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Photochemical Synthesis of 4*H*-Thieno[3,2-*c*]chromene and Their Optical Properties

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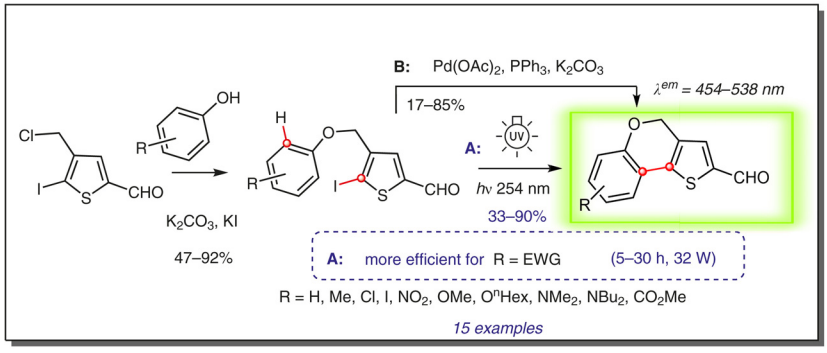

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Abstract 4-{[(2-Iodoaryl)oxy]methyl}thiophene-2-carbaldehydes and 5-iodo-4-(aryloxymethyl)thiophene-2-carbaldehydes were obtained by the reaction of phenols with 4-(chloromethyl)thiophene-2-carbaldehyde or its 5-iodo analogue, respectively. These products underwent ring closure upon irradiation with UV light (254 nm) to form the corresponding 4*H*-thieno[3,2-*c*]chromene-2-carbaldehydes in high yield. The formation of intermediate radical species was detected by EPR spectroscopy. Comparative analysis of ring-closure methods showed that photochemical cyclization of 5-iodo-4-(aryloxymethyl)thiophene-2-carbaldehyde is superior to Pd-catalyzed intramolecular arylation. A series of substituted 4*H*-thieno[3,2-*c*]chromene-2-carbaldehydes were synthesized by the photochemical cyclization of the corresponding precursors, and the photophysical properties of the products were studied. The 4*H*-thieno[3,2-*c*]chromene-2-carbaldehydes can be used as covert marking pigments.

Key words photochemistry, cyclization, thienochromenes, luminescence, arylation, pigments

4*H*-Thieno[3,2-*c*]chromene derivatives are of interest as biologically active compounds. Among them are substances that exhibit analgesic,[1] mucoregulating,[2] antiosteoporotic,[3] antiinflammatory, anti-Parkinsonian,[4] or antiulcer effects.[5] Some are also used to treat diabetes, hyperlipidemia,[6] or cancer.[7] Substituted 4*H*-thieno[3,2-*c*]chromenes are luminophores, and their luminescent properties permit their localization and transformation within cells. Consequently, luminescent probes for medical and biological use,[8] as well as materials for organic electronics,[9] have been developed.

Currently, several approaches are used to synthesize 4*H*-thieno[3,2-*c*]chromenes. These are based on annulation reactions of benzopyrans with a thiophene core[10] or on the formation of a pyran ring.[11–13] In the latter case, cross-coupling reactions catalyzed by transition metals are most often used to form the C–C bond between the benzene and thiophene rings. Despite its effectiveness, this approach has disadvantages associated with the toxicity and high cost of the catalyst, the use of ligands, and the laborious purification of the reaction products. Therefore, the development of an ecofriendly photochemical method for the preparation of 4*H*-thieno[3,2-*c*]chromenes is an urgent task.

Previously, we have developed two methods for the synthesis of 4*H*-thieno[3,2-*c*]chromenes based on palladium-catalyzed intramolecular arylation of compounds **5a** (Method B)[11] or compounds **6a–o** (Method D),[12] differing in the position of iodine in the molecule (Table 1); the yields of compounds **7a–i** obtained by these methods were in the ranges 20–69% and 44–85%, respectively.

