JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

Formation and Disproportionation of Xanthenols to Xanthenes and Xanthones and Their Use in Synthesis

Zeyu Shi,[†] Si Chen,[†] Qiong Xiao,* and Dali Yin

Cite This: J. Org. Chem. 2021, 86, 3334−3343 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A facile and versatile strategy employing $TiCl_4$-mediated cyclization followed by a Cannizzaro reaction has been developed for the synthesis of various xanthene derivatives. The reaction proceeded smoothly to afford both xanthenes/xanthones or their sulfur derivatives and tolerated a wide range of electronically diverse substrates. Using this methodology, pranoprofen was synthesized in three steps in 59% overall yield from commercially available starting materials.

INTRODUCTION

Xanthenes and xanthones (Figure 1) are important structural motifs and found in the central core of a variety of

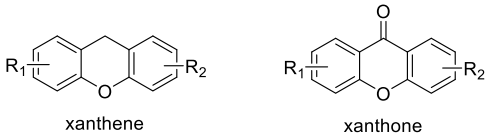


Figure 1. Motif in xanthenes and xanthones.

phytochemicals derived from plants in the families Bonnetiaceae, Clusiaceae, and Podostemaceae.[1] Xanthene derivatives are also widely used as dyes and dye precursors. Additionally, they are privileged scaffolds within medicinal chemistry and have been shown to possess a wide range of biological activities, including pronounced antiviral, anti-inflammatory, and anti-cancer properties.[2] As such, the synthesis and application of these compounds have received much attention over the past century.

In recent years, efforts have been focused on the development of practical methods to synthesize xanthones from readily available starting materials. Pinto's team reported some reviews on the synthesis of xanthones during this year.[3] In 1958 and 2002, Suschitzky and Gobbi, respectively, reported that polyphosphoric acid or concentrated sulfuric acid catalyzed the cyclization of 2-phenoxybenzoic acids to construct derivatives of xanthones.[4] In 2012, Lei and co-workers developed a $Pd(OAc)_2$-catalyzed double C−H functionalization/carbonylation of diaryl ethers to produce functionalized xanthones.[5] During the same period, Li and Studer independently reported a transition metal-catalyzed cross-dehydrogenative coupling (CDC) strategy to construct xanthones from 2-aryloxybenzaldehydes.[6] Subsequently, Li and co-workers reported a metal-free oxidative coupling of a formyl C−H bond with an aromatic C−H group using tetrabutylammonium bromide (TBAB) as a promoter in aqueous medium to form xanthones.[7] In 2020, Verma reported a Lewis acid-catalyzed reaction-formed 9*H*-xanthenes and thioxanthenes.[8] These methods generally suffer from the use of strong acids, toxic CO gas, precious metal catalysts, or harsh reaction conditions. Meanwhile, they represent the limit in terms of general methods to afford xanthenes directly.

The Cannizzaro reaction is the disproportionation of aldehydes to the corresponding alcohols and acids as a 1:1 mixture. Although useful, this named reaction has not been applied in complex synthesis as it generates a typically unwanted mixture and leads to the loss of half of the starting material used. Herein, we reported a novel $TiCl_4$-mediated cyclization−disproportionation process as an efficient method to produce xanthenes and xanthones in a 1:1 ratio. Furthermore, this mixture can be reduced by Et_3SiH in a telescoped strategy to afford xanthenes in one pot, or further oxidized by CrO_3/H_5IO_6 to afford xanthones.[9] We envisage that this strategy will become a useful and well-exploited method to form these important scaffolds.

RESULTS AND DISCUSSION

We recently developed a telescoped strategy for the synthesis of tetrahydroisoquinolines (THIQs) via a $TiCl_4$-catalyzed cyclization and subsequent triethylsilane reduction.[10] Therein, we postulated that 2-aryloxybenzaldehydes could also undergo

Received: November 11, 2020
Published: January 5, 2021

https://dx.doi.org/10.1021/acs.joc.0c02694
J. Org. Chem. 2021, 86, 3334−3343

Scheme 1. Proposed Synthesis Stemming from Our Previous Work

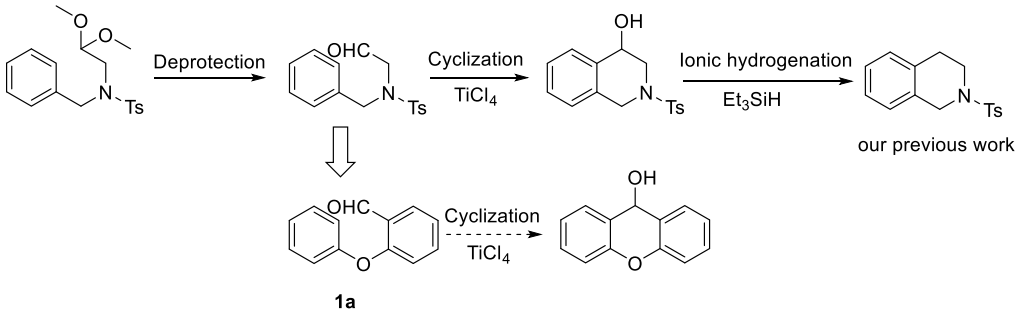
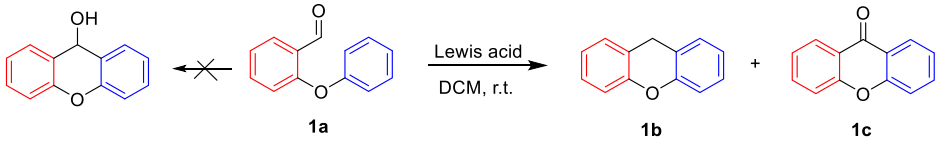


Table 1. Optimization of Reaction Conditions[a]



entry	Lewis acid (equiv.)	time (h)	yield (**1b**:**1c**)
1	$TiCl_4$ (1.0)	3	na
2	$TiCl_4$ (1.0)	12	14:18
3[b]	$TiCl_4$ (2.0)	12	30:33
4	$TiCl_4$ (4.0)	12	32:37
5[c]	$TiCl_4$ (4.0)	24	42:45
6	$AlCl_3$ (4.0)	24	30:36
7	$Al(OTf)_3$ (4.0)	24	na
8	$BF_3{\cdot}Et_2O$ (4.0)	24	na
9	$FeCl_3$ (4.0)	24	na

[a]Reaction conditions: the reactions are carried out with **1a** (1.0 mmol) and $TiCl_4$ (1 M solution in DCM) at room temperature. [b]Using 2.0 equiv. or 3.0 equiv. of $TiCl_4$ and then prolonging the reaction time to 36 h cannot convert to the cyclization product completely. [c]Under the refluxing reaction, there is no obvious improvement compared with the reaction at room temperature.

