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Transformation of a hydroxyl into an acyl group on α-pyrone ring: a novel route to 3,4-diacylcoumarins

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ABSTRACT

The transformation of a hydroxyl into an acyl group, a transformation which has been extensively investigated on the benzene nucleus of several substrates, is now applied successfully for the first time to a heterocyclic ring and specifically to the pyrone ring of coumarin to yield novel 3,4-diacylcoumarins in good yields. The reaction involves formation of a new C–C bond.

1. Introduction

Coumarins, a class of fused ring heterocycles, also known as chromen-2-ones or benzopyran-2-ones, occur widely in nature and show interesting biological activity.[1] Coumarins are found in several plants, including grasses, orchids, citrus fruits, and legumes and are involved in the actions of plant growth hormones and growth regulators, the control of respiration, photosynthesis as well as defense against infection.[1,2] In addition, these compounds exhibit a variety of pharmacological properties.[2–4] Coumarins vary in structure due to the various types of substituents on their basic structure, which can influence their biological activity.[5]

Among the substituted coumarins, 3,4-disubstituted coumarins constitute an interesting class of derivatives with important pharmaceutical properties. Coumestans, which occur naturally in alfalfa and ladino clover are typical examples among the natural 3,4-substituted coumarin derivatives with estrogenic activity.[6] Novobiocin and clorobiocin are coumarin antibiotics of natural origin, which are inhibitors of DNA gyrase, and have a broad spectrum of activity toward Gram-positive bacteria, including methicilin-resistant strains of *Staphylococci* species.[7–9] Dicoumarol, a natural anticoagulant drug is metabolized from coumarin in sweet clover by mold.[10] It has been also found that antimutagenicity of coumarins is linked to the presence of polar functions at the 3-, 4-, and 7-positions.[11,12] Thus, it is understandable why development of new synthetic methods for coumarins and study of their biological properties are topics of growing interest for a great number of research groups. For example several coumarins bearing various groups on the pyrone ring at the 3- and 4-positions were synthesized and tested and many new syntheses of 3,4-disubstituted coumarins appeared recently in the literature.[13–19] Gilvocarcins (Fig. 1) are interesting natural 3,4-disubstituted coumarin derivatives with antibiotic activity synthesized recently by Snieckus et al.[20] The synthetic compound warfarin (Fig. 1) has been widely used as an oral anticoagulant.[15,19,21,22] Phenprocoumon has been found to possess antiviral activity and it significantly inhibits the HIV-1 protease.[6]

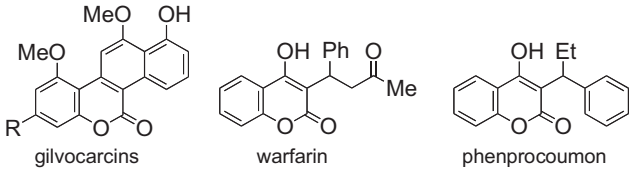

Fig. 1. 3,4-Disubstituted coumarins with biological activity.

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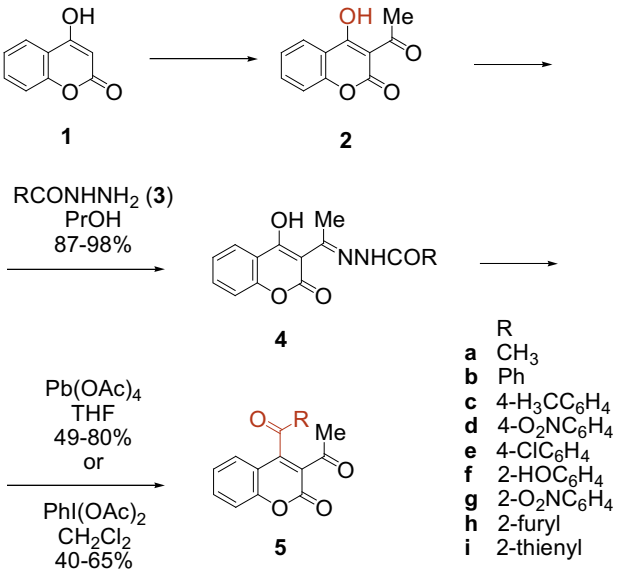
Recently, we synthesized[23–25] 6,7- and 7,8-diacylcoumarins in our laboratory and here we extend that work and describe the synthesis of novel 3,4-diacylcoumarins **4** (Scheme 1).



Scheme 1. Synthesis of 3,4-diacylcoumarins **5**.

2. Results and discussion

We have reviewed the synthesis of aromatic 1,2-diacyl compounds by the transformation of the phenolic hydroxy group of an *ortho*-hydroxyaryl ketone into an acyl group.[26] This transformation has been applied[26] to a variety of aromatic substrates and it has proved valuable for the synthesis of interesting heterocycles.[27,28] In the present context, we chose to synthesize a series of functionally diverse 3-acetyl-4-acyl coumarins. Following our earlier work, 3-acetyl-4-hydroxycoumarin *N*-acylhydrazones were the desired precursors, which would then be treated with lead tetraacetate (LTA) in order to apply the transformation of hydroxy into an acyl group, this time on the pyrone ring of coumarin (Scheme 1). The starting ketone **2** was prepared according to the literature[29] by direct acetylation of 4-hydroxycoumarin **1** with acetic anhydride.

