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Graphical abstract

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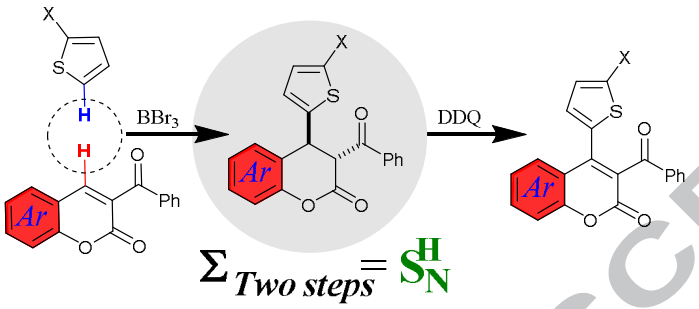

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Synthesis of 4-(thien-2-yl)-substituted coumarins through Lewis acid catalyzed Michael addition of thiophenes to 3-benzoylcoumarins followed by oxidation

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A B S T R A C T

3-Benzoyl-4-(thien-2-yl)coumarins have been obtained in good yields according to the S_N^H addition-oxidation protocol, involving the diastereoselective addition of thiophenes at C-4 of 3-benzoylcoumarins under BBr_3 catalysis, followed by oxidation of the intermediate 3,4-*trans*-3-benzoyl-4-(thien-2-yl)-3,4-dihydrocoumarins with DDQ. This two-step procedure can be regarded as nucleophilic substitution of hydrogen (S_N^H) on the heterocyclic ring of coumarins.

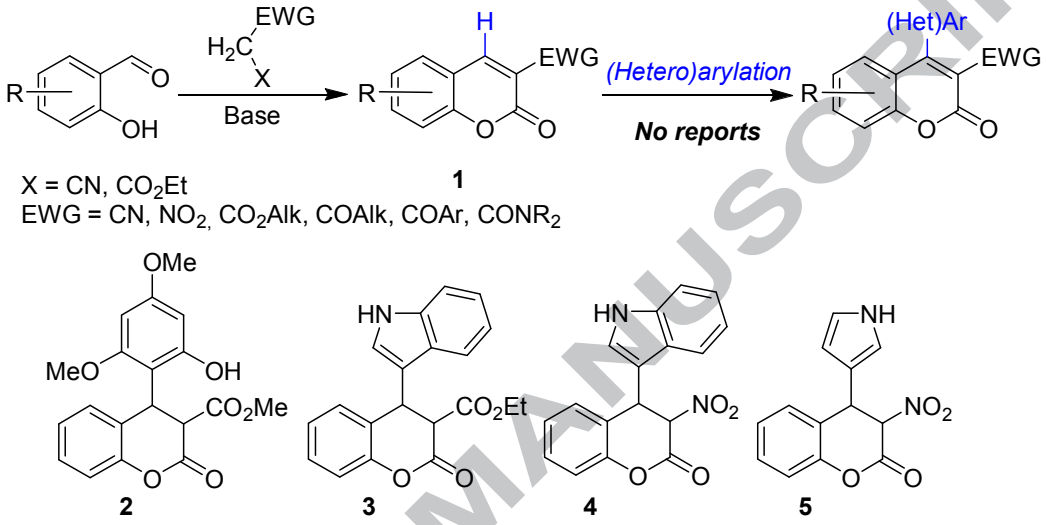
Keywords: Thiophenes, 3-Benzoylcoumarins, Lewis acid, Nucleophilic aromatic substitution of hydrogen, Metal-free cross-coupling reactions, Oxidative coupling reactions, Direct heteroarylation

Coumarins (2*H*-chromen-2-ones) belong to an important class of oxygen-containing heterocycles, which are found widely in Nature, mostly in the plant kingdom. Both synthetic and natural coumarins are known to exhibit a wide spectrum of pharmacological properties.[1,2] Due to their unique optical properties, coumarin derivatives have found wide application as basic components of organic materials used in lasers, sensors, photosensitizers, light-emitting diodes and fluorescent markers for biomedical imaging.[3] In this respect, the practical value of coumarin derivatives is incredibly high. This is the reason why research on modifying the structure of this heterocyclic system has continued.