The starting compounds **5a–c** were synthesized by treating[14] *o*-iodophenols **3a–c** with 4-(chloromethyl)thiophene-2-carbaldehyde (**1**), prepared by chloromethylation of thiophene-2-carbaldehyde.[15] Compounds **6a–o** were synthesized by the reaction of the appropriate phenol **4a–o** with 5-iodo-4-(chloromethyl)thiophene-2-carbaldehyde (**2**), obtained by iodination of aldehyde **1**.[12] Note that the latter approach is preferable because of the ready availability of phenols **4a–o**.

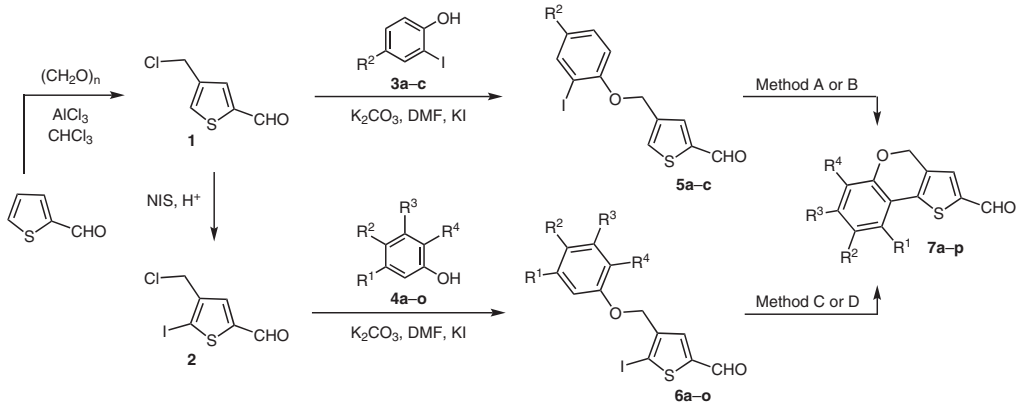
UV light-initiated arylation of 2-iodothiophenes has been known for a long time;[16] however, this approach has not been used to obtain 4*H*-thieno[3,2-*c*]chromenes. Therefore, it was of interest to study the possibility of intramolecular photocyclization of model compounds **5a** (Method A) and **6a** (Method C). To select the optimal irradiation wavelength, the absorption spectra of solutions of compounds **5a** and **6a** in acetonitrile were recorded (Figure 1). The absorption maxima of compounds **5a** and **6a** are in the range 250–330 nm, so a mercury lamp was chosen as a light

source. Irradiation with UV radiation (254 nm, 32 W) of 10 mM solutions of compounds **5a** and **6a** in acetonitrile both gave 4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde (**7a**) in 90% yield (Table 1, entries 1 and 2). The changes in the concentrations of the reaction product **7a** and the reactant **5a** or **6a** were recorded by HPLC.

We found that photocyclization of **6a** proceeded completely in five hours, whereas the conversion of aldehyde **5a** into thienochromene **7a** occurred twice as slowly, requiring irradiation for ten hours (Figure 2).[17]

The rate-limiting stage of the reaction is probably the formation of a radical, which proceeds faster in the case of compound **6a**. No signals were observed in the EPR spectrum upon UV irradiation of acetonitrile solutions of substrate **5a** or **6a** (mercury lamp, 100 W) at room temperature. This absence of EPR signals might be associated with a low concentration or a short lifetime (less than 10^{-8} s) of the radical species that is formed. However, irradiation of compounds **5a** and **6a** as glass solutions in acetonitrile at 77 K led to the appearance of signals in the EPR spectra (Figure

Table 1 Synthesis of 4*H*-Thieno[3,2-*c*]chromene-2-carbaldehydes **7a–p**



Method A/C: *hν* 254 nm, 32 W, 10 mM in MeCN, 33–90%
Method B: $Pd(OAc)_2$, $P(Ph)_3$, $C_{16}H_{33}NMe_3Br$, K_2CO_3, DMF, 110 °C, 5–6 h, 44–85%
Method D: $Pd(OAc)_2$, $P(Ph)_3$, $C_{16}H_{33}NMe_3Br$, K_2CO_3, MeCN, 80 °C, 5 h, 20–69%