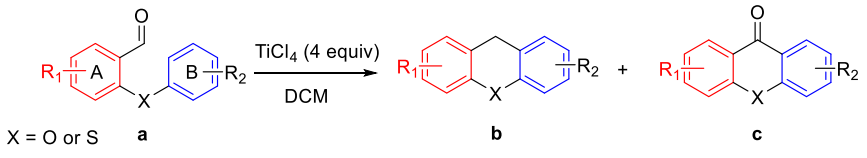
this cyclization under the same reaction conditions to afford xanthenols (Scheme 1). To examine this possibility, we began our study employing commercially available 2-phenoxybenzaldehyde (**1a**) as the model substrate.

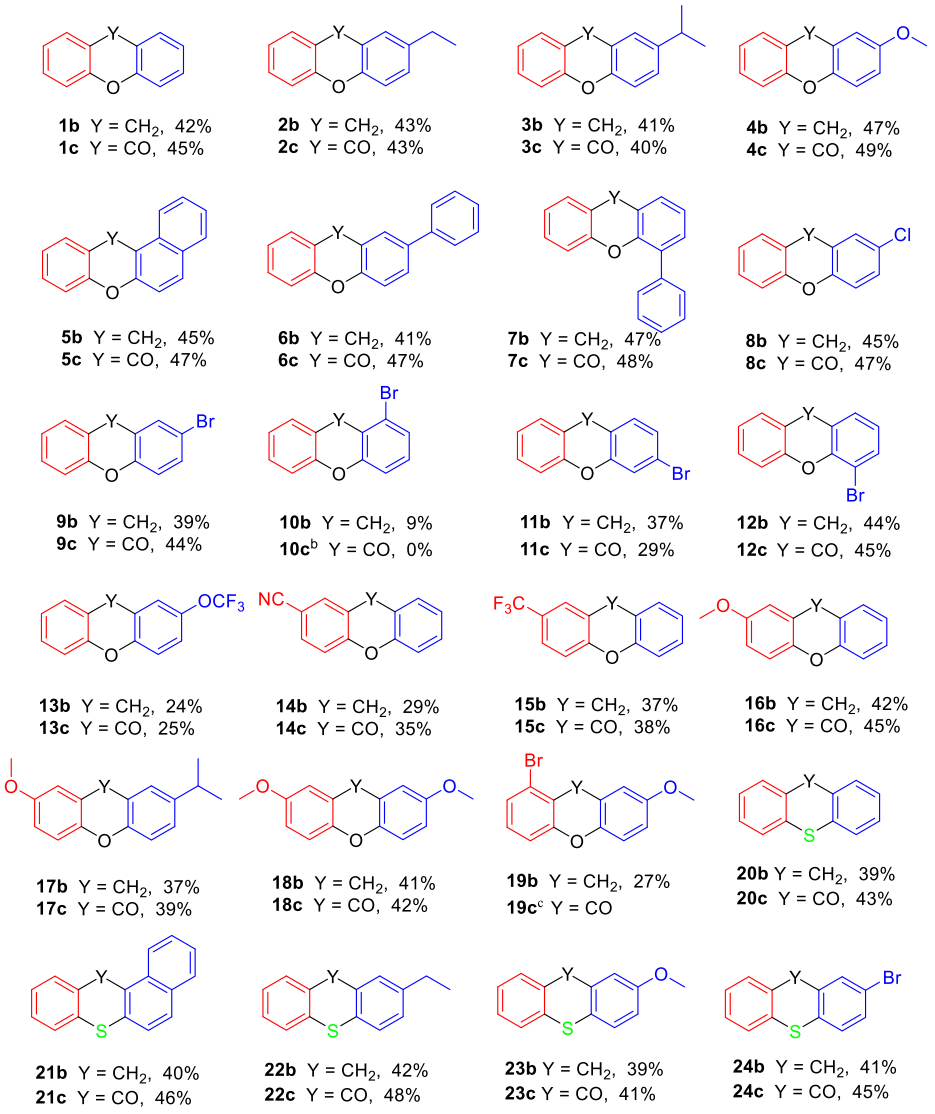
We began our investigation by treating **1a** with 1 equiv. of $TiCl_4$ (1 M solution in DCM) at room temperature for 3 h. To our disappointment, we did not observe any of the expected annulated product (Table 1, entry 1). However, upon stirring the reaction mixture for 12 h, we observed that two distinct products had formed. After careful analysis of the reaction mixture, we identified these products as xanthene (**1b**) and xanthone (**1c**), which were obtained in 14 and 18% yields, respectively (Table 1, entry 2). Increasing the amount of $TiCl_4$ used, as well as increasing the reaction time, had an advantageous effect of the isolated yield of the products obtained (Table 1, entries 3−4). After further optimization, focusing solely on stoichiometry and reaction times, we found that running the reaction for 24 h in the presence of 4 equiv. of $TiCl_4$ provided reproducible yields of 42 and 45%, respectively (Table 1, entry 5). We then turned our attention to screening other Lewis acids and observed that $AlCl_3$ afforded the desired product in reduced yields (Table 1, entry 6). Surprisingly, no other Lewis acid screened as part of our optimization mediated the reaction to result in yielder yields of the products (Table 1, entries 7−9).

With these optimized reaction conditions now in hand (Table 1, entry 5), we turned our attention toward the scope and limitation of the reaction (Table 2). To our delight, the reaction successfully afforded in varying yields a range of xanthenes and xanthones. In most cases, the substrates were fully converted to the desired xanthenes and xanthones cleanly, without any apparent side reactions occurring. As mentioned, the reaction performed well, employing electron-donating groups (**2**−**4**) and mildly electron-withdrawing groups (**8**−**12**). However, upon subjecting substrates bearing more strongly electron-withdrawing substituents on the aromatic ring B, we observed no reaction occurring, even under prolonged reaction times. This process is a kind of aromatic electrophilic substitution. The strongly electron-withdrawing functional groups will deactivate this process. Switching the electron-withdrawing substituent to the aromatic ring A once again provided the desired products in a moderate overall yield (**14**, **15**). Expanding the pattern of substitution, we successfully synthesized the desired heterocycles with substituents on both the A and B aromatic rings (**17**-**19**). It is worth noting here that using 2-(3-bromophenoxy) benzaldehyde (**10a**) as the substrate, a variety of cyclization products were formed. Theoretically, there would be four products formed in one pot (**10b**, **10c**, **11b**, **11c**); however, only three of these (**10b**, **11b**, **11c**) were identified. However, we cannot rule out the possibility of small quantities of **10c** being formed and lost during isolation/purification. Interestingly, **5a** only gave **5b** and **5c** without 12*H*-benzo[*b*]xanthene and 12*H*-benzo[*b*]-xanthen-12-one, indicating that the α-position is more active than the β-position at naphthalene in this reaction. We have tried both aniline and protected amine as the substrate. Unfortunately, these substrates cannot work at all. We speculated that the lone pair electron of nitrogen may

https://dx.doi.org/10.1021/acs.joc.0c02694
J. Org. Chem. 2021, 86, 3334−3343

Table 2. Synthesis of Xanthenes, Xanthones, and Sulfur Heterocycles[a]





[a]Reaction conditions: **a** (1.0 mmol) and $TiCl_4$ (1 M solution in DCM) at room temperature for 24 h. [b]**10c** is formed with very little amount, then lost in silica gel column chromatography. [c]**19c** is unstable.

coordinate with $TiCl_4$ to form a strong electron-withdrawing effect, thus deactivating the aromatic system.