Coumarins **1**, unsubstituted at C-4 and bearing an acceptor substituent at C-3, are easily available: these heterocyclic compounds can be obtained by using the Perkin condensation of salicylaldehydes with active methylene compounds, such as β-ketoesters or β-ketonitriles, under basic conditions (Scheme 1). Due to the electron-deficient character of coumarins **1**, the main

This paper is dedicated to Professor Oleg N. Chupakhin on the occasion of his 80th birthday.

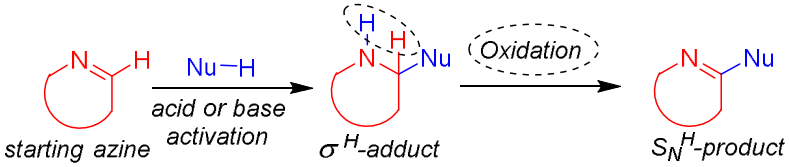
type of reaction they undergo is nucleophilic (Michael type) addition at C-4. However, the list of reactions of coumarins **1** with aromatic (heteroaromatic) C-nucleophiles is limited by a few examples of the Michael adduct formation. Indeed, the reactions of 3-alkoxycarbonyl substituted coumarins with 3,5-dimethoxyphenol[4] and indole,[5] as well as nucleophilic addition of indole or pyrrole at C-4 of 3-nitrocoumarin[6] have resulted in the formation of 3,4-dihydrocoumarins **2**-**5**, respectively (Scheme 1).



Scheme 1. The Perkin synthesis of 3-substituted coumarins **1**.
Structures of the Michael adducts **2-5**.

At present, there are no reports in the literature on metal-catalyzed or metal-free methods for the direct (hetero)arylation of coumarins **1** at C-4 (Scheme 1).

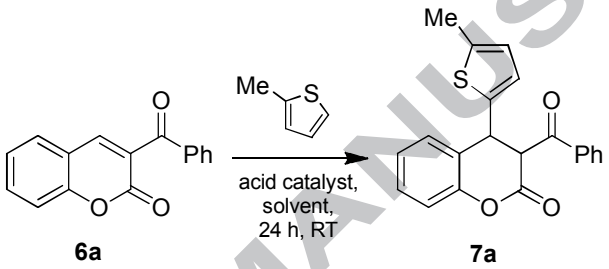
It is worth noting that a very efficient approach for the direct functionalization of electron-deficient azines (pyridines, pyrimidines, 1,2,4-triazines and their fused derivatives) is via nucleophilic aromatic substitution of hydrogen (S_N^H).[7,8] The two-step S_N^H reactions usually involve addition of nucleophiles to electron-deficient azines under acidic or basic catalysis, followed by oxidation of the intermediate σ^H-adducts (Scheme 2). In particular, the S_N^H methodology provides access to a variety of nitrogen-containing heterocyclic compounds through direct metal-free oxidative coupling of azines with electron-rich nucleophiles.



Scheme 2. Direct C-H functionalization of azines using the S_N^H methodology

In this Letter we report a convenient method for the preparation of 3-benzoyl-4-(thien-2-yl)coumarins by nucleophilic aromatic substitution of hydrogen. This approach corresponds to one of the principles of green chemistry, i.e., atom economy, since the direct C-H/C-H coupling of 4-unsubstituted 3-benzoylcoumarins with thiophenes takes place.

The addition of 2-methylthiophene at C-4 of 3-benzoylcoumarin (**6a**) was first studied under catalysis with various Lewis acids and CF_3SO_3H. 2-Methylthiophene was selected as the model reagent, bearing one active nucleophilic center, namely C-5. The reaction of **6a** with two molar equivalents of 2-methylthiophene was carried out in dry dichloromethane at ambient temperature for 24 hours to give 3-benzoyl-4-(5-methylthien-2-yl)-3,4-dihydrocoumarin (**7a**), the yield of which varied depending on the catalyst used (Scheme 3, Table 1).