3-Acetyl-4-hydroxycoumarin *N*-acylhydrazones **4** were synthesized via treatment of 3-acetyl-4-hydroxycoumarin **2** with the appropriate hydrazide **3** in propanol, as depicted in Scheme 1. The molar ratio of the reactants was 1/1 and the reaction was performed under reflux either for 24 h to yield hydrazones **4a**–**i** in very good yields (70–98%) or for 2 h to lead to the formation of hydrazones **4a**–**i** in slightly lower yield (60–81%). Hydrazones **4** were subsequently treated with lead tetraacetate (LTA) in THF at rt to give the desired products **5** in good yields, 49–70%. Alternatively, 3,4-diacylcoumarins **5** were obtained via (diacetoxyiodo)benzene (DIB) treatment of 3-acetyl-4-hydroxycoumarin *N*-acylhydrazones **4** (Scheme 1). DIB is known to exhibit reactivity analogous to that of LTA and is less hazardous and toxic than lead(IV) compounds.[30] Reaction of hydrazones **4a**–**i** with DIB in dichloromethane at rt afforded the corresponding 3,4-diacylcoumarins **5** in yields of 62–90%, which are slightly lower than those of comparable products obtained using LTA oxidation. The reaction conditions, the yields of formation of the new compounds **4** and **5** as well as their melting points are presented in Table 1.

Hydrazones **4a**–**i** were purified via recrystallization from propanol, whereas the desired 3,4-diacylcoumarins **5** were isolated by column chromatography. Products **4b**–**i** and **5a**–**i** are new compounds and their structures were identified by their ^{1}H, ^{13}C NMR and mass spectra as well as by either their elemental analysis or high resolution exact mass measurement.

In their ^{1}H NMR spectra, hydrazones **4** showed a characteristic singlet at about 2.65–2.77 ppm, which is assigned to the methyl protons attached at the 3-C=N carbon. The proton at C-5 of the coumarin appeared mainly as doublet of doublets at about 7.95–8.02 ppm, whereas the signals for the protons at C-6 and C-7 were ddds at about 7.32–7.34 and 7.66–7.69 ppm, respectively, and the proton at C-8 appeared at about 7.31 ppm. Finally, the amide protons give a singlet at 11.30–12.18 ppm, and the hydroxy protons appeared as broad peaks at 15.50–15.95 ppm. All the above data are in accordance with the literature data for other 3-substituted-4-hydroxycoumarin derivatives.[31–33] It should be noted that the ddd peaks for the protons at C-6 and C-7 have also been referred to as 'pseudotriplet' (pst) in the literature.[32]

In the ^{13}C NMR spectra of compounds **4**, characteristic peaks appeared at 17.3–18.1 ppm, assigned to methyl carbon attached at the 3-C=N carbon. The signals at the highest δ values at 178.7–179.7 were assigned to C-4, whereas those at 169.2 to 170.5 and 161.4–167.0 ppm were assigned to the amide carbon =NHCO–

Table 1
4-Hydroxy-3-acetyl *N*-acylhydrazones **4a**–**i** and 3,4-diacylcoumarins **5a**–**i** produced via Scheme 1

Compound	R	Reagents method A (method B)	Ratio of reactants	React. time (h)	Solvent	React. temp	Yield %	Mp (°C)
4a	CH_3	**2**+**3a**	1/1	24 (2)	PrOH	Reflux	87 (81)	248–249
							lit. 86[35]	250–251[a, 35]
4b	Ph	**2**+**3b**	1/1	24 (2)	PrOH	Reflux	95 (91)	225–226
4c	4-$H_3CC_6H_4$	**2**+**3c**	1/1	24 (2)	PrOH	Reflux	87 (79)	250–251
4d	4-$O_2NC_6H_4$	**2**+**3d**	1/1	24 (2)	PrOH	Reflux	98 (93)	264–265
4e	4-ClC_6H_4	**2**+**3e**	1/1	24 (2)	PrOH	Reflux	98 (91)	248–248.5
4f	2-HOC_6H_4	**2**+**3f**	1/1	24 (2)	PrOH	Reflux	97 (95)	271–272
4g	2-$O_2NC_6H_4$	**2**+**3g**	1/1	24 (2)	PrOH	Reflux	91 (89)	219
4h	2-Furyl	**2**+**3h**	1/1	24 (2)	PrOH	Reflux	89 (86)	254.5–255
4i	2-Thienyl	**2**+**3i**	1/1	24 (2)	PrOH	Reflux	94 (94)	228–228.5
5a	CH_3	**4a**+LTA (**4a**+DIP)	1/1.5 (1/1.5)	2 (2)	THF (CH_2Cl_2)	rt	49 (45)	137–138
5b	Ph	**4b**+LTA (**4b**+DIP)	1/1.5 (1/1.5)	2 (1.5)	THF (CH_2Cl_2)	rt	60 (45)	182–183
5c	4-$H_3CC_6H_4$	**4c**+LTA (**4c**+DIP)	1/1.5 (1/1.5)	24 (2)	THF (CH_2Cl_2)	rt	53 (65)	199–200
5d	4-$O_2NC_6H_4$	**4d**+LTA (**4d**+DIP)	1/1.5 (1/1.5)	2 (2)	THF (CH_2Cl_2)	rt	60 (40)	234–236
5e	4-ClC_6H_4	**4e**+LTA (**4e**+DIP)	1/1.6 (1/1.5)	24 (2)	THF (CH_2Cl_2)	rt	66 (45)	239–240
5f	2-HOC_6H_4	**4f**+LTA (**4f**+DIP)	1/1.1 (1/1.5)	24 (2)	THF (CH_2Cl_2)	rt	63 (48)	177–179
5g	2-$O_2NC_6H_4$	**4g**+LTA (**4g**+DIP)	1/1.5 (1/2)	24 (2)	THF (CH_2Cl_2)	rt	60 (49)	206–208
5h	2-Furyl	**4h**+LTA (**4h**+DIP)	1/1.5 (1/1.5)	24 (2)	THF (CH_2Cl_2)	rt	68 (63)	200–201
5i	2-Thienyl	**4i**+LTA (**4i**+DIP)	1/2 (1/1.5)	0.5 (1)	THF (CH_2Cl_2)	rt	60 (45)	158–159