To further expand the substrate scope, the preparation of thioxanthenes and thioxanthones was also conducted. Under the same condition, five substrates were converted into the corresponding sulfur heterocycles (**20b**/**c**-**24b**/**c**) in good yields. Also, we tried to get the fluorenene or fluorenone but failed. The cyclization did not work when there was no bridging atom at all.

To give us an understanding of a plausible mechanism, some control experiments were carried out (Figure 2). During the reaction optimization, we isolated the key intermediate 9*H*-xanthen-9-ol (**1d**) and observed that **1d** slowly transformed into **1b** and **1c** (−8 °C). We observed that the reaction did not improve significantly at a higher substrate concentration (compared two concentrations at 0.2 and 0.4 M). Addition of Brønsted acids (like 1 M HCl) or Lewis acids (1 M $TiCl_4$ in DCM) to **1d** accelerated this transformation, which was often complete within a few hours. In addition, we observed that 1 M HCl was more favorable for disproportionation than $TiCl_4$.

To reveal the intriguing 9-xanthenol **1d** disproportionation mechanism, **1c** was reduced by $NaBD_4$ in CD_3OD to afford deuterated 9-xanthenol (**1d-D**). We then treated **1d-D** with $TiCl_4$ in DCM and observed the formation of **1e**. Additionally, comparing the ^1H NMR spectra of **1e** and **1b**, **1e** clearly shows the absence of the signal corresponding to the hydrogen at 9-position and plainly shows that the two hydrogen atoms at this position were replaced by two deuterium atoms. This result

https://dx.doi.org/10.1021/acs.joc.0c02694
J. Org. Chem. 2021, 86, 3334−3343

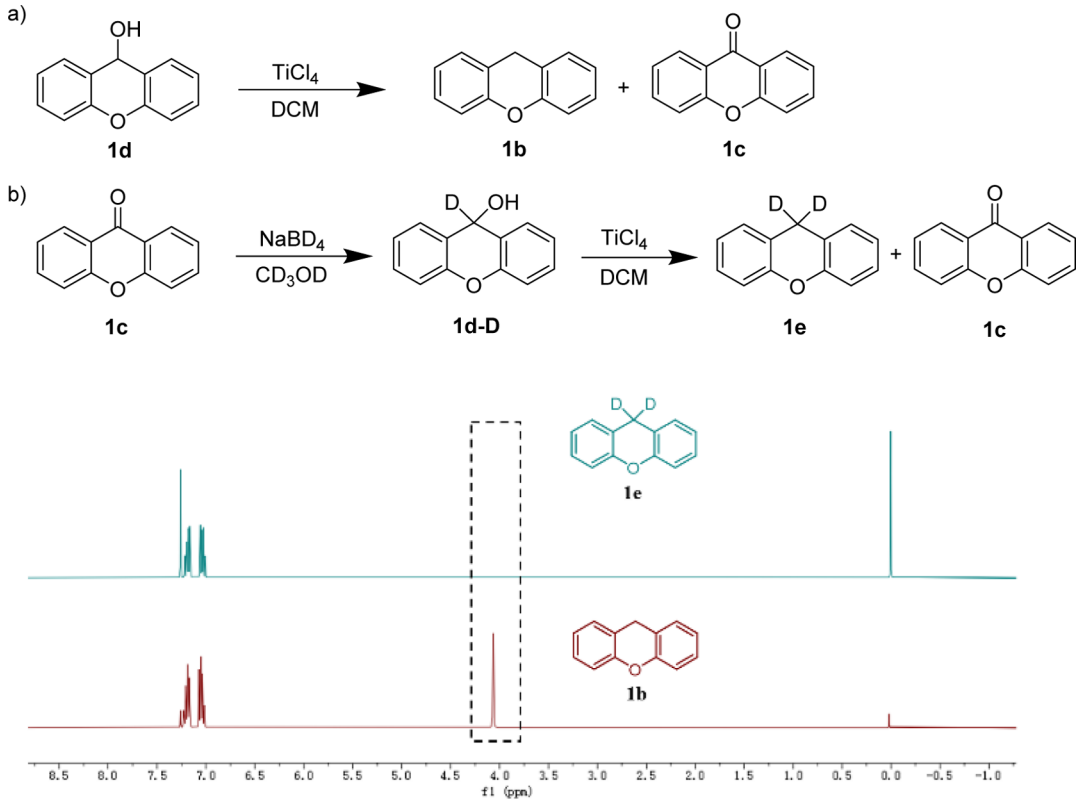
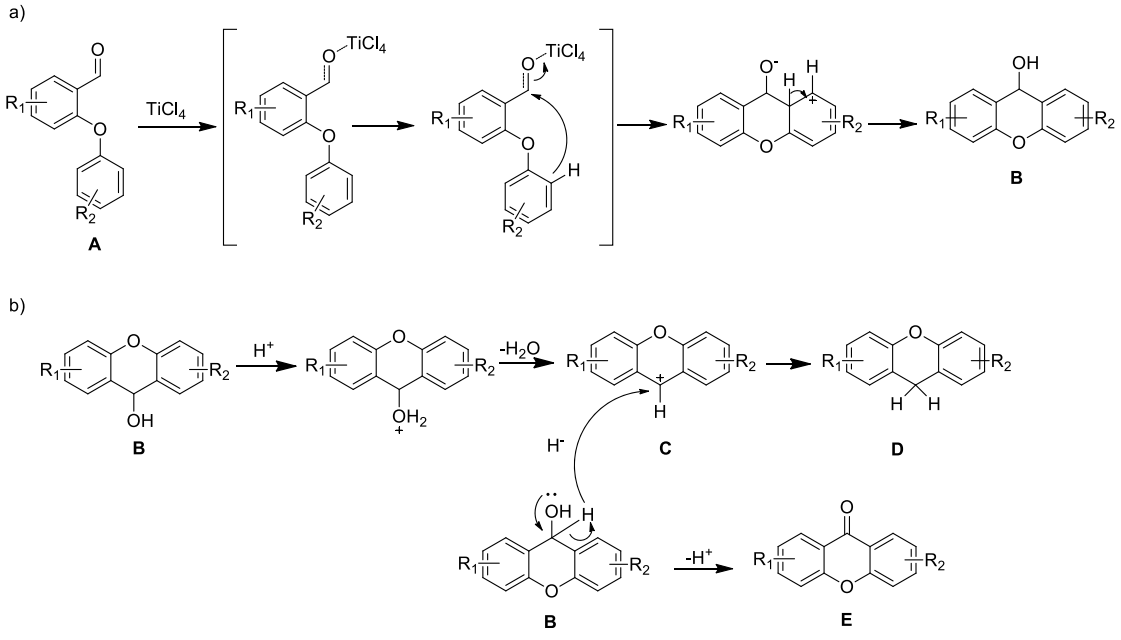


Figure 2. Investigations on the mechanism.

