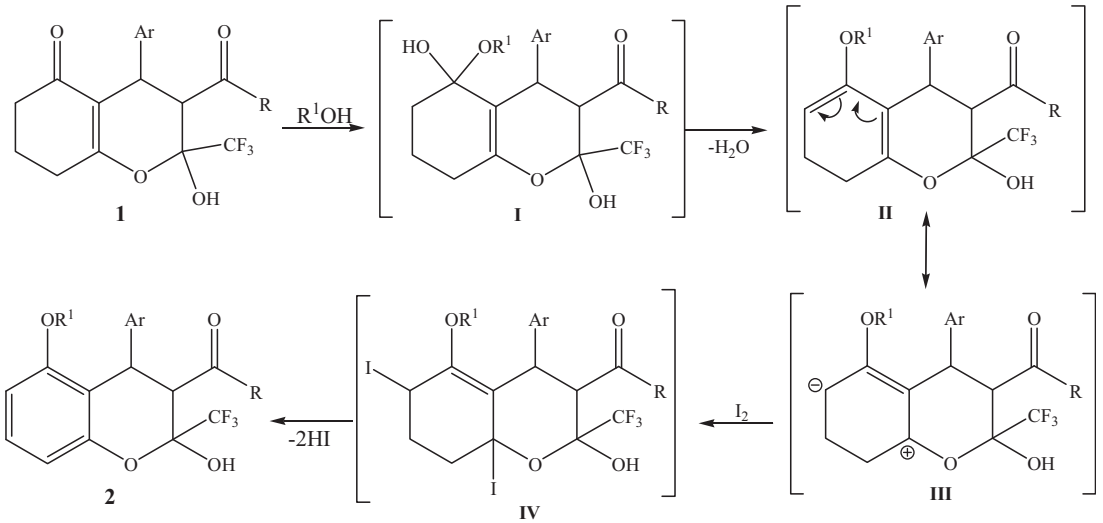
Fig. 1. ORTEP representation of the X-ray-determined molecular structure of 3-benzoyl-2-hydroxy-5-methoxy-4-methoxyphenyl-2-(trifluoromethyl)chromane (**2h**) with atoms labeled (CCDC 872165) [18]. Displacement ellipsoids are drawn in at the 50% probability level.

The corresponding mechanism for the preparation of chromanes **2** could be proposed from the conversion of some α,β-unsaturated cyclohexanones into anisoles by iodine in alcohol or with metal alkoxide, as reported previously [2–5]. We therefore proposed a suitable mechanism for this reaction, as shown in Scheme 2. The first step of the reaction mechanism would be an initial 1,2-addition of the alcohol to carbonyl carbon C-5 at the chromenones **1** with the formation of a hemiketal **I**. A subsequent dehydration affords an enol ether intermediate **II**, which might be present in equilibrium with the intermediate **III** also. It is thus possible that the 1,4-addition of iodine occurs with the formation of intermediate **IV**. Finally, a double dehydrohalogenation of **IV** can furnish the desired 5-(alkoxy)chromanes **2**.

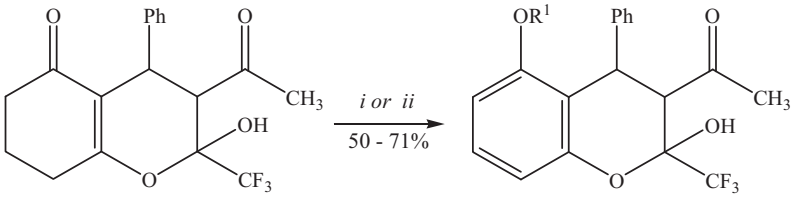
An analysis of the oxidation number of carbon atoms C4a, C5, C8a, C6, C7 and C8 shows that although the carbons C8a (+2 to +1) and C6 (+1 to −1) were reduced from the intermediate **IV** to the products **2**, the second oxidation process occurs in the intermediate **IV** due to the elimination of two molecules of HI and the formation of two double bonds. In this last step, the carbons C7 and C8 (−2 to −1) were oxidized while C5 did not change its oxidation number (+1). Thus, when we analyzed the oxidation numbers for the carbons of the cyclohexenone moiety in the precursors (**1a–i**) and in the products **2a–i**, we found for **1a–i**: C4a(0), C5(+2), C6(−2), C7(−2), C8(−2), C8a(+1) and for the products **2a-i**: C4a(0), C5(+1), C6(−1), C7(−1), C8(−1), C8a(+1). We can see that the oxidation number for the carbons C4a and C8a did not change; C5 was reduced (+2 to +1), but the carbons C6, C7 and C8 were oxidized (−2 to −1). Finally, the average oxidation number of the carbons belonging to the cyclohexenone ring changed from (−3) to (−1), resulting in an oxidative aromatization process in the molecules **1a–i**.