Entry	R^1	R^2	R^3	R^4	Ether **5** or **6**	Yield (%) of **6** (**5**)	Time (h)	Product	Yield (%) of **7** [Method A/C]	Yield (%) of **7** [Method D[12] or (B)[11]]
1	H	H	H	H	**5a**	47	10	**7a**	90	– (85)[c]
2	H	H	H	H	**6a**	65	5	**7a**	90	63[b]
3	H	Me	H	H	**6b**	67	7	**7b**	50	62[b] (69)[c]
4	H	Cl	H	H	**6c**	72	5	**7c**	67	75[b] (20)[c]
5	H	H	H	Cl	**6d**	76	7	**7d**	84	74[b]
6	H	H	Cl	H	**6e**	87	7	**7e**	20[a]	44[b]
7	H	OMe	H	H	**6f**	64	14	**7f**	57	82[b]
8	H	$O(CH_2)_5Me$	H	H	**6g**	73	20	**7g**	87	83[b]
9	H	H	H	CO_2Me	**6h**	81	30	**7h**	74	17
10	H	NO_2	H	H	**6i**	83	26	**7i**	75	33
11	H	H	H	NO_2	**6j**	87	10	**7j**	67	–
12	H	I	H	H	**6k**	65	7	**7k**	65	–
13	H	F	H	H	**6l**	82	11	**7l**	64	–
14	H	H	$N(Me)_2$	H	**6m**	54	5	**7m**	33	–
15	H	H	$N(Bu)_2$	H	**6n**	47	4	**7n**	35	–
16	–CH=CH–CH=CH–		H	H	**6o**	92	5	**7o**	51	-
17	Cl	H	H	H	**6e**	–	7	**7p**	51[a]	–

[a] Isomeric products **7e** and **7p** (entries 6 and 17) were obtained as a mixture using Method C in a 2:5 ratio according to the NMR data.
[b] According to the literature data.[12]
[c] According to the literature data.[11]

3). This indicated the formation of radical species during the photochemical reaction. Analyses of the solutions after irradiation showed the progress of cyclization. A blank experiment with UV irradiation of acetonitrile at 77 K in the absence of substrates did not reveal the formation of any significant amounts of any radical species. The spectra of compounds **5a** and **6a** contain broadened multiplet signals due to the coupling of the ^{1}H and ^{13}C nuclei. The higher value of the *g*-factor for substrate **6a** (2.0050) compared with that of compound **5a** (2.0032) indicates the localization of the unpaired electron in the thiophene ring. Such an increase in the *g*-factor value of an unpaired electron in a sulfur-containing heterocycle is explained by the higher spin–orbit coupling constant of the S atom compared with that of the C atom.[18]