Scheme 2. Plausible Mechanism



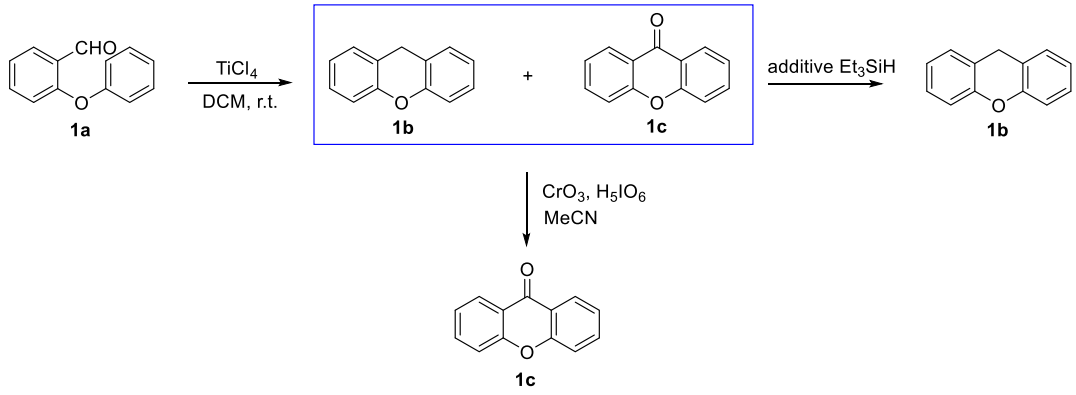
indicates that one of the deuterium atoms at this position in **1e** is derived from another molecule of **1d-D** in the reaction mixture.

Based on the above investigations, a plausible mechanism for this $TiCl_4$-mediated cyclization and disproportionation is provided in Scheme 2. The carbonyl is activated through $TiCl_4$ complexation, which facilitates the intramolecular cyclization of **A** to form 9-xanthenol **B**, via facile aromatization. We believe that once the concentration of **B** reaches a certain point (explaining the requirement for prolonged reaction times), a molecule of **B** undergoes an elimination to afford the stabilized carbocation **C**. This subsequently reacts with another equivalent of **B**, facilitating the production of **E** as well as providing the reduced product **D**.

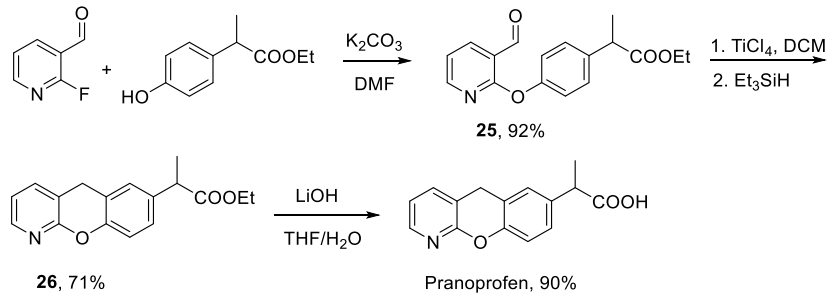
We next wanted to explore the applicability of this disproportionation reaction. Upon completion of the $TiCl_4$-promoted cyclization of **1a**, Et_3SiH (4 equiv.) was added after 24 h, and the mixture was stirred for a further 12 h to afford

https://dx.doi.org/10.1021/acs.joc.0c02694
J. Org. Chem. 2021, 86, 3334−3343

Scheme 3. Synthesis of Xanthene 1b or Xanthone 1c



Scheme 4. Synthesis of Pranoprofen



the desired xanthene **1b** in 85% yield. Furthermore, xanthone **1c** can be obtained in 86% yield through treating the crude mixture of **1b** and **1c** with CrO_3 in the presence of H_5IO_6 (Scheme 3).

Pranoprofen (PRA) is a nonsteroidal anti-inflammatory drug (NSAID), which is used as an anti-inflammatory following strabismus and cataract surgery.[11] We wanted to investigate if our methodology could be used for the synthesis of this important medicine. As shown (Scheme 4), an Ullmann condensation employing commercially available 2-fluoronicotinaldehyde with ethyl 2-(4-hydroxyphenyl)propanoate in DMF at 100 °C for 2 h furnished **25** in 92% yield. We then employed our cyclization/reduction strategy using our previously discussed conditions to afford **26** in 71% yield. Finally, hydrolysis of the ester group with LiOH in THF/H_2O (3:1 v/v) produced pranoprofen in 90% yield. Importantly, this strategy provides a shorter and more efficient way to prepare pranoprofen than that currently used.[12]

CONCLUSIONS

In summary, xanthenes and xanthones can be obtained via a $TiCl_4$-mediated cyclization from the corresponding aldehydes as a 1:1 mixture. This mixture can be transformed into a single product via a telescoped reduction for xanthene or via an oxidation for xanthone. The method is noteworthy for its wide substrate tolerance and accommodation of diverse functional groups on each aromatic ring. This strategy provides a facile and versatile synthesis of this type of heterocycle, providing a bespoke synthesis of these important scaffolds. Finally, pranoprofen was synthesized in three steps using this method in 59% overall yield.

EXPERIMENTAL SECTION

General Information. ^1H NMR spectra were recorded on Mercury-300, Mercury-400, Mercury-500, and Bruker-600 spectrometers. Chemical shifts are referenced to the residual solvent peak and reported in ppm (δ scale), and all coupling constant (J) values are given in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Melting points were determined on a Yanaco MP-J3 microscope melting point apparatus. High-resolution mass spectrometry (HRMS) experiments were performed in electrospray ionization (ESI) mass spectrometry and measured on a Thermo Exactive Orbitrap plus spectrometer. Flash column chromatography was performed on Biotage Isolera one (mesh 300−400). All the solvents and chemicals were obtained from commercial sources and used without further purification.