Scheme 3. Synthesis of 3,4-dihydrocoumarin **7a**

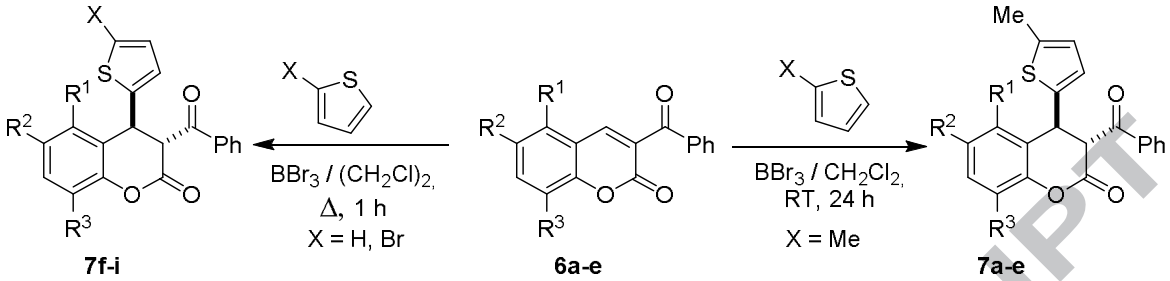
Table 1. Reaction conditions and obtained yields of 3,4-dihydrocoumarin (**7a**)[a]

Entry	Acid catalyst	Solvent	Yield **7a** (%)
1	$AlCl_3$	CH_2Cl_2-THF (3:1)	40
2	$TiCl_4$	CH_2Cl_2-THF (3:1)	**6a/7a**[b]
3	BF_3•Et_2O	CH_2Cl_2	30
4	$SnCl_4$	CH_2Cl_2-THF (3:1)	**6a/7a**[b]
5	CF_3SO_3H	CH_2Cl_2	0 (dec.)
6	$AlBr_3$	CH_2Cl_2	35
7	BBr_3	CH_2Cl_2	77

[a] 1 mmol of **6a**, 1.1 mmol of catalyst and 2 mmol of 2-methylthiophene were used.
[b] A mixture of **6a** and **7a** was obtained with a low conversion of the starting compound

The formation of adduct **7a** was achieved in a good yield (77%) when BBr_3 was used as the catalyst (Table 1, entry 7). The optimal reaction conditions for the addition of 2-methylthiophene at C-4 of coumarin **6a** were further applied to obtain 3,4-dihydro-coumarins **7b-e** in 68–80% yields (Scheme 4, Table 2, entries 1-5).[9] Unfortunately, the adducts of coumarins **6** with thiophene or 2-bromothiophene were not formed under the above mentioned reaction conditions. Nevertheless, the C-C coupling of these thiophenes with coumarins **6a,b,d**

was accomplished on refluxing the reagents with BBr_3 in 1,2-dichloroethane (DCE) for one hour, thus giving 3,4-dihydrocoumarins **7f-i** (Scheme 4, Table 2, entries 6-9).[10]



Scheme 4. The synthesis of 3,4-dihydrocoumarins **7**

Table 2. Yields and melting points of 3,4-dihydrocoumarins **7**[a]

Entry	Compounds **6** / **7**	R^1	R^2	R^3	X	Mp **7** (°C)	Yield **7** (%)
1	**6a** / **7a**	H	H	H	Me	161–162	77
2	**6b** / **7b**	H	Br	H	Me	207–208	70
3	**6c** / **7c**	H	Br	Br	Me	157–158	80
4	**6d** / **7d**	H	Cl	H	Me	190–191	73
5	**6e** / **7e**	benzo[*f*]		H	Me	147–148	68
6	**6a** / **7f**	H	H	H	H	144–145	69
7	**6a** / **7g**	H	H	H	Br	157–158	84
8	**6b** / **7h**	H	Br	H	Br	191–192	63
9	**6d** / **7i**	H	Cl	H	H	184–185	59