[a] Recrystallized from $MeOCH_2CH_2OH/H_2O$.

and the hydrazono 3-C=N carbon, respectively. Furthermore, hydrazones **4** showed prominent ions corresponding to [M+Na] in their mass spectra.

Based on the above data, we concluded that compounds **4** exist in the hydroxy tautomeric form A (Fig. 2), stabilized by hydrogen bonding, as shown, and this is also in accordance with relevant literature data.[30] Interestingly, X-ray analysis of **4i** has shown that the pyran ring adopts a 2,4-dione tautomeric form in the solid state (Fig. 2, structure B).

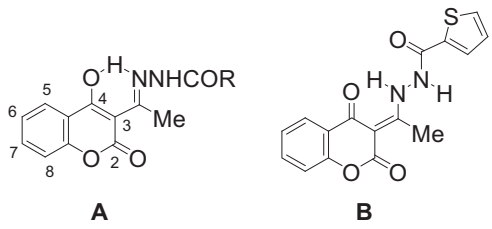


Fig. 2. Tautomeric forms of 3-acetyl-4-hydroxycoumarin hydrazones **4**.

The benzopyran ring system is almost coplanar with the thiophene ring [dihedral angle 0.9 (2)°]. The exocyclic C=C double bond has an *E* geometry.

The molecular conformation is stabilized by an intramolecular N–H···O hydrogen bond.[34]

3,4-Diacylcoumarins **5** display in their ^{1}H NMR spectra a singlet at about 2.52–2.61 ppm for the methyl protons attached at the 3-C=O carbon; the proton at C-5 of the coumarin appeared as a doublet of doublets at about 7.51–7.62 ppm. The protons at C-6 and C-7 both gave characteristic ddd peaks at about 7.30–7.44 and 7.67 to 7.62 ppm, respectively; the proton at C-8 appeared at 7.16–7.59 ppm. The resonances of the methyl protons in diacylcoumarins **5** were at higher field values than the relevant methyl protons in hydrazones **4** due to the relative anisotropy of carbonyl C=O and hydrazonic C=N bonds, respectively.

In ^{13}C NMR characteristic resonances appeared at 30.4–31.0 ppm and can be assigned to methyl carbon attached at the 3-C=N carbon, whereas the signals that were obtained at the lowest field values at 179.3–201.2 ppm are assigned to the carbonyl carbons. Finally, 3,4-diacylcoumarins **5** showed prominent ions corresponding to [M+1] in their mass spectra.

An X-ray diffraction analysis was carried out on diketone **5f**. As well as confirming the overall connectivity, and thus the operation of the rearrangement process, the three-dimensional structure showed the planarity of the coumarin moiety and that its 3-acetyl substituent is fully conjugated with it, there being only a dihedral angle of 10° between the coumarin C3–C4 bond and the acetyl C=O bond. In the 2-hydroxybenzoyl subunit, the phenolic hydroxyl hydrogen is hydrogen bonded to the aromatic carbonyl oxygen making this a second essentially planar moiety. However this second acyl unit (the 2-hydroxybenzoyl unit) is totally out of conjugation with the coumarin unit, as one can see from the dihedral angle between the C3–C4 and the benzoyl C=O bonds, being 89°. Chem3D representations of compound **5f** taken from the atomic coordinates determined by X-ray crystallography are shown in Fig. 3.