General Procedure for the Synthesis of Substrate a.[6] To a solution of corresponding benzaldehyde (2.4 mmol, 1 equiv.) in DMF (3 mL), phenol (2.9 mmol, l.2 equiv.) and potassium carbonate (2.9 mmol, l.2 equiv.) were added, and the mixture was stirred at 100 °C for 6 h. After adding water, the reaction solution was extracted three times with dichloromethane, washed with saturated brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (PE/EA = 10:1) to afford the desired product **a**. Except **14a**, **17a**, **19a**, and **22a**, other substrates are known compounds.[6−8]

*3-Formyl-4-phenoxybenzonitrile (**14a**).* Yellow solid; yield 77.3% (1.6 g); mp: 60−63 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 10.56 (d, J = 1.8 Hz, 1H), 8.22 (dd, J = 4.2, 2.2 Hz, 1H), 7.71 (dd, J = 8.7, 2.3 Hz, 1H), 7.49 (ddd, J = 10.9, 5.7, 2.1 Hz, 2H), 7.32 (td, J = 7.4, 1.4 Hz, 1H), 7.17−7.11 (m, 2H), 6.94−6.81 (m, 1H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 187.6, 163.5, 154.1, 138.8, 133.3, 130.9, 129.8, 126.4, 120.9, 118.0, 117.7, 115.6, 106.7; HRMS (ESI): m/z calcd for $C_{14}H_{10}O_2N$ $[M + H]^+$, 224.0706; found, 224.0705.

*2-(4-Isopropylphenoxy)-5-methoxybenzaldehyde (**17a**).* Yellow oil; yield 11.1% (240 mg); ^1H NMR (400 MHz, $CDCl_3$): δ 10.41 (s, 1H), 7.39 (d, J = 3.2 Hz, 1H), 7.23−7.16 (m, 2H), 7.11 (dd, J = 9.0, 3.2 Hz, 1H), 6.95−6.89 (m, 3H), 3.84 (s, 3H), 2.90 (p, J = 6.9 Hz, 1H), 1.25 (d, J = 6.9 Hz, 6H); ^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ

https://dx.doi.org/10.1021/acs.joc.0c02694
J. Org. Chem. 2021, 86, 3334−3343

189.5, 155.6, 154.0, 144.3, 127.8, 127.6, 127.4, 123.9, 121.3, 118.1, 115.1, 109.5, 55.9, 33.5, 24.3, 24.2; HRMS (ESI): m/z calcd for $C_{17}H_{19}O_3$ $[M + H]^+$, 271.1329; found, 271.1349.

*2-Bromo-6-(4-methoxyphenoxy)benzaldehyde (**19a**).* Yellow oil; yield 76.8% (1.9 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.50 (s, 1H), 7.33 (dd, J = 8.0, 0.9 Hz, 1H), 7.26−7.19 (m, 1H), 7.02−6.97 (m, 2H), 6.94−6.89 (m, 2H), 6.76 (dd, J = 8.4, 1.0 Hz, 1H), 3.81 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 189.9, 161.4, 156.8, 148.8, 134.6, 128.3, 124.8, 124.2, 121.4, 116.5, 115.2, 55.8; HRMS (ESI): m/z calcd for $C_{14}H_{12}O_3Br$ $[M + H]^+$, 306.9964; found, 306.9962.

*2-((4-Ethylphenyl)thio)benzaldehyde (**22a**).* Yellow oil; yield 83.2% (1.6 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.36 (s, 1H), 7.83 (dd, J = 7.5, 1.7 Hz, 1H), 7.39−7.33 (m, 3H), 7.29−7.24 (m, 1H), 7.23−7.20 (m, 2H), 7.02 (d, J = 8.0 Hz, 1H), 2.66 (q, J = 7.6 Hz, 2H), 1.24 (t, J = 7.6 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 191.6, 145.3, 142.8, 134.0, 133.4, 132.2, 129.5, 129.5, 129.3, 125.8, 28.7, 15.4; HRMS (ESI): m/z calcd for $C_{15}H_{15}OS$ $[M + H]^+$, 243.0838; found, 243.0832.

General Procedure for the Synthesis of Xanthenes and Xanthones. To a solution of the corresponding substrate **a** (1.0 mmol, 1 equiv.) in DCM (5 mL) was added $TiCl_4$ (1 M solution in DCM, 4 mL, 4 equiv.) at room temperature, and the mixture was stirred at room temperature for 24 h. The reaction was quenched by the addition of H_2O, stirred for 30 min, then was extracted three times with DCM (20 mL), washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash column chromatography (PE/EA = 10:1) to afford the desired products **b** and **c**.

*9H-xanthene (**1b**).*[13] White solid; yield 42.0% (72 mg); mp: 99−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25−7.14 (m, 4H), 7.09−7.00 (m, 4H), 4.07 (s, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 152.1, 129.0, 127.8, 123.1, 120.7, 116.6, 28.0; HRMS (ESI): m/z calcd for $C_{13}H_{11}O$ $[M + H]^+$, 183.0810; found, 183.0808.

*9H-Xanthen-9-one (**1c**).*[7] White solid; yield 45.4% (89 mg); mp: 172−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (dd, J = 8.0, 1.4 Hz, 2H), 7.73 (td, J = 7.9, 7.2, 1.6 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.4, 156.3, 135.0, 126.9, 124.1, 122.2, 118.1; HRMS (ESI): m/z calcd for $C_{13}H_9O_2$ $[M + H]^+$, 197.0603; found, 197.0600.

*2-Ethyl-9H-xanthene (**2b**).* White solid; yield 42.9% (90 mg); mp: 97−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25−7.15 (m, 2H), 7.13−6.96 (m, 5H), 4.04 (s, 2H), 2.62 (q, J = 7.6 Hz, 2H), 1.25 (t, J = 7.6 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 152.3, 150.1, 138.9, 129.0, 128.2, 127.6, 127.1, 122.9, 120.7, 120.3, 116.5, 116.3, 28.3, 28.1, 16.0; HRMS (ESI): m/z calcd for $C_{15}H_{15}O$ $[M + H]^+$, 221.1123; found, 221.1118.

*2-Ethyl-9H-xanthen-9-one (**2c**).*[14] Pale yellow solid; yield 43.0% (96 mg); mp: 69−71 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (dd, J = 8.0, 1.4 Hz, 1H), 8.15 (d, J = 1.7 Hz, 1H), 7.77−7.65 (m, 1H), 7.57 (dd, J = 8.6, 2.0 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 8.6 Hz, 1H), 7.40−7.33 (m, 1H), 2.78 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 177.5, 156.3, 154.7, 140.2, 135.2, 134.8, 126.9, 124.9, 123.8, 121.9, 121.6, 118.1, 118.0, 28.4, 15.7; HRMS (ESI): m/z calcd for $C_{15}H_{13}O_2$ $[M + H]^+$, 225.0916; found, 225.0904.

*2-Isopropyl-9H-xanthene (**3b**).* White solid; yield 40.9% (91 mg); mp: 83−85 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (dd, J = 12.8, 6.9 Hz, 2H), 7.09−6.95 (m, 5H), 4.04 (s, 2H), 2.96−2.79 (m, 1H), 1.25 (d, J = 7.0 Hz, 6H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 152.2, 150.1, 143.6, 129.0, 127.7, 126.7, 125.7, 122.9, 120.8, 120.3, 116.5, 116.3, 33.6, 28.2, 24.4; HRMS (ESI): m/z calcd for $C_{16}H_{17}O$ $[M + H]^+$, 225.1279; found, 225.1284.