[a] 3 mmol of **6**, 3.3 mmol of BBr_3 and 6 mmol of 2-methyl- or 2-bromothiophene or 30 mmol of thiophene were used

It should be noted that the addition of thiophenes to coumarins **6** proceeds in a highly diastereoselective manner and leads to the formation of the thermodynamically controlled products, 3,4-*trans*-substituted dihydrocoumarins **7**. No *cis*-isomers of **7** were detected in the ^{1}H NMR spectra of the crude reaction products. The NMR spectra of compounds **7** exhibited two characteristic doublets for the H-3 and H-4 protons of the heterocyclic ring with ^{1}H-^{1}H coupling constants of 6.0–6.9 Hz, which are in a good correlation with those (6.0–7.0 Hz) of the corresponding signals in the ^{1}H NMR spectra of 3,4-*trans*-3-benzoyl-4-aryl-3,4-dihydrocoumarins.[11] In addition, the structures of 3,4-dihydrocoumarins **7** were unequivocally established by X-ray crystallographic analysis, performed on compound **7g** (Figure 1).[12]

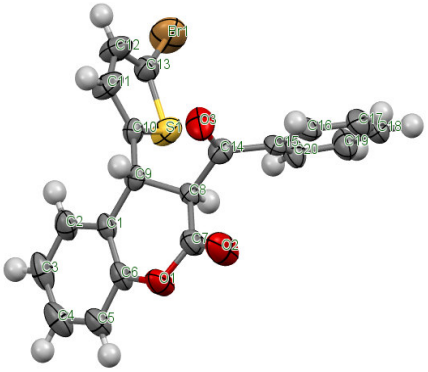
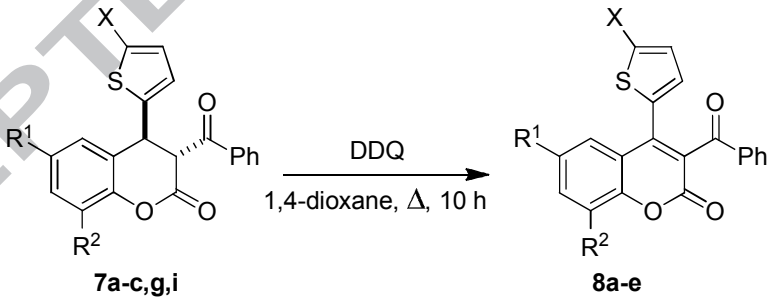


Figure 1. *Mercury*[13] representation of the X-ray crystal structure of **7g**. Thermal ellipsoids at 50% probability.

Oxidation of 3,4-dihydrocoumarins **7** was the final step to complete the functionalization of 3-benzoylcoumarins **6** at C-4 *via* the S_N^H methodology. Several oxidizing agents (*N*-bromo-succinimide or SO_2Cl_2/pyridine-CH_2Cl_2 at RT; chloranil or DDQ/1,4-dioxane at reflux) were tested for this purpose, while 3,4-dihydrocoumarin **7a** was chosen as a model compound to find the optimum oxidation conditions. The reactions of **7a** with *N*-bromosuccinimide or SO_2Cl_2 led to decomposition of compound **7a**. The use of DDQ for the oxidation of **7a** proved to be successful and 4-substituted 3-benzoylcoumarin **8a** was obtained in 69% yield. Coumarin **8a** was also obtained in the case of oxidation with chloranil, but the conversion of the starting material **7a** was rather poor and the yield of the target product was only 17%. The best reaction conditions for the oxidation of **7a** with DDQ were applied for the preparation of coumarins **8b-e** (Scheme 5, Table 3).[14]