Concerning the mechanism of the transformations of hydroxy into an acyl group as well as of the formation of a new C–C bond, we assume it to be completely analogous to the mechanism that has been proposed and discussed in detail for the transformation of *o*-hydroxyacetophenone *N*-benzoylhydrazone into 1-acetyl-2-benzoylbenzene.[36,37]

3. Conclusion

In conclusion, the transformation of a hydroxy into an acyl group (**2**→**4**→**5** in Scheme 1) was successfully applied in the pyrone ring in coumarin derivatives, giving the ability for the synthesis of 3,4-diacyl substituted coumarin derivatives. The presence of two acyl groups at neighboring positions is often desirable in alicyclic or heterocyclic derivatives. It is significant that there are no other general methods for the preparation of such derivatives.[20] The above transformation which has been already proved to be the most appropriate way for the synthesis of *ortho*-diacyl substituted aromatic derivatives has now been extended to the synthesis of *ortho*-diacyl substituted heterocycles. The simplicity of the method as well as the low cost of the reagents and the good yields add to the synthetic value of the transformation. 3,4-Diacylcoumarins **5** could serve as very useful intermediates to new coumarin derivatives with possible pharmaceutical properties.

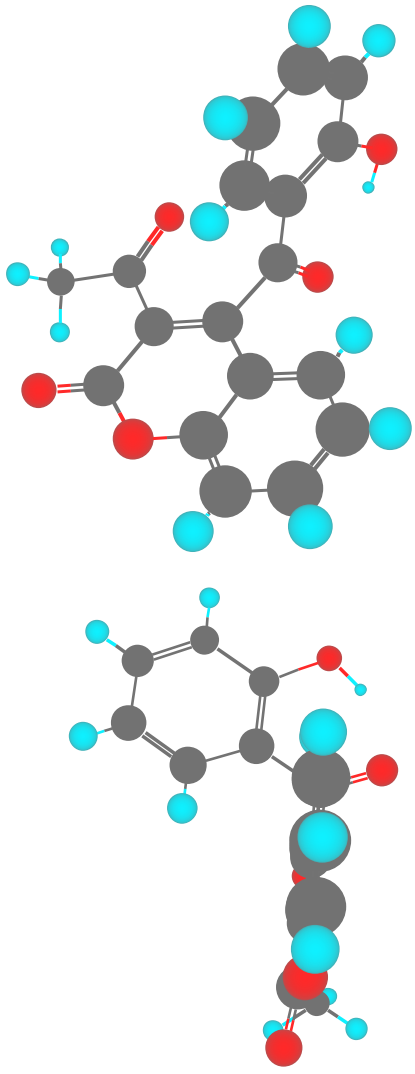


Fig. 3. Chem3D representations of compound **5f**.

4. Experimental section

4.1. General

All solvents were purchased from Merck or Panreac, whereas all reagents were purchased from Aldrich. Compound **2** was prepared according to the literature procedure.[29] TLC plates were Merck plastic plates with silica gel 60 F_{254} (70–230 mesh). Column chromatography was performed on silica gel 60 F_{254} (70–230 mesh). Melting points were recorded by a Fischer Scientific melting point measurement apparatus. ^{1}H (400 MHz) and ^{13}C

(100 MHz) NMR spectra were recorded on a Bruker Avance 400 instrument and the chemical shifts are reported in δ (ppm) values relative to DMSO-d_6 (δ=2.50 and 39.5 ppm for ^{1}H and ^{13}C NMR, respectively, for DMSO-d_6). Coupling constants are reported in hertz (Hz). MS were measured on a Platform II spectrometer. Either elemental analysis or high resolution mass measurement was acquired for all new compounds **4b**–**i** and **5a**–**i** as well as for **4a**, which has been mentioned in the literature but for which there is no spectral data.[34]

4.2. Procedure for the synthesis of 3-[1-(acyl-hydrazono)-ethyl]-4-hydroxy-2*H*-1-benzopyran-2-ones (4)

The appropriate hydrazide (**3**, 1 mmol) was added to a solution of 3-acetyl-4-hydroxy-coumarin **2** (1 mmol) in *n*-propanol (15–20 mL). The mixture was refluxed for 24 h and cooled to rt. The resulting precipitate was collected by filtration, dried in vacuum, and recrystallized from *n*-propanol to give the 3-[1-(acyl-hydrazono)ethyl]-4-hydroxy-coumarins (**4a**–**i**) as solids in very good yields. The yields of formation of the new compounds **4** as well as their melting points are presented in Table 1.

*4.2.1. 3-[1-(Acetylhydrazono)ethyl]-4-hydroxy-2H-1-benzopyran-2-one (**4a**).* Light yellow solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.07 (s, 3H), 2.66 (s, 3H), 7.29 (dd, *J*=8.3, 1.0 Hz, 1H), 7.32 (ddd, *J*=7.9, 7.3, 1.0 Hz, 1H), 7.66 (ddd, *J*=8.3, 7.3, 1.8 Hz), 7.97 (dd, *J*=7.9, 1.8 Hz), 11.42 (s, 1H), 15.90 (br s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 17.3, 20.4, 94.9, 116.3, 119.5, 123.8, 125.5, 134.2, 153.0, 161.8, 167.0, 169.2, 178.7 ppm. HRMS (ESI$^+$): *m*/*z* [M+H]$^+$ calcd for $C_{13}H_{12}N_2O_4$: 261.08698. Found 261.08688.