*2-Isopropyl-9H-xanthen-9-one (**3c**).*[14] White solid; yield 40.4% (96 mg); mp: 80−82 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35 (dd, J = 8.0, 1.6 Hz, 1H), 8.18 (d, J = 2.2 Hz, 1H), 7.72 (ddd, J = 8.6, 7.2, 1.7 Hz, 1H), 7.62 (dd, J = 8.6, 2.3 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 8.6 Hz, 1H), 7.41−7.34 (m, 1H), 3.11−2.98 (m, 1H), 1.33 (s, 3H), 1.31 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 177.6, 156.3, 154.7, 144.8, 134.8, 133.9, 126.9, 123.8, 123.6, 121.9, 121.6, 118.1, 118.0, 33.8, 24.1; HRMS (ESI): m/z calcd for $C_{16}H_{15}O_2$ $[M + H]^+$, 239.1072; found, 239.1060.

*2-Methoxy-9H-xanthene (**4b**).*[15] Pale yellow solid; yield 47.2% (100 mg); mp: 63−65 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24−7.16 (m, 2H), 7.08−6.98 (m, 3H), 6.78 (dd, J = 8.8, 2.9 Hz, 1H), 6.72 (d, J = 2.8 Hz, 1H), 4.06 (s, 2H), 3.82 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 155.3, 152.3, 146.1, 129.0, 127.7, 122.8, 121.4, 120.1, 117.23, 116.5, 113.5, 113.4, 55.8, 28.4; HRMS (ESI): m/z calcd for $C_{14}H_{13}O_2$ $[M + H]^+$, 213.0916; found, 213.0902.

*2-Methoxy-9H-xanthen-9-one (**4c**).*[7] White solid; yield 48.7% (110 mg); mp: 128−130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35 (dd, J = 8.0, 1.5 Hz, 1H), 7.77−7.67 (m, 2H), 7.49 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 9.1 Hz, 1H), 7.42−7.36 (m, 1H), 7.33 (dd, J = 9.1, 3.1 Hz, 1H), 3.92 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 177.3, 156.3, 156.1, 151.2, 134.8, 126.9, 125.2, 123.9, 122.3, 121.4, 119.6, 118.2, 105.9, 56.2; HRMS (ESI): m/z calcd for $C_{14}H_{11}O_3$ $[M + H]^+$, 227.0708; found, 227.0697.

*12H-benzo[a]xanthene (**5b**).*[16] Pale red solid; yield 44.8% (104 mg); mp: 90−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91−7.81 (m, 2H), 7.73 (d, J = 8.9 Hz, 1H), 7.58 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 7.44 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.26−7.21 (m, 2H), 7.13−7.04 (m, 2H), 4.38 (s, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.2, 148.8, 132.2, 130.3, 129.6, 128.6, 128.4, 127.9, 126.8, 124.3, 123.3, 122.4, 119.7, 118.1, 116.6, 111.7, 24.9; HRMS (ESI): m/z calcd for $C_{17}H_{13}O$ $[M + H]^+$, 233.0966; found, 233.0956.

*12H-benzo[a]xanthen-12-one (**5c**).*[7] Yellow solid; yield 46.8% (115 mg); mp: 148−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.11 (d, J = 8.7 Hz, 1H), 8.48−8.39 (m, 1H), 8.14 (d, J = 9.1 Hz, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.83−7.70 (m, 2H), 7.65−7.54 (m, 3H), 7.49−7.42 (m, 1H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$): δ 178.7, 157.8, 154.8, 136.8, 134.1, 131.3, 130.3, 129.7, 128.5, 127.1, 126.9, 126.3, 124.5, 123.8, 118.2, 117.7, 114.8; HRMS (ESI): m/z calcd for $C_{17}H_{11}O_2$ $[M + H]^+$, 247.0759; found, 247.0744.

*2-Phenyl-9H-xanthene (**6b**).*[17] White solid; yield 41.0% (105 mg); mp: 124−126 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60−7.54 (m, 2H), 7.46−7.39 (m, 4H), 7.36−7.31 (m, 1H), 7.24−7.16 (m, 2H), 7.12 (d, J = 8.4 Hz, 1H), 7.10−7.02 (m, 2H), 4.13 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 152.0, 151.6, 140.7, 136.2, 129.1, 128.9, 127.8, 127.7, 127.1, 126.9, 126.6, 123.2, 120.9, 120.5, 116.9, 116.6, 28.1; HRMS (ESI): m/z calcd for $C_{19}H_{15}O$ $[M + H]^+$, 259.1123; found, 259.1119.

*2-Phenyl-9H-xanthen-9-one (**6c**).*[7] Pale red solid; yield 47.1% (128 mg); mp: 202−204 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (d, J = 2.4 Hz, 1H), 8.38 (dd, J = 7.9, 1.6 Hz, 1H), 7.98 (dd, J = 8.7, 2.2 Hz, 1H), 7.78−7.72 (m, 1H), 7.69 (d, J = 7.3 Hz, 2H), 7.58 (d, J = 8.7 Hz, 1H), 7.55−7.45 (m, 3H), 7.44−7.35 (m, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 177.4, 156.3, 155.7, 139.5, 137.2, 135.0, 133.8, 129.1, 127.6, 127.3, 126.9, 124.7, 124.1, 122.1, 121.9, 118.7, 118.2; HRMS (ESI): m/z calcd for $C_{19}H_{13}O_2$ $[M + H]^+$, 273.0916; found, 273.0899.

*4-Phenyl-9H-xanthene (**7b**).*[17] Yellow oil; yield 46.5% (120 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, J = 7.1 Hz, 2H), 7.49 (t, J = 7.6 Hz, 2H), 7.40 (t, J = 7.4 Hz, 1H), 7.28 (d, J = 6.1 Hz, 1H), 7.19 (q, J = 7.9 Hz, 3H), 7.12 (t, J = 7.5 Hz, 1H), 7.05 (t, J = 7.4 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H), 4.12 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 152.2, 149.0, 137.9, 129.9, 129.8, 129.3, 128.7, 128.3, 128.2, 127.6, 127.2, 123.2, 123.0, 121.6, 121.1, 116.7, 28.6; HRMS (ESI): m/z calcd for $C_{19}H_{15}O$ $[M + H]^+$, 259.1123; found, 259.1116.