It is important to mention also that the reaction was highly chemoselective because there are two carbonyls on the starting material but only the endocyclic carbonyl reacted with the alkoxyde anion and iodine underwent an oxidative aromatization. Another important point is the fact that the *geminal* hydroxyl group to the trifluoromethyl group could be eliminated under the employed reaction conditions to give an α,β-unsaturated ketone with an exocyclic carbonyl, which could then have an analogous reaction to the endocyclic carbonyl leading to the other products.

Because a long reaction time is required by the conventional procedure, a large amount of solvent and a difficult workup by column chromatography are necessary to obtain the compounds of the series **2**, an oxidative aromatization reaction of 2-trifluoromethyl-2*H*-chromenones **1** was also investigated using the microwave (MW) irradiation methodology. The reactions were performed in sealed vessels containing the substrates; **1**: iodine (1:2 molar ratio) in methanol (3 mL) and were submitted to microwave irradiation (200 W) for 0.5 h at a temperature of 100 °C and at 2.5 bar of pressure. After the reaction time, the mixture was transferred to a flask where the solvent was evaporated under reduced pressure and the residue was taken up into dichloromethane. The organic solution was sequentially washed with saturated aqueous sodium thiosulfate, sodium bicarbonate and brine and then dried over Na_2SO_4. The mixture was filtered and evaporated under reduced pressure. All the products **2** obtained were identified by ^{1}H NMR experiments and GC/MS and comparison with the conventional methodology (Table 1).



Scheme 2. Plausible mechanism for the oxidative aromatization of the chromenones **1**.



1a

3a (R^1 = Et)
4a (R^1 = Pr^n)

i = I_2 (2 equiv.), R^1OH (20mL), 16 h, reflux (CTH)
ii = I_2 (2 equiv.), R^1OH (3mL), 0.5 h, 100 °C (MW)

Scheme 3. Synthesis of 5-(alkoxy)chromane derivatives **3a** and **4a**.

Table 1
Synthesis of 5-(alkoxy)chromane derivatives (**2**–**4**) using conventional thermal heating and microwave irradiation procedures.

Compound	R	R^1	Ar	Yield (%)	
				CTH[a]	MW[b]
2a	CH_3	CH_3	Ph	89	54
2b	Ph	CH_3	Ph	80	71
2c	2-Furyl	CH_3	Ph	71	86
2d	CH_3	CH_3	4-$NO_2C_6H_4$	85	70
2e	Ph	CH_3	4-$NO_2C_6H_4$	76	75
2f	2-Furyl	CH_3	4-$NO_2C_6H_4$	[c]	72
2g	CH_3	CH_3	4-$MeOC_6H_4$	79	60
2h	Ph	CH_3	4-$MeOC_6H_4$	75	78
2i	2-Furyl	CH_3	4-$MeOC_6H_4$	68	60
3a	CH_3	CH_2CH_3	Ph	60	50
4a	CH_3	$CH_2CH_2CH_3$	Ph	71	63
5a	CH_3	CH_2Ph	Ph	[c]	[c]

[a] Conventional thermal heating (CTH).
[b] Microwave irradiation (MW).
[c] Recovery of reagents.