*4.2.2. 3-[1-(Benzoylhydrazono)ethyl]-4-hydroxy-2H-1-benzopyran-2-one (**4b**).* White solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.77 (s, 3H), 7.31 (dd, *J*=8.6, 1.0 Hz, 1H), 7.35 (ddd, *J*=7.8, 7.2, 1.0 Hz, 1H), 7.57–7.61 (m, 2H), 7.66–7.71 (m, 2H), 7.95–7.97 (m, 2H, 2′,6′-H), 8.01 (dd, *J*=7.8, 1.5 Hz, 1H, 5-H), 11.82 (s, 1H, NNH), 15.80 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 17.7, 95.3, 116.4, 119.7, 123.9, 125.7, 127.9, 128.7, 131.2, 132.7, 134.4, 153.1, 161.5, 164.9, 172.2 (NHCO), 179.3 (C-4). HRMS (ESI$^+$) calcd for $C_{18}H_{14}N_2O_2$ *m*/*z* 345.08458 (M+Na$^+$), 667.17993 (2M+Na$^+$). Found 345.08471 (M+Na$^+$), 667.18067 (2M+Na$^+$).

*4.2.3. 3-{1-[(4-Methylbenzoyl)hydrazono]ethyl}-4-hydroxy-2H-1-benzopyran-2-one (**4c**).* White solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.41 (s, 3H), 2.76 (s, 3H), 7.31 (dd, *J*=8.3, 1.0 Hz, 1H), 7.34 (ddd, *J*=7.8, 7.2, 1.0 Hz, 1H), 7.39 (d, *J*=8.1 Hz, 2H), 7.68 (ddd, *J*=8.3, 7.2, 1.6 Hz, 1H), 7.87 (d, *J*=8.1 Hz, 2H), 8.01 (dd, *J*=7.8, 1.6 Hz, 1H), 11.73 (s, 1H), 15.70 (br s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 17.6, 21.1, 95.3, 116.3, 119.7, 123.8, 125.7, 127.9, 128.3, 129.2, 134.3, 142.9, 153.1, 161.4, 164.7, 172.1, 179.2 ppm. HRMS (ESI$^+$) calcd for $C_{19}H_{16}N_2O_4$ *m*/*z* 359.10023 (M+Na$^+$), 695.21124 (2M+Na$^+$). Found 359.10015 (M+Na$^+$), 695.21124 (2M+Na$^+$).

*4.2.4. 3-{1-[(4-Chlorobenzoyl)hydrazono]ethyl}-4-hydroxy-2H-1-benzopyran-2-one (**4d**).* White solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.76 (s, 3H), 7.31 (dd, *J*=8.6, 1.0 Hz, 1H), 7.34 (ddd, *J*=8.1, 7.0, 1.0 Hz, 1H), 7.66 (d, *J*=8.6 Hz, 2H), 7.68 (ddd, *J*=8.6, 7.0, 1.5 Hz, 1H), 7.98 (d, *J*=8.6 Hz, 2H), 7.99 (dd, *J*=8.1, 1.5 Hz, 1H), 11.89 (br, 1H), 15.72 (br, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 17.6, 95.4, 116.3, 119.6, 123.9, 125.7, 128.8, 129.8, 130.0, 134.5, 137.5, 153.1, 161.4, 163.9, 172.3, 179.2 ppm; MS (ESI$^+$) *m*/*z* 356 (M$^+$). Anal. Calcd for $C_{18}H_{13}ClN_2O_4$: C, 60.60; H, 3.67; N, 7.85; Cl, 9.94. Found C, 60.36; H, 3.52; N, 7.92; Cl, 9.91.

*4.2.5. 3-{1-[(4-Nitrobenzoyl)hydrazono]ethyl}-4-hydroxy-2H-1-benzopyran-2-one (**4e**).* Yellow solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.77 (s, 3H), 7.30–7.36 (m, 2H), 7.68 (ddd, *J*=7.5 Hz, 1H), 8.01 (d, *J*=7.6 Hz, 1H), 8.19 (d, *J*=8.5 Hz, 2H), 8.41 (d, *J*=8.3 Hz, 2H), 12.1 (br, 1H), 15.75 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 18.1, 95.9, 116.8, 120.1, 124.2, 124.4, 126.2, 130.0, 134.9, 137.7, 150.2, 153.6, 161.9, 163.9, 172.6, 179.7 ppm; MS (ESI$^+$): *m*/*z* 368 (M+1). Anal. Calcd for $C_{18}H_{13}N_3O_6$: C, 58.86; H, 3.57; N, 11.44. Found: C, 58.59; H, 3.39; N, 11.40.