*4-Phenyl-9H-xanthen-9-one (**7c**).*[7] Gray solid; yield 47.8% (130 mg); mp: 137−139 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41−8.32 (m, 2H), 7.77 (dd, J = 7.3, 1.7 Hz, 1H), 7.72−7.64 (m, 3H), 7.54 (t, J = 7.5 Hz, 2H), 7.51−7.43 (m, 2H), 7.43−7.35 (m, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 177.5, 156.1, 153.1, 136.5, 136.0, 134.9, 131.6, 129.8, 128.5, 128.0, 126.8, 126.3, 124.2, 124.0, 122.4, 121.6, 118.3; HRMS (ESI): m/z calcd for $C_{19}H_{13}O_2$ $[M + H]^+$, 273.0916; found, 273.0910.

*2-Chloro-9H-xanthene (**8b**).*[16] White solid; yield 44.7% (96 mg); mp: 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24−7.12 (m, 4H), 7.08−6.95 (m, 3H), 4.03 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz,

https://dx.doi.org/10.1021/acs.joc.0c02694
J. Org. Chem. 2021, 86, 3334−3343

$CDCl_3$): δ 151.7, 150.6, 129.0, 128.7, 128.0, 127.8, 127.7, 123.4, 122.3, 119.8, 117.9, 116.6, 27.9; HRMS (ESI): *m/z* calcd for $C_{13}H_{10}OCl$ $[M + H]^+$, 217.0420; found, 217.0402.

2-Chloro-9H-xanthen-9-one (**8c**).[6b] White solid; yield 46.6% (107 mg); mp: 170−172 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.30 (d, *J* = 2.6 Hz, 1H), 7.79−7.72 (m, 1H), 7.67 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.54−7.45 (m, 2H), 7.45−7.36 (m, 1H). ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 176.3, 156.2, 154.6, 135.4, 135.1, 129.8, 126.9, 126.2, 124.4, 122.8, 121.6, 119.9, 118.2; HRMS (ESI): *m/z* calcd for $C_{13}H_8O_2Cl$ $[M + H]^+$, 231.0213; found, 231.0201.

2-Bromo-9H-xanthene (**9b**). White solid; yield 38.9% (101 mg); mp: 118−120 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.33−7.27 (m, 2H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 7.0 Hz, 1H), 7.07−7.01 (m, 2H), 6.93 (d, *J* = 8.8 Hz, 1H), 4.02 (s, 2H); ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 151.6, 151.1, 131.6, 130.6, 129.0, 128.0, 123.4, 122.8, 119.75, 118.3, 116.6, 115.1, 27.7; HRMS (ESI): *m/z* calcd for $C_{13}H_{10}OBr$ $[M + H]^+$, 260.9915; found, 260.9900.

2-Bromo-9H-xanthen-9-one (**9c**).[6b] White solid; yield 43.8% (120 mg); mp: 151−153 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.43 (d, *J* = 2.4 Hz, 1H), 8.31 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.78 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.76−7.71 (m, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.44−7.33 (m, 2H); ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 176.1, 156.1, 155.0, 137.8, 135.3, 129.3, 126.9, 124.4, 123.2, 121.6, 120.1, 118.2, 117.2; HRMS (ESI): *m/z* calcd for $C_{13}H_8O_2Br$ $[M + H]^+$, 274.9708; found, 274.9695.

3-Bromo-9H-xanthene & 1-Bromo-9H-xanthene (**10b & 11b**). White solid; yield 46.3% (120 mg); ^1H NMR (500 MHz, $CDCl_3$): δ 7.32−7.15 (m, 5H), 7.11−6.99 (m, 4H), 4.02 (s, 2H); ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 152.7, 151.6, 151.2, 130.2, 129.3, 129.1, 128.6, 128.1, 128.0, 126.7, 126.1, 124.6, 123.5, 121.0, 120.4, 120.1, 119.8, 119.7, 116.7, 116.3, 115.8, 29.2, 27.6; HPLC-HRMS (ESI): *m/z* calcd for $C_{13}H_{10}OBr$ $[M + H]^+$, 260.9915; found, 260.9910. HPLC (1260, Agilent) was performed using an Eclipse ZORBAX XDB column (Agilent; 4.6 × 150 mm) packed with C_{18} silica (5 μm) and an eluent of MeCN/H_2O = 55:45 at a flow rate of 1.0 mL/min. λ = 254 nm: t_R = 15.6 min (major) and t_R = 18.7 min (minor).

3-Bromo-9H-xanthen-9-one (**11c**).[6b] Scarlet solid; yield 29.4% (80 mg); mp: 111−113 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.32 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.78−7.71 (m, 1H), 7.69 (d, *J* = 1.7 Hz, 1H), 7.54−7.46 (m, 2H), 7.45−7.37 (m, 1H);^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 176.7, 156.3, 156.1, 135.3, 129.3, 128.3, 127.8, 126.9, 124.5, 121.9, 121.2, 120.9, 118.1; HRMS (ESI): *m/z* calcd for $C_{13}H_8O_2Br$ $[M + H]^+$, 274.9708; found, 274.9698.

4-Bromo-9H-xanthene (**12b**).[18] Yellow solid; yield 44.3% (115 mg); mp: 114−116 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46−7.41 (m, 1H), 7.26−7.15 (m, 3H), 7.13−7.09 (m, 1H), 7.09−7.03 (m, 1H), 6.89 (t, *J* = 7.7 Hz, 1H), 4.06 (s, 2H); ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 151.8, 148.9, 131.5, 128.1, 127.9, 123.7, 122.7, 120.5, 117.0, 110.9, 28.4; HRMS (ESI): *m/z* calcd for $C_{13}H_{10}OBr$ $[M + H]^+$, 260.9915; found, 260.9907.

4-Bromo-9H-xanthen-9-one (**12c**). Yellow solid; yield 45.0% (123 mg); mp: 110−112 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.33−8.28 (m, 2H), 7.97−7.96 (m, 1H), 7.78−7.74 (m, 1H), 7.62−7.60 (m, 1H), 7.43−7.39 (m, 1H), 7.26−7.25 (m, 1H); ^{13}C $\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 176.7, 156.0, 152.7, 138.3, 135.3, 126.8, 126.2, 124.6, 124.5, 123.2, 121.4, 118.3, 111.6.; HRMS (ESI): *m/z* calcd for $C_{13}H_8O_2Br$ $[M + H]^+$, 274.9702; found, 274.9690.

2-Trifluoromethoxy-9H-xanthene (**13b**). White solid; yield 23.8% (63 mg); mp: 110−112 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23−7.12 (m, 2H), 7.08−6.99 (m, 5H), 4.04 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 151.7, 150.5, 144.3, 129.0, 128.1, 123.5, 122.1, 121.7, 120.8, 119.6, 117.6, 116.6, 28.1; HRMS (ESI): *m/z* calcd for $C_{14}H_{10}O_2F$ $[M + H]^+$, 267.0627; found, 267.0620.