The reactions that yield the compound **2f** do not occurred when conventional procedures for oxidative aromatization are employed and only the starting material **1f** was recovered, to our surprise, when the microwave irradiation methodology was used, this compound was obtained in 72% yield without byproducts.

The beneficial effects of microwave irradiation are playing an increasing role in chemical developments, specifically in this synthetic process where the classical method (CTH) forced and prolonged the times that resulted in unsuccessful reactions. The oxidative aromatization under microwave irradiation offered shorter reaction times, use of a smaller amount of solvent, easier reaction workup, good yields and no by-products as the main advantages for the synthesis of chromane **2f**.

Finally, we investigated oxidative aromatization reactions employing conventional procedures and microwave irradiation, as well as different alcohols such as ethanol, *n*-propanol and benzyl alcohol (Scheme 3). The reaction was performed for compound 3-acetyl-2-hydroxy-4-phenyl-2-trifluoromethyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (**1a**) in the presence of iodine and the alcohols mentioned above, using both of the heating methods described in this work. As a result, we found that the reactions with ethanol and *n*-propanol were successful in obtaining chromane products **3a** and **4a**. However, when the reaction was performed in benzyl alcohol, the formation of the product **5a** was not observed using either method (CTH and MW). From the proposed mechanism, we suggest that the repulsion between the aromatic moiety of the benzyl alcohol and the phenyl substituent at the C-4 could be responsible.

3. Conclusion

In summary, we applied the well-known method of oxidative aromatization using iodine/methanol for the selective synthesis of new trifluoromethyl-substituted chromanes from the respective tetrahydro-2*H*-chromen-5(6*H*)-ones. This synthesis was performed using both conventional and microwave heating procedures, where the microwave demonstrated advantages such as shorter reaction times, simplicity of the reaction, a reduced amount of solvent and good yields.

4. Experimental

4.1. Synthesis

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on a Reichert Thermovar apparatus. The ^1H and ^{13}C spectra were recorded at 298 K on a Bruker DPX 400 spectrometer (^1H at 400.13 MHz, ^{13}C at 100.63 MHz) with digital resolution of ±0.01 ppm, in $CDCl_3$ using TMS as the internal reference. Mass spectra were recorded on an HP 5973 MSD connected to a HP 6890 GC and interfaced to a Pentium PC. The GC was equipped with a split–splitless injector, autosampler, cross-linked HP-5 capillary column (30 m, 0.32 mm internal diameter), and helium was used as the carrier gas. Elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (São Paulo University-São Paulo, Brazil). The diffraction measurements were carried out by graphite-monochromatized Mo Kα radiation with l = 0.71073 Å on a Bruker SMART CCD diffractometer [19]. The structure of **2h** was solved by direct methods using the SHELXS-97 program [20] and refined on F2 using the full-matrix least squares component of the SHELXL-97 package [21]. The absorption correction was performed by Gaussian methods [22]. Anisotropic displacement parameters for non-hydrogen atoms were applied. The hydrogen atoms were placed at calculated positions with 0.96 Å (methyl CH_3), 0.97 Å (methylene CH_2), 0.98 Å (methyne CH), 0.93 Å (aromatic CH) and 0.82 Å (OH) using a riding model. The hydrogen isotropic thermal parameters were kept equal to Uiso(H) = *x*Ueq (carrier C atom), with *x* = 1.5 for methyl groups and *x* = 1.2 otherwise. The valence angles C–C–H and H–C–H of methyl groups were set to 109.58, and the H atoms were allowed to rotate around the C–C bond. A molecular graph was prepared using ORTEP3 for Windows [23]. Microwave irradiation was conducted in a multimode microwave ETHOS-1 (Milestone Inc.) with a twin magnetron having maximum delivered power of 1300 W. The temperature was set to 100 °C, and the irradiation was automatically stopped at this temperature. The temperature and pressure were measured throughout with an ATC-400 CE and APC-55 detector, respectively.