*4.2.6. 3-{1-[(2-Hydroxybenzoyl)hydrazono]ethyl}-4-hydroxy-2H-1-benzopyran-2-one (**4f**, Scheme 1).* White solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.74 (s, 3H, 3-CCH$_3$), 6.99 (ddd, *J*=7.8, 7.0, 1.0 Hz, 1H, 5′-H), 7.02 (dd, *J*=8.0, 1.0 Hz, 1H, 3′-H), 7.32 (dd, *J*=8.6, 1.0 Hz, 1H, 8-H), 7.35 (ddd, *J*=7.8, 7.2, 1.0 Hz, 1H, 6-H), 7.47 (ddd, *J*=8.0, 7.0, 1.5 Hz, 1H), 7.68 (ddd, *J*=8.5, 7.2, 1.5 Hz, 1H), 7.87 (dd, *J*=7.8, 1.5 Hz, 1H), 8.01 (dd, *J*=7.8, 1.5 Hz, 1H), 11.55 (br s, 1H), 15.93 (br, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 17.5, 95.3, 116.2, 116.3, 117.0, 119.44, 119.51, 123.9, 125.6, 130.0, 134.1, 134.3, 153.1, 157.3, 161.4, 164.2, 170.5, 178.8 ppm. HRMS (ESI$^+$) calcd for $C_{18}H_{14}N_2O_5$ *m*/*z* 361.07949 (M+Na$^+$), 699.16976 (2M+Na$^+$). Found 361.07939 (M+Na$^+$), 699.17016 (2M+Na$^+$).

*4.2.7. 3-{1-[(2-Nitrobenzoyl)hydrazono]ethyl}-4-hydroxy-2H-1-benzopyran-2-one (**4g**).* Yellow solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.73 (s, 3H), 7.32 (dd, *J*=8.6, 1.0 Hz, 1H), 7.36 (ddd, *J*=7.9, 7.4, 1.0 Hz, 1H), 7.69 (ddd, *J*=8.6, 7.4, 1.5 Hz, 1H), 7.84 (ddd, *J*=8.1, 6.9, 2.1 Hz, 1H), 7.91 (dd, *J*=8.0, 2.1 Hz, 1H), 7.94 (ddd, *J*=8.0, 6.9, 1.0 Hz, 1H), 8.02 (dd, *J*=7.8, 1.5 Hz, 1H), 8.22 (dd, *J*=8.1, 1.0 Hz, 1H), 12.18 (br, 1H), 15.95 (br, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 17.3, 95.5, 116.4, 119.4, 123.9, 124.5, 125.6, 129.2, 129.9, 132.0, 134.2, 134.4, 146.7, 153.1, 161.3, 163.3, 171.4, 178.9 ppm. HRMS (ESI$^+$) calcd for $C_{18}H_{13}N_3O_6$ *m*/*z* 390.06966 (M+Na$^+$), 757.15009 (2M+Na$^+$). Found 390.06973 (M+Na$^+$), 757.15048 (2M+Na$^+$).

*4.2.8. 3-{1-[(2-Furoyl)hydrazono]ethyl}-4-hydroxy-2H-1-benzopyran-2-one (**4h**).* Yellow solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.71 (s, 3H), 6.76 (dd, *J*=3.5, 1.8 Hz, 1H), 7.31 (dd, *J*=8.3, 1.0 Hz, 1H), 7.34 (ddd, *J*=7.8, 7.2, 1.0 Hz, 1H), 7.40 (dd, *J*=3.5, 1.0 Hz, 1H), 7.68 (ddd, *J*=8.3, 7.4, 1.6 Hz, 1H), 8.00 (ddd, *J*=7.9, 7.4, 1.6 Hz, 1H), 8.03 (dd, *J*=1.8, 1.0 Hz, 1H), 11.80 (br, 1H), 15.50 (br, 1H) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz) δ 17.7, 95.6, 112.4, 116.4, 116.6, 119.6, 123.9, 125.8, 134.5, 145.0, 146.8, 153.2, 156.0, 161.4, 173.5, 179.4 ppm. HRMS (ESI$^+$) calcd for $C_{16}H_{12}N_2O_5$ *m*/*z* 335.06384 (M+Na$^+$), 647.13846 (2M+Na$^+$). Found 335.06379 (M+Na$^+$), 647.13832 (2M+Na$^+$).

*4.2.9. 3-{1-[(2-Thienylcarbonyl)hydrazono]ethyl}-4-hydroxy-2H-1-benzopyran-2-one (**4i**, Scheme 1).* Light yellow solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.73 (s, 3H), 7.28 (dd, *J*=5.1, 3.8 Hz, 1H), 7.31 (dd, *J*=8.6, 1.0 Hz, 1H), 7.34 (ddd, *J*=7.8, 7.2, 1.0 Hz, 1H), 7.68 (ddd, *J*=8.3, 7.4, 1.6 Hz, 1H), 7.95 (dd, *J*=3.8, 1.0 Hz, 1H), 7.98 (dd, *J*=5.1, 1.0 Hz, 1H), 8.00 (dd, *J*=7.9, 1.6 Hz, 1H), 11.80 (br, 1H), 15.60 (br s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.1, 96.0, 116.8, 120.1, 124.3, 126.2, 128.8, 131.1, 133.5, 134.9, 135.7, 153.6, 160.2, 161.9, 173.5, 179.7 ppm. HRMS (ESI$^+$) calcd for $C_{16}H_{12}N_2O_4S$ *m*/*z*: 329.05905 (M+H$^+$). Found 329.05893 (M+H$^+$).