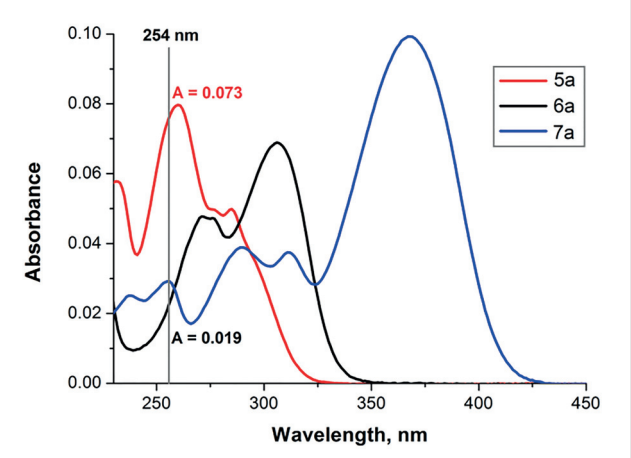


Figure 1 Absorption spectra of compounds **5a**, **6a**, and **7a**

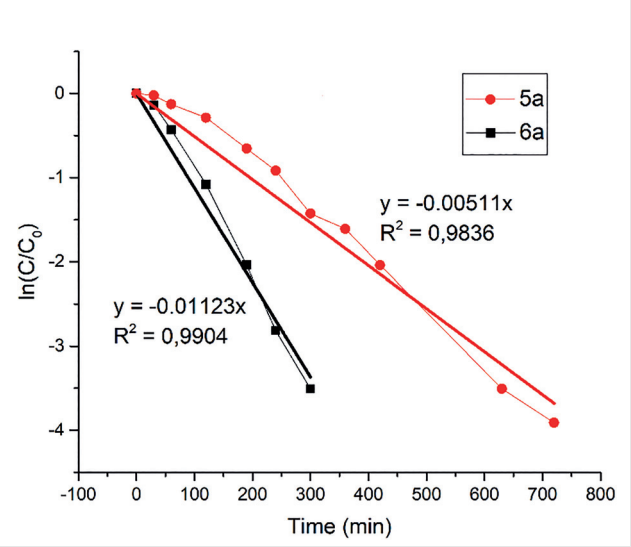


Figure 2 Plot of $\ln(C/C_0)$ against the exposure time for compounds **5a** and **6a**

Because the photochemical cyclization of 5-iodo-4-(phenoxymethyl)thiophene-2-carbaldehyde (**6a**) proceeded faster than that of **5a**, compounds **6a–o** were used to synthesize thienochromenes **7a–p**. The cyclization was performed under the same conditions as those used for compound **6a**, and the reaction progress was monitored by TLC. Complete cyclization of compounds **6b–o** required irradiation for 4–30 hours and the yields of thienochromenes **7b–p** were in the range 33–90% (Table 1, entries 3–17).

A comparative analysis of Methods A–D shows that the use of the more accessible 5-iodo-4-(phenoxymethyl)thiophene-2-carbaldehyde (**6a**) as a starting compound is more rational. The yields of compounds **7b** and **7f** with electron-donor substituents in the benzene ring obtained by palladium-catalyzed cyclization of **6b** and **6f**, respectively, were slightly higher than those of the photochemical reaction (Table 1, entries 3 and 7), whereas photochemical cyclization of compounds **6h** and **6i** bearing electron-withdrawing substituents proceeds with significantly higher yields of thienochromenes **7h** and **7i**, respectively (entries 9 and 10). The photochemical cyclization of **6m–o** gave compounds **7m–o**, respectively, as the sole reaction products (entries 14–16). Only in the case of **6e** were the isomeric 4*H*-thieno[3,2-*c*]chromene-2-carbaldehydes **7e** (entry 6) and **7p** (entry 17) obtained in a 2:5 ratio according to NMR data. However, compound **7e** was the main product in the case of Pd-catalyzed cyclization **6e** using method D.[12]

The UV spectra of 4*H*-thieno[3,2-*c*]chromene-2-carbaldehydes have been reported only for compounds **7a–f**.[19] The main emission band in the luminescence spectra of