2-Trifluoromethoxy-9H-xanthen-9-one (**13c**).[19] White solid; yield 24.6% (69 mg); mp: 170−172 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.19 (dt, *J* = 2.5, 0.9 Hz, 1H), 7.83−7.70 (m, 1H), 7.63−7.48 (m, 3H), 7.45−7.38 (m, 1H); ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 176.5, 156.2, 154.3, 145.2, 135.5, 128.3, 126.9, 124.6, 122.6, 121.3, 120.1, 118.6, 118.2; HRMS (ESI): *m/z* calcd for $C_{14}H_8O_3F_3$ $[M + H]^+$, 281.0420; found, 281.0410.

9H-xanthene-2-carbonitrile (**14b**).[20] White solid; yield 29.2% (60 mg); mp: 123−125 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 4.2, 2.4 Hz, 2H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.4 Hz, 1H), 7.12−7.04 (m, 3H), 4.07 (s, 2H); ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 155.3, 151.0, 133.5, 132.1, 129.1, 128.3, 124.2, 122.0, 119.3, 119.0, 117.7, 116.8, 106.5, 27.4; HRMS (ESI): *m/z* calcd for $C_{14}H_{10}ON$ $[M + H]^+$, 208.0757; found, 208.0750.

9-Oxo-9H-xanthene-2-carbonitrile (**14c**).[7] White solid; yield 35.4% (78 mg); mp: 110−112 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.68 (d, *J* = 2.1 Hz, 1H), 8.34 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.95 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.84−7.77 (m, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H); ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 175.6, 158.2, 156.0, 137.1, 136.0, 132.6, 127.1, 125.2, 122.3, 121.8, 119.9, 118.3, 117.9, 108.2; HRMS (ESI): *m/z* calcd for $C_{14}H_8O_2N$ $[M + H]^+$, 222.0550; found, 222.05442.

2-Trifluoromethyl-9H-xanthene (**15b**). White solid; yield 36.8% (92 mg); mp: 123−125 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49−7.43 (m, 2H), 7.25−7.16 (m, 2H), 7.14−7.03 (m, 3H), 4.10 (s, 2H); ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 154.4, 151.4, 129.1, 128.2, 126.5, 125.1, 123.8, 121.2, 119.8, 117.0, 116.7, 27.8; HRMS (ESI): *m/z* calcd for $C_{14}H_{10}OF_3$ $[M + H]^+$, 251.0684; found, 251.0679.

2-Trifluoromethyl-9H-xanthen-9-one (**15c**).[7] White solid; yield 38.3% (101 mg); mp: 110−112 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.68−8.61 (m, 1H), 8.36 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.97−7.93 (m, 1H), 7.81−7.76 (m, 1H), 7.66−7.60 (m, 1H), 7.54 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.47−7.42 (m, 1H); ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 176.5, 157.9, 156.2, 135.7, 131.4, 131.3, 127.1, 125.1, 121.9, 121.8, 119.4, 118.3; HRMS (ESI): *m/z* calcd for $C_{14}H_8O_2F_3$ $[M + H]^+$, 265.0476; found, 265.0461.

2-Isopropyl-7-methoxy-9H-xanthene (**17b**). White solid; yield 36.7% (93 mg); mp: 78−80 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.04 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.00 (s, 1H), 6.96 (dd, *J* = 8.6, 4.4 Hz, 2H), 6.74 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.69 (d, *J* = 2.9 Hz, 1H), 4.00 (s, 2H), 3.78 (s, 3H), 2.86 (p, *J* = 6.9 Hz, 1H), 1.24 (s, 3H), 1.23 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 155.1, 150.3, 146.3, 143.4, 126.6, 125.7, 121.4, 119.7, 117.2, 116.2, 113.4, 55.8, 33.6, 28.6, 24.3; HRMS (ESI): *m/z* calcd for $C_{17}H_{19}O_2$ $[M + H]^+$ 255.1385, found 255.1376.

2-Isopropyl-7-methoxy-9H-xanthen-9-one (**17c**).[21] White solid; yield 38.7% (103 mg); mp: 90−92 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.23−8.12 (m, 1H), 7.70 (d, *J* = 3.1 Hz, 1H), 7.60 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.45−7.42 (m, 1H), 7.41 (s, 1H), 7.31 (dd, *J* = 9.1, 3.1 Hz, 1H), 3.92 (s, 3H), 3.05 (p, *J* = 6.9 Hz, 1H), 1.32 (s, 3H), 1.31 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 177.4, 155.9, 154.7, 151.1, 144.6, 133.7, 124.9, 123.4, 122.1, 121.0, 119.5, 118.0, 105.9, 56.1, 33.8, 24.1; HRMS (ESI): *m/z* calcd for $C_{17}H_{17}O_3$ $[M + H]^+$, 269.1178; found, 269.1170.

2,7-Dimethoxy-9H-xanthene (**18b**). White crystal; yield 40.8% (98 mg); mp: 127−129 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 6.91 (d, *J* = 8.7 Hz, 2H), 6.84−6.58 (m, 4H), 3.95 (s, 2H), 3.73 (s, 6H); ^{13}C $\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.2, 146.4, 120.9, 117.2, 113.5, 113.4, 55.8, 28.9; HRMS (ESI): *m/z* calcd for $C_{15}H_{15}O_3$ $[M + H]^+$, 243.1021; found, 243.1010.

2,7-Dimethoxy-9H-xanthen-9-one (**18c**).[5] White solid; yield 42.1% (107 mg); mp: 181−183 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 2H), 7.59−7.24 (m, 4H), 3.93 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 177.0, 155.9, 151.1, 125.0, 121.5, 119.5, 105.6, 56.1; HRMS (ESI): *m/z* calcd for $C_{15}H_{13}O_4$ $[M + H]^+$, 257.0814; found, 257.0801.

1-Bromo-7-methoxy-9H-xanthene (**19b**). White crystal; yield 27.0% (78 mg); mp: 127−129 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.27−7.24 (m, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.96 (dd, *J* = 8.0, 3.0 Hz, 2H), 6.80−6.65 (m, 2H), 4.04 (s, 2H), 3.80 (s, 3H); ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 155.6, 153.0, 145.3, 128.6, 126.4, 124.6, 120.4, 120.3, 117.1, 115.7, 114.0, 113.3, 55.8, 29.7; HRMS (ESI): *m/z* calcd for $C_{14}H_{12}O_2Br$ $[M + H]^+$, 291.0015; found, 291.0008.

9H-thioxanthene (**20b**).[22] White solid; yield 39.0% (77 mg); mp: 129−131 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47−7.41 (m, 2H),

https://dx.doi.org/10.1021/acs.joc.0c02694
J. Org. Chem. 2021, 86, 3334−3343

7.34−7.28 (m, 2H), 7.24−7.19 (m, 2H), 7.19−7.16 (m, 2H), 3.85 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 136.3, 133.9, 128.1, 127.0, 126.7, 126.6, 39.3; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{11}S$ [M + H]$^