4.3. Reaction of *N*-acylhydrazones 4 with lead tetraacetate

Lead tetraacetate (LTA) was added to a stirred solution of hydrazone **4** (1 mmol) in THF (20 mL), in an ice bath. The molar ratio of hydrazone/LTA and the reaction time are presented in Table 1. The mixture was then stirred at rt. The oily product obtained after filtration of lead diacetate and evaporation of solvent from the filtrate was subjected to column chromatography (silica gel 70–230 mesh) and products were eluted with a mixture of petroleum ether/ethyl acetate 1/1 to afford the pure products **5** as solids.

The yields of formation of the new compounds **5** as well as their melting points are presented in Table 1.

*4.3.1. 3,4-Diacetyl-2H-1-benzopyran-2-one (**5a**).* Pale yellow solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.48 (s, 3H), 2.61 (s, 3H), 7.44 (ddd, J=8.1, 7.1, 1.2 Hz, 1H), 7.50 (dd, J=7.9, 1.6 Hz, 1H), 7.55 (d, J=7.8 Hz, 1H), 7.82 (ddd, J=8.3, 7.1, 1.8 Hz, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 30.9, 31.1, 115.6, 117.4, 119.6, 125.9, 128.0, 135.5, 154.9, 157.6, 158.9, 197.0, 201.2 ppm; MS (ESI$^+$): m/z 231 (M+1). Anal. Calcd for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: C, 67.88; H, 4.27.

*4.3.2. 3-Acetyl-4-benzoyl-2H-1-benzopyran-2-one (**5b**).* White solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.54 (s, 3H), 7.18 (dd, J=8.0, 1.4 Hz, 1H), 7.32 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.51–7.59 (m, 3H), 7.69 (t, J=7.5 Hz, 1H), 7.77 (ddd, J=8.6, 7.1, 1.5 Hz, 1H), 7.95 (d, J=7.9 Hz, 2H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 30.5, 116.7, 117.0, 122.1, 125.3, 127.7, 128.6, 129.1, 134.3, 134.8, 135.1, 154.3, 154.9, 158.3, 193.2, 196.2 ppm. HRMS (ESI$^+$): m/z [M+Na]$^+$ calcd for $C_{18}H_{12}O_4$: 315.06278. Found: 315.06309.

*4.3.3. 3-Acetyl-4-(4-methylbenzoyl)-2H-1-benzopyran-2-one (**5c**).* Pale yellow solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.38 (s, 3H), 2.52 (s, 3H), 7.16 (dd, J=8.1, 1.5 Hz, 1H), 7.29–7.34 (m, 3H), 7.57 (d, J=7.6 Hz, 1H), 7.77 (ddd, J=8.3, 7.4, 1.5 Hz, 1H), 7.84 (d, J=8.1 Hz, 2H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 21.7, 31.0, 117.2, 117.4, 122.6, 125.7, 128.1, 129.2, 130.1, 133.3, 135.2, 145.6, 154.7, 155.3, 158.9, 193.2, 196.7 ppm. HRMS (ESI$^+$): m/z [M+Na]$^+$ calcd for $C_{19}H_{14}O_4$: 329.07843. Found: 329.07873.

*4.3.4. 3-Acetyl-4-(4-chlorobenzoyl)-2H-1-benzopyran-2-one (**5d**).* White solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.55 (s, 3H), 7.18 (dd, J=7.8, 1.5 Hz, 1H), 7.32 (ddd, J=8.1, 7.3, 1.0 Hz, 1H), 7.57–7.62 (m, 3H), 7.78 (ddd, J=8.6, 7.1, 1.5 Hz, 1H), 7.98 (d, J=8.6, 2H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 31.0, 117.0, 117.5, 122.6, 125.8, 128.1, 129.8, 130.8, 134.4, 135.4, 139.8, 154.8, 155.0, 158.8, 192.7, 196.7 ppm. HRMS (ESI$^+$): m/z [M+H]$^+$ calcd for $C_{18}H_{11}ClO_4$: 327.04240. Found: 327.04260.

*4.3.5. 3-Acetyl-4-(4-nitrobenzoyl)-2H-1-benzopyran-2-one (**5e**).* White solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.57 (s, 3H), 7.19 (d, J=7.8, 1H), 7.32 (ddd, J=8.1, 7.3, 1.0 Hz, 1H), 7.61 (d, J=8.4 Hz, 1H), 7.80 (ddd, J=8.3, 7.3, 1.2 Hz, 1H), 8.22 (d, J=8.6 Hz, 2H), 8.33 (dd, J=8.6, Hz, 2H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 31.0, 116.9, 117.6, 122.5, 124.7, 125.9, 128.1, 130.2, 135.7, 139.9, 151.0, 154.9, 155.0, 158.7, 192.6, 196.77 ppm. HRMS (ESI$^+$): m/z [M+H]$^+$ calcd for $C_{18}H_{11}NO_6$: 338.06650. Found: 338.06670.