*4.2. General procedure for the synthesis of 3-acyl-2-hydroxy-5-alkoxy-4-aryl-2-(trifluoromethyl)chromenes (**2a–i**) and (**3a**, **4a**)*

4.2.1. Conventional thermal heating procedure (CTH)

A stirred mixture of chromenes **1** (1 mmol) and iodine (2 mmol) in 20 mL of alcohol (**2a**, **2d**, **3a**, **4a**) or 50 mL of alcohol (**2b–c**, **2e–i**) was boiled under reflux for 16–24 h. The solvent was evaporated under pressure, and the residue was taken up into dichloromethane. The organic solution was sequentially washed with saturated aqueous sodium thiosulfate, sodium bicarbonate and brine and then dried over Na_2SO_4. The mixture was filtered and evaporated under reduced pressure, and the residue was purified by column chromatography (hexane/ethyl acetate 1:1) and dried in a desiccator over P_2O_5 under reduced pressure. The results were chromanes **2** in high purity (as determined by elemental analysis data).

4.2.2. Microwave irradiation procedure (MW)

A solution of chromenes **1** (0.25 mmol) and iodine (0.50 mmol) diluted in 3 mL of alcohol was irradiated in an ETHOS-1 microwave at 200 W, 2.5 bar of pressure for 0.5 h, enough time to complete the reaction. The temperature was set to 100 °C, and the irradiation was automatically stopped at this temperature. The reaction mixture was subsequently cooled to room temperature. The solvent was evaporated under pressure, and the residue was taken up in dichloromethane. The organic solution was sequentially washed with saturated aqueous sodium thiosulfate, sodium bicarbonate and brine and then dried over Na_2SO_4. The mixture was filtered, and the solvent was evaporated under reduced pressure. The chromanes **2** were obtained as solids and later dried under vacuum in a desiccator containing P_2O_5. The products **2** showed a high degree of purity and were not recrystallized.

*4.2.3. 3-Acetyl-2-hydroxy-5-methoxy-4-phenyl-2-(trifluoromethyl)chromane (**2a**): yellow oil*

^{1}H NMR ($CDCl_3$): δ = 7.25–7.19 (m, 4H, Ph), 7.09–7.07 (m, 2H, Ph), 6.70 (d, *J* = 8 Hz, 1H, H6), 6.47 (d, *J* = 8 Hz, 1H, H8), 4.25 (d, *J* = 11 Hz, 1H, H3), 3.48 (d, *J* = 11 Hz, 1H, H4), 3.32 (s, 3H, OCH_3), 1.82 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 212.4 (C=O), 157.6 (C5), 150.6 (C8a), 143.0 (Ph), 128.7 (C7), 128.6, 127.0, 126.8 (5C, Ph), 122.4 (q, *J* = 286, CF_3), 112.5 (C4a), 110.3 (C8), 105.9 (C6), 93.8 (q, *J* = 33 Hz, C2), 55.2 (OCH_3), 54.3 (C3), 41.9 (CH_3), 33.0 (C4).

GC–MS (EI, 70 eV) *m*/*z* (%): 366 (M^+, 5), 305 (100), 211(25), 91 (27).

Anal. calcd. for $C_{19}H_{17}F_3O_4$ (366.10): C, 62.29; H, 4.68%. Found: C, 62.14; H, 4.78%.