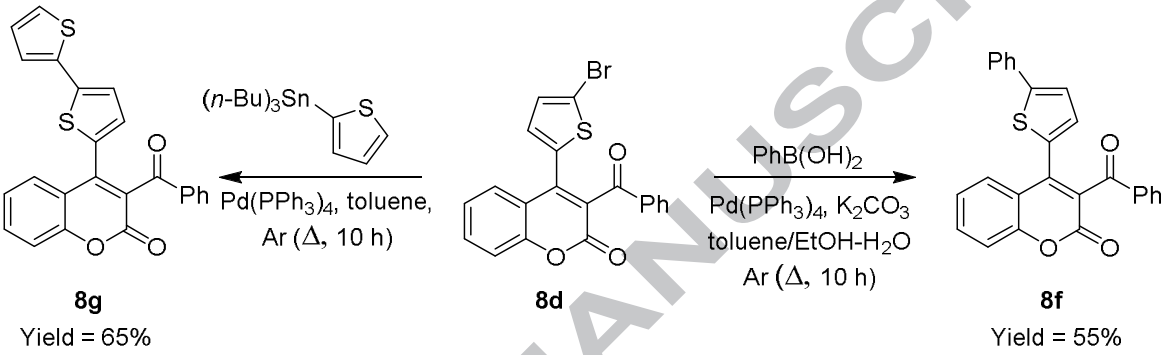
Scheme 5. Oxidation of 3,4-dihydrocoumarins **7**

Table 3. Yields and melting points of coumarins **8**

Entry	Compounds **7** / **8**	X	R^1	R^2	Mp **8** (°C)	Yield **8** (%)
1	**7a** / **8a**	Me	H	H	162–163	69
2	**7b** / **8b**	Me	Br	H	179–180	65
3	**7c** / **8c**	Me	Br	Br	183–184	79
4	**7g** / **8d**	Br	H	H	153–154	87
5	**7i** / **8e**	H	Cl	H	191–192	78

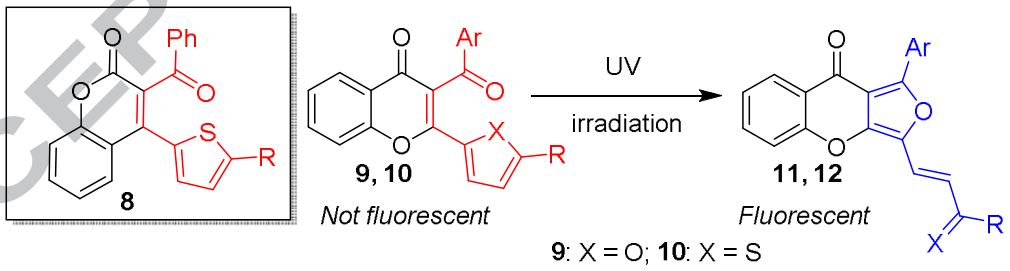
It is worth noting that the reaction conditions found for the oxidation of 3,4-dihydrocoumarins **7** with DDQ are far from perfect, and they need to be improved as low conversions of the starting 3,4-dihydrocoumarins were observed with compounds **7d-f,h**.

The range of coumarins **8** can be expanded through modification of 4-(5-bromothien-2-yl) substituted 3-benzoylcoumarins by means of cross-coupling reactions. Indeed, 4-[5-(het)arylthien-2-yl]-3-benzoylcoumarins **8f,g** were prepared from coumarin **8d** *via* the Suzuki and Stille cross-coupling reactions with phenylboronic acid and 2-(tributylstannyl)thiophene, respectively (Scheme 6).



Scheme 6. Cross-coupling reactions of coumarin **8d**

4-(Thien-2-yl)-substituted 3-benzoylcoumarins **8** can be regarded as structural analogs of 3-aroylchromones **9** and **10**, which upon irradiation with UV light are transformed irreversibly into fluorescent derivatives of fused chromones **11** and **12** (Scheme 7).



Scheme 7. UV-transformation of 3-aroylchromones **9** and **10**

Due to this ability 3-aroylchromones, compounds **9** and **10** are used as components of materials for multilayer optical discs of ultra-high information capacity.[15] In this respect, 3-benzoylcoumarins **8** can also be considered as promising compounds for the development of photosensitive materials.