*4.3.6. 3-Acetyl-4(2-hydroxybenzoyl)-2H-1-benzopyran-2-one (**5f**).* White solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.53 (s, 3H), 6.93–6.97 (m, 2H), 7.28 (dd, J=8.1, 1.5 Hz, 1H), 7.34 (ddd, J=8.1, 7.5, 1.0 Hz, 1H), 7.51–7.58 (m, 2H), 7.77 (ddd, J=8.3, 7.3, 1.8 Hz, 1H), 7.83 (dd, J=8.4, 1.8 Hz, 1H) 10.85 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 30.4, 116.6, 116.9, 117.6, 119.6, 120.3, 121.4, 125.3, 127.3, 130.4, 134.6, 136.6, 154.1, 156.5, 158.6, 159.5, 193.8, 196.1 ppm. HRMS (ESI$^+$): m/z [M+H]$^+$ calcd for $C_{18}H_{12}O_5$: 309.07575. Found: 309.07559.

4.3.6.1. Crystal structure determination. Data were collected on a Bruker Smart Apex CCD diffractometer. Wavelength: 0.71073 Å; temperature: 100(2) K; reflections collected/unique: 7820/2885 [R(int)=0.0863]; completeness to theta=26.43:99.8%; space group: monoclinic, $P21/c$; a=9.099(3) Å; b=11.584(4) Å; c=13.341(4) Å; V=1404.9(8) Å^3; Z=4; R indices [$I>2\sigma(I)$]: $R1$=0.0567, $wR2$=0.1101; R indices (all data): $R1$=0.0963, $wR2$=0.1227. The structure was solved with SIR2004 and refined with SHELXL97.

*4.3.7. 3-Acetyl-4-(2-nitrobenzoyl)-2H-1-benzopyran-2-one (**5g**).* White solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.57 (s, 3H), 7.34 (dd, J=7.8, 1.5 Hz, 1H), 7.40 (ddd, J=8.1, 7.1, 1.0 Hz, 1H), 7.60 (d, J=7.8 Hz, 1H), 7.67 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 7.80 (ddd, J=8.3, 7.5, 1.5 Hz, 1H), 7.90 (ddd, J=8.1, 7.6, 1.2 Hz, 1H), 8.00 (dd, J=8.1, 1.0 Hz, 2H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 30.9, 116.8, 117.6, 123.5, 124.3, 126.0, 126.8, 127.5, 132.5, 133.1, 135.5, 136.0, 148.8, 152.9, 154.8, 158.6, 190.8, 196.9 ppm. HRMS (ESI$^+$): m/z [M+H]$^+$ calcd for $C_{18}H_{11}NO_6$: 338.06650. Found: 338.06670.

*4.3.8. 3-Acetyl-4-(2-furylcarbonyl)-2H-1-benzopyran-2-one (**5h**).* White solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.53 (s, 3H), 6.74 (ddd, J=3.6, 1.8 Hz, 1H), 7.33–7.39 (m, 2H), 7.54 (d, J=3.6 Hz, 1H), 7.57 (d, J=8.3 Hz, 1H), 7.78 (ddd, J=8.3, 6.6, 2.3 Hz, 1H), 8.11 (d, J=1.0 Hz, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 30.5, 113.1, 116.4, 116.9, 121.6, 123.3, 125.3, 127.4, 134.7, 149.5, 150.8, 151.9, 154.1, 158.3, 179.3, 196.7 ppm. HRMS (ESI$^+$): m/z [M+H]$^+$ calcd for $C_{16}H_{15}O_5$: 283.06010. Found: 283.05996.

*4.3.9. 3-Acetyl-4(2-thienylcarbonyl)-2H-1-benzopyran-2-one (**5i**).* Yellow solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.53 (s, 3H), 6.93–6.97 (m, 2H), 7.28 (dd, J=8.1, 1.5 Hz, 1H), 7.34 (ddd, J=8.1, 7.5, 1.0 Hz, 1H), 7.51–7.58 (m, 2H), 7.77 (ddd, J=8.3, 7.3, 1.8 Hz, 1H), 7.83 (dd, J=8.4, 1.8 Hz, 1H) 10.85 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 30.4, 116.6, 116.9, 117.6, 119.6, 120.3, 121.4, 125.3, 127.3, 130.4, 134.6, 136.6, 154.1, 156.5, 158.6, 159.5, 193.8, 196.1 ppm. HRMS (ESI$^+$): m/z [M+H]$^+$ calcd for $C_{16}H_{15}O_4S$: 299.03726. Found: 299.03707.

4.4. Oxidation of hydrazones 4 with (diacetoxyiodo)benzene (DIB)

(Diacetoxyiodo)benzene (DIB) was added to hydrazones **4** (1 mmol) in dichloromethane (20 mL), under stirring, in an ice bath. The molar ratio of hydrazone/DIB and the reaction time are presented in Table 1. The mixture was then stirred at rt. The oily product obtained after evaporation of the solvent was subjected to column chromatography (silica gel 70–230 mesh) and was eluted with a mixture of petroleum ether/ethyl acetate 1/1 to afford the pure coumarins **5** as white solids in good yields (Table 1).

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