*4.2.4. 3-Benzoyl-2-hydroxy-5-methoxy-4-phenyl-2-(trifluoromethyl)chromane (**2b**): white solid, mp 124–126 °C*

^{1}H NMR ($CDCl_3$): δ = 7.46–7.39 (m, 3H, Ph), 7.27–7.19 (m, 4H, Ph), 7.03–6.98 (4H, Ph, H7), 6.75 (d, *J* = 8 Hz, 1H, H6), 6.49 (d, *J* = 8 Hz, 1H, H8), 4.45 (d, *J* = 11 Hz, 1H, H3), 4.30 (d, *J* = 11 Hz, 1H, H4), 3.33 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$): δ = 204.0 (C=O), 157.6 (C5), 150.7 (C8a), 142.9, 136.3, 134.2, 128.7, 128.4, 128.3 (Ph), 126.5 (C7), 122.3 (q, *J* = 286, CF_3), 112.9 (C4a), 110.5 (C8), 105.9 (C6), 94.4 (q, *J* = 33 Hz, C2), 55.2 (OCH_3), 48.8 (C3), 42.8 (C4).

GC–MS (EI, 70 eV) *m*/*z* (%): 428 (M^+, 5), 305 (45), 211 (45), 105 (100), 77 (55).

Anal. calcd. for $C_{24}H_{19}F_3O_4$ (428.12): C, 67.29; H, 4.47%. Found: C, 67.55; H, 4.96%.

*4.2.5. 3-(Furan-2-oyl)-2-hydroxy-5-methoxy-4-phenyl-2-(trifluoromethyl)chromane (**2c**): yellow solid, mp 47–49 °C*

^{1}H NMR ($CDCl_3$): δ = 7.44 (dd, *J* = 1 Hz, 1H, Fur), 7.20 (s, 1H, Fur), 7.11–7.03 (m, 5H, Ph), 6.99–6.98 (m, 1H, H7), 6.74 (d, *J* = 8 Hz, 1H, H6), 6.45 (d, *J* = 8 Hz, 1H, H8), 6.33 (d,d, *J* = 2 Hz, 1H, Fur), 4.42 (d, *J* = 11 Hz, 1H, H3), 4.00 (d, *J* = 11 Hz, 1H, H4), 3.33 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$): δ = 189.6 (C=O), 157.6 (C5), 151.9 (1C, Fur), 150.6 (C8a), 148.8 (1C, Fur), 142.9, 128.7, 128.1, 126.9 (6C, Ph), 126.4 (C7), 122.4 (q, *J* = 286, CF_3), 120.9 (1C, Fur), 112.8 (C4a), 112.6 (1C, Fur), 110.4 (C8), 105.9 (C6), 94.4 (q, *J* = 33 Hz, C2), 53.3 (OCH_3), 49.6 (C3), 42.1 (C4).

GC–MS (EI, 70 eV) *m*/*z* (%): 418 (M^+, 5), 305 (68), 211 (91), 95 (100).

Anal. calcd. for $C_{22}H_{17}F_3O_5$ (418.10): C, 63.16; H, 4.10%. Found: C, 63.30; H, 4.29%.

*4.2.6. 3-Acetyl-2-hydroxy-5-methoxy-4-(4-nitrophenyl)-2-(trifluoromethyl)chromane (**2d**): yellow oil, mp 68–70 °C*

^{1}H NMR ($CDCl_3$): δ = 8.15 (d, *J* = 8 Hz, 2H, Ph), 7.30–7.32 (m, 3H, Ph, H7), 6.72 (d, *J* = 8 Hz, 1H, H6), 6.47 (d, *J* = 8 Hz, 1H, H8), 4.42 (d, *J* = 11 Hz, 1H, H3), 3.43 (d, *J* = 11 Hz, 1H, H4), 3.33 (s, 3H, OCH_3), 1.87 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 210.7 (C=O), 157.0 (C5), 150.9 (C8a), 150.4, 146.8, 129.6, (4C, Ph), 128.2 (C7), 123.9 (2C, Ph), 122.1 (q, *J* = 286, CF_3), 110.8 (C4a), 110.4 (C8), 105.5 (C6), 93.5 (q, *J* = 33 Hz, C2), 55.1 (OCH_3), 54.0 (C3), 41.4 (CH_3), 33.1 (C4).

GC–MS (EI, 70 eV) *m*/*z* (%): 411 (M^+, 14), 369 (100), 258 (87), 136 (68), 106 (51).