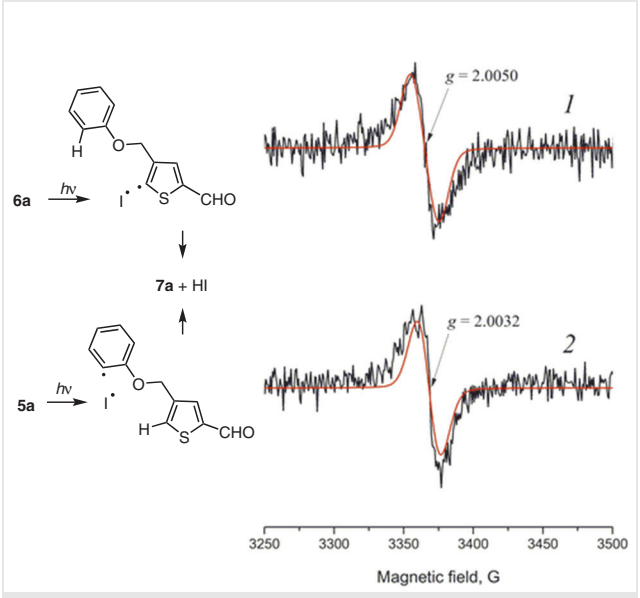


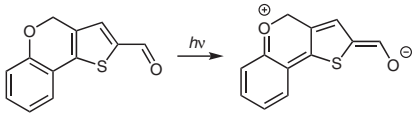
Figure 3 In situ experimental (black curves) and simulated (red curves) EPR spectra of glass solutions of compounds **6a** (Spectrum 1) and **5a** (Spectrum 2) in acetonitrile after UV irradiation at 77 K

Table 2 UV and Luminescence Spectral Parameters of Acetonitrile Solutions of 4*H*-Thieno[3,2-*c*]chromene-2-carbaldehydes **7e–o** and [(8-Fluoro-4*H*-thieno[3,2-*c*]chromen-2-yl)methylene]malononitrile (**8**)[a]

	UV absorption	Luminescence			
	λ_{max} (nm)	λ_{ex} (nm)	λ_{em} (nm)	Stokes shift[b] (nm) (eV)	Φ_{fl}
7e	241, 259, 291, 311, 368	360, 370	454	86 (0.64)	0.33[c]
7g	215, 257, 289, 321, 389	380, 390	522	133 (0.81)	0.45[c]
7h	262, 290, 318, 360	350, 360	453	93 (0.70)	0.18[c]
7i	229, 295, 357	355	–	–	0.00
7j	231, 276, 367	365	–	–	0.00
7k	218, 263, 293, 317, 372	365, 375	467	95 (0.68)	0.35[d]
7l	236, 254, 291, 311, 371	360, 370	468	97 (0.69)	0.65[d]
7m	211, 264, 296, 427	420, 430	535	108 (0.58)	0.55[c]
7n	212, 268, 438	425, 435	538	100 (0.53)	0.62[c]
7o	218, 238, 272, 337, 398	390, 400	484	86 (0.56)	0.57[d]
8	211, 262, 311, 340, 432	430	–	–	0.00

[a] $c = 2.4 \times 10^{-5}$ mol/L.
[b] Minimum Stokes shift.
[c] Quantum yield relative to that of a solution of coumarin in EtOH ($\Phi_f = 0.38$).
[d] Quantum yield relative to that of a solution of perylene in EtOH ($\Phi_f = 0.92$).

these compounds is known to be due to intramolecular charge transfer, which should be influenced by substituents on the benzene ring (Scheme 1).



Scheme 1 Intramolecular charge transfer in 4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde (**7a**)

The parameters of the UV and luminescence spectra of compounds **7g–o** are presented in Table 2. The introduction of an electron-accepting substituent such as a methoxycarbonyl (**7h**) or nitro group (**7i** and **7g**) onto the benzene ring, which hinders charge transfer, led to a significant decrease in or complete quenching of luminescence, whereas the presence of an electron-donating substituent such as an alkoxy (**7f**) or dialkylamino group (**7m**, **7n**) led to an increase in luminescence. Note that some compounds have an abnormally large Stokes shift in excess of 100 nm. Moreover, their absorption bands are outside the visible region, making these compounds colorless in daylight. Such luminophores are used in preventing counterfeiting of banknotes, securities, or other important documents.

To demonstrate a practical application of our synthesized compounds, Figure 4 shows photographs of paper treated with a solution of compound **7l** in ethanol before and after development by visible light or UV radiation (Figure 4).