In conclusion, we have shown for the first time that the S_N^H methodology is an efficient approach for the direct heteroarylation of 4-unsubstituted coumarins. A convenient metal-free method for the synthesis of 3-benzoyl-4-(thien-2-yl)coumarins has been developed through the addition of thiophenes at C-4 of 3-benzoylcoumarins under BBr_3 catalysis, followed by oxidation of the 3,4-dihydrocoumarins with DDQ to give 4-(thien-2-yl)-substituted 3-benzoylcoumarins, which are of interest as potential optical materials. Further studies on the photochemical properties of these coumarins and optimization of the second synthetic step are in progress.

Acknowledgments

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9. General procedure for the synthesis of 4-(5-methylthien-2-yl)-substituted 3-benzoyl-3,4-dihydrocoumarins **7a-e**: BBr_3 (0.32 ml, 3.3 mmol) and 2-methylthiophene (0.58 ml, 6 mmol) were added to a solution of an appropriate 3-benzoylcoumarin **6** (3 mmol) in dry CH_2Cl_2 (30 ml) and the resulting solution was stirred at room temperature for 24 h. The mixture was treated with H_2O (30 ml) and stirred for 2 h. The organic layer was separated and then filtered through a silica gel pad. The filtrate was concentrated under reduced pressure and the residue was recrystallized from EtOH/CH_2Cl_2 affording the target product **7**.

10. General procedure for the synthesis of 4-(thien-2-yl)-substituted 3-benzoyl-3,4-dihydrocoumarins **7f-i**: BBr_3 (0.32 ml, 3.3 mmol), thiophene (2.37 ml, 30 mmol) or 2-bromothiophene (0.58 ml, 6 mmol) were added to a solution of the appropriate 3-benzoylcoumarin **6** (3 mmol) in dry $(CH_2Cl)_2$ (30 ml) and the resulting solution was stirred at reflux for 1 h. The mixture was treated with H_2O (30 ml) and stirred for 2 h. The organic layer was separated and then filtered through a silica gel pad. The filtrate was concentrated under reduced pressure and the residue recrystallized from EtOH/CH_2Cl_2, thus affording the target product **7**. The analytical data for 3,4-dihydrocoumarins **7a-i** are available in the *Supplementary information*.

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12. *Crystal data for **7g**:* Yellow crystals 0.4×0.2×0.15 mm, $\theta < 26.38^{o}$, 12968 reflections were collected, 3518 independent reflections (R_{int} 0.0493), completeness 99.6%. Crystal is monoclinic, space group P2(1)/c, a= 5.4868(5) Å, b= 13.9319(13) Å, c= 22.588(3) Å, $\alpha= 90.00^{o}$, $\beta= 92.261(9)^{o}$, $\gamma= 90.00^{o}$, $\mu= 2.520$ mm^{-1}. The SHELXTL program[16] was used for solution and

structure refinement. Refinement and the final R indices: R_1= 0.0337 [I>2σ(I)], wR_2= 0.0444 [I>2σ(I)], R_1= 0.1042 (all data), wR_2= 0.0473 (all data), S= 1.001. Deposition number CCDC 985930 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

13. *Mercury* 3.1, available from http://www.ccdc.cam.ac.uk/mercury/

14. General procedure for the synthesis of 4-(thien-2-yl)-substituted 3-benzoylcoumarins **8a-e**: A solution of 3,4-dihydrocoumarin **7** (1.5 mmol) and DDQ (0.68 g, 3 mmol) in 1,4-dioxane (15 ml) was heated at reflux for 10 h. After cooling, the mixture was filtered through Al_2O_3 and the residue washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure and the residue was recrystallized from EtOH/CH_2Cl_2, thus affording coumarins **8**. The analytical data for coumarins **8a-e** are available in the *Supplementary information*.

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