Anal. calcd. for $C_{19}H_{16}F_3NO_6$ (411.09): C, 55.48; H, 3.92; N, 3.41%. Found: C, 55.20; H, 4.30; N, 3.13%.

*4.2.7. 3-Benzoyl-2-hydroxy-5-methoxy-4-(4-nitrophenyl)-2-(trifluoromethyl)chromane (**2e**): white solid, mp 166–168 °C*

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8 Hz, 2H, Ph), 7.50–7.47 (m, 2H, Ph), 7.31–7.26 (m, 4H, Ph), 7.18–7.14 (m, 2H, Ph, H7), 6.78 (d, *J* = 8 Hz, 1H, H6), 6.50 (d, *J* = 8 Hz, 1H, H8), 4.59 (d, *J* = 11 Hz, 1H, H3), 4.27 (d, *J* = 11 Hz, 1H, H4), 3.35 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$): δ = 202.6 (C=O), 157.0 (C5), 150.7 (C8a), 146.5, 135.8, 134.9, 128.5, 128.7 (6C, Ph), 128.2 (C7), 127.8, 123.6 (4C, Ph), 122.1 (q, *J* = 286, CF_3), 111.1 (C4a), 110.6 (C8), 105.5 (C6), 94.1 (q, *J* = 33 Hz, C2), 55.1 (OCH_3), 47.7 (C3), 42.5 (C4).

GC–MS (EI, 70 eV) *m*/*z* (%): 455 (18), 358 (45), 333 (100), 282 (22), 207 (83), 105 (81), 77 (45).

Anal. calcd. for $C_{24}H_{18}F_3NO_6$ (473.10): C, 60.97; H, 3.83; N, 2.96%. Found: C, 60.50; H, 3.70; N, 3.15%.

*4.2.8. 3-(Furan-2-oyl)-2-hydroxy-5-methoxy-4-(4-nitrophenyl)-2-(trifluoromethyl)chromane (**2f**): yellow solid, mp 101–103 °C*

^{1}H NMR ($CDCl_3$): δ = 7.87 (d, *J* = 8 Hz, 1H, Ph), 7.42 (s, 1H, Fur), 7.27 (m, 2H, Fur, H7), 7.19 (d, d, *J* = 8 Hz, 1H, Ph), 6.77 (d, *J* = 2 Hz, 1H, H6), 6.49 (d, *J* = 2 Hz, 1H, H8), 6.40 (d,d, *J* = 1 Hz, 1H, Fur), 4.59 (d, *J* = 11 Hz, 1H, H3), 4.03 (d, *J* = 11 Hz, 1H, H4), 3.35 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$): δ = 188.7 (C=O), 157.2 (OCH_3), 151.9 (C8a), 150.8 (Fur), 150.7 (Fur), 149.0 (Ph), 146.7 (Ph), 129.5 (C7), 127.8 (Ph), 123.8 (q, *J* = 286, CF_3), 123.4 (Ph), 120.6, 113.3 (Fur), 111.1 (C4a), 110.6 (C8), 105.6 (C6), 94.4 (q, *J* = 33 Hz, C2), 55.1 (OCH_3), 48.8 (C3), 41.85 (C4).

GC–MS (EI, 70 eV) *m*/*z* (%): 433 (5), 334 (11), 207 (16), 95 (100).

Anal. calcd. for $C_{22}H_{16}F_3NO_7$ (463,09) C, 57.03; H, 3.48; N, 3.02%; C, 57.01; H, 3.52; N, 2.99%.