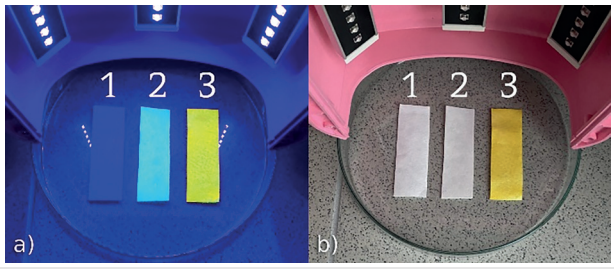
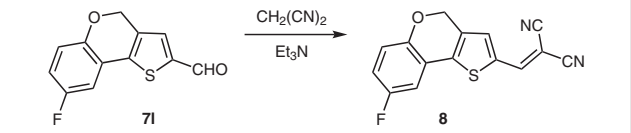


Figure 4 Photographs (a) in UV light and (b) in daylight of strips of raw paper (1), strips of paper moistened with a solution of compound **7l** in ethanol and then dried (2), and strips of paper treated with compound **7l** and a developer (1% malonodinitrile with a catalytic amount of Et_3N in ethanol) after drying.

Compound **7l** and malonodinitrile in the presence of a base undergo a Knoevenagel condensation to form the conjugated structure **8**, which has a deeper color (Scheme 2). The optical properties of condensation product **8** are presented in Table 2. The absorption bands of compound **7l** lie outside the visible region (236–371 nm), in contrast to the emission band (468 nm). This makes the strips of paper treated with compound **7l** colorless in daylight (2b), but colored in UV light (2a) (Figure 4). The authenticity of the luminophore is checked using a developer. A strip of paper (2) turned yellow after treatment with 1% alcohol solution of malonodinitrile (3).

In summary, a method has been developed for the preparation of 4*H*-thieno[3,2-*c*]chromene-2-carbaldehydes through photochemical cyclization of 5-iodo-4-(aryloxymethyl)thiophene-2-carbaldehydes. The optical properties of the synthesized compounds were studied. A possibility of their use as covert marking pigments was shown.



Scheme 2 Reaction of compound **7l** with malonodinitrile

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1392-2209.

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(14) **5-Iodo-4-(aryloxymethyl)thiophene-2-carbaldehydes 6a–o**; **General Procedure**
K_2CO_3 (138 mg, 1 mmol) and KI (17 mg, 0.1 mmol) were added to a solution of the appropriate phenol **4a–o** (1.1 mmol) and aldehyde **2** (287 mg, 1 mmol) in anhyd DMF (3 mL) under an inert atmosphere, and the mixture was stirred for 60 h. The resulting mixture was poured into cold H_2O and extracted with Et_2O (3 × 5 mL). The organic layer was washed sequentially with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuum. Crystalline products were purified by recrystallization from EtOH whereas liquid products were purified by column chromatography.

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(17) **Thieno[3,2-*c*]chromene-2-carbaldehydes 7a–p**; **General Procedure**
The appropriate ether **5a** or **6a–o** (1 mmol) was dissolved in anhyd MeCN (100 mL) and the solution was added to a 2.5 cm-diameter quartz tube with a volume of 150 mL. The stirred solution was irradiated by four low-pressure Hg lamps (Philips TUV G8 T5, λ_{max} = 254 nm; 32W in total) while it was cooled by a fan. The solvent was then evaporated in vacuum, and the residue was purified by column chromatography.
8-Fluoro-4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde (**7l**)
Yellow solid; yield: 150 mg (64%); mp 170–171 °C (EtOH). IR (KBr): 1656 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.27 (s, 2 H, CH_2). 6.91–7.01 (m, 2 H, H-6,7), 7.10 (dd, ^3J = 8.12, ^4J = 2.64, 1 H, H-9), 7.55 (s, H-3, 1 H), 9.88 (s, 1 H, CHO). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 65.50, 110.28, 117.60, 118.30, 119.80, 132.69, 133.38, 141.28, 142.05, 148.82, 157.43, 182.86.

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