*4.2.9. 3-Acetyl-2-hydroxy-5-methoxy-4-(4-methoxylphenyl)-2-(trifluoromethyl)chromane (**2g**): yellow oil*

^{1}H NMR ($CDCl_3$): δ = 7.15 (t, *J* = 8 Hz, 1H, H7), 6.98 (d, *J* = 8 Hz, 2H, Ph), 6.79 (d, *J* = 8 Hz, 2H, Ph), 6.68 (d, *J* = 8 Hz, 1H, H6), 6.44 (d, *J* = 8 Hz, H8), 4.20 (d, *J* = 11 Hz, 1H, H3), 3.47 (d, *J* = 11 Hz, 1H, H4), 3.47 (s, 3H, *p*-OCH_3), 3.3 3 (s, 3H, OCH_3), 1.84 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 212.8 (C=O), 158.3 (C5), 157.7 (Ph), 150.4 (C8a), 134.8 128.7 (3C, Ph), 128.0 (C7), 122.3 (q, *J* = 286, CF_3), 114.0

(2C, Ph), 112.7 (C4a), 110.3 (C8), 105.9 (C6), 93.7 (q, J = 33 Hz, C2), 55.3, 55.1 (2C, OCH_3), 54.2 (C3), 41.1 (CH_3), 33.2 (C4).

GC–MS (EI, 70 eV) m/z (%): 396 (M^+, 12), 353 (15) 243 (45), 121 (100).

Anal. calcd. for $C_{20}H_{19}F_3O_5$ (396.35): C, 60.61; H, 4.83%. Found: C, 60.80; H, 4.98%.

*4.2.10. 3-Benzoyl-2-hydroxy-5-methoxy-4-(4-methoxyphenyl)-2-(trifluoromethyl)chromane (**2h**): white solid, mp 158–160 °C*

^{1}H NMR ($CDCl_3$): δ = 7.49–7.43 (M, 4H, Ph), 7.30 7.27 (m, 2H, Ph), 7.23–7.17 (m, 1H, H7), 6.89 (d, J = 8 Hz, 2H, Ph), 6.74 (d, J = 8 Hz, 1H, H6), 6.60 (d, J = 8 Hz, 2H, Ph), 6.50 (d, J = 8 Hz, 1H, H8), 4.42 (d, J = 11 Hz, 1H, H3), 4.30 (d, J = 11 Hz, 1H, H4), 3.67, 3.37 (s, 6H, OCH_3).

^{13}C NMR ($CDCl_3$): δ = 204.1 (C=O), 158.1 (C5), 157.6 (Ph), 150.7 (C8a), 136.2, 134.9, 134.2 128.6, 128.5, 128.4 (Ph), 128.0 (C7), 122.3 (q, J = 286, CF_3), 113.7 (2C, Ph), 113.3 (C4a), 110.4 (C8), 105.9 (C6), 94.4 (q, J = 33 Hz, C2), 55.3, 55.1 (2C, OCH_3), 48.9 (C3), 42.01 (C4).

GC–MS (EI, 70 eV) m/z (%): 458 (M^+, 5), 353 (9), 105 (100), 77 (32).

Anal. calcd. for $C_{25}H_{21}F_3O_5$ (458.13): C, 65.50; H, 4.62%. Found: C, 65.78; H, 4.94%.

*4.2.11. 3-(Furan-2-oyl)-2-hydroxy-5-methoxy-4-(4-methoxyphenyl)-phenyl-2-(trifluoromethyl)chromane (**2i**): white solid, mp 144–146 °C*

^{1}H NMR ($CDCl_3$): δ = 7.65 (d,d, J = 1 Hz, 1H, Fur), 7.19 (t, J = 8 Hz, 1H, H7), 7.07 (d,d, J = 1 Hz, 1H, Fur), 6.92–6.88 (m, 3H, Fur, Ph), 6.74 (d, J = 8 Hz, 1H, H6), 6.61 (d J = 8 Hz, 2H, Ph), 6.49 (d, J = 8 Hz, 1H, H8), 4.40 (d, J = 11 Hz, 1H, H3), 4.02 (d, J = 11 Hz, 1H, H4), 3.68, 3.37 (s, 6H, OCH_3).

^{13}C NMR ($CDCl_3$): δ = 189.8 (C=O), 158.0 (C5), 157.6 (Ph), 151.9 (Fur), 150.6 (C8a), 148.9 (Fur), 134.9, 128.8 (3C, Ph), 127.9 (C7), 122.3 (q, J = 286, CF_3), 121.0 (fur), 113.6 (Fur), 113.0 (2C, Ph), 112.9 (C4a), 110.4 (C8), 105.9 (C6), 94.2 (q, J = 33 Hz, C2), 55.4, 55.1 (2C, OCH_3), 49.8 (C3), 41.3 (C4).

GC–MS (EI, 70 eV) m/z (%): 448 (M^+, 5), 241 (9), 121 (23), 95 (100).

Anal. calcd. for $C_{23}H_{19}F_3O_6$ (448.11): C, 61.61; H, 4.27%. Found: C, 62.05; H, 4.40%.

*4.2.12. 3-Acetyl-5-ethoxy-2-hydroxy-4-phenyl-2(-trifluoromethyl)chromane (**3a**): yellow oil*

^{1}H NMR ($CDCl_3$): δ = 7.25–7.20 (m, 4H, Ph), 7.11–7.05 (m, 2H, Ph, H7), 6.66 (d, J = 8 Hz, 1H, H6), 6.42 (d, J = 8 Hz, 1H, H8), 4.25 (d, J = 11 Hz, 1H, H3), 3.84–3.69 m (m, 1H, CH_2), 3.47 (d, J = 11 Hz, 1H, H4), 3.40–3.36 (m, 1H, CH_2), 1.80 (s, 3H, CH_3), 0.73 (t, J = 7 Hz, 3H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 212.9 (C=O), 156.8 (C5), 150.5 (C8a), 143.0 128.8, 128.6 127.1 (6C, Ph), 126.6 (C7), 122.3 (q, J = 286, CF_3), 111.7 (C4a), 109.9 (C8), 105.9 (C6), 93.5 (q, J = 33 Hz, C2), 63.5 (CH_2), 54.0 (C3), 42.0 (C4), 33.0, 13.8 (CH_3).

GC–MS (EI, 70 eV) m/z (%): 380 (M^+, 14), 319 (100), 291 (20), 105 (14).

Anal. calcd. for $C_{20}H_{19}F_3O_4$ (380.35): C, 63.15; H, 5.03%. Found: C, 63.14; H, 5.09%.

*4.2.13. 3-Acetyl-2-hydroxy-4-phenyl-5-propoxy-2-(trifluoromethyl)chromane (**4a**): yellow oil*

^{1}H NMR ($CDCl_3$): δ = 7.27–7.20 (m, 3H, Ph), 7.15 (t, J = 8 Hz, 1H, H7), 7.08–7.06 (m, 2H, Ph), 6.67 (J = 8 Hz, 1H, H8), 6.43 (d, J = 8 Hz, 1H, H6), 4.26 (d, J = 11 Hz, 1H, H3), 3.65–3.60 (m, 1H, CH_2), 3.46 (d, J = 11 Hz, 1H, H4), 3.40–3.35 (m, 1H, CH_2), 1.79 (s, 3H, CH_3), 1.13 (sex, J = 7 Hz, 2H, CH_2), 0.60 (t, J = 7 Hz, 3H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 204.2 (C=O), 156.85 (C5), 150.5 (C8a), 143.1, 128.4, 128.0, 127.0 (Ph), 126.1 (C7), 122.3 (q, J = 286, CF_3), 112.9 (C4a), 109.5 (C8), 105.9 (C6), 93.5 (q, J = 33 Hz, C2), 69.5 (OCH_2), 58.7 (C3), 39.1 (CH_3), 29.6 (C4), 21.4 (CH_2), 10.0 (CH_3).

GC–MS (EI, 70 eV) m/z (%): 394 (M^+, 19), 333 (100), 291 (62), 207 (69), 91 (50), 69 (38).

Anal. calcd. for $C_{21}H_{21}F_3O_4$ (394.13): C, 63.95; H, 5.37%. Found: C, 64.03%; H, 5.41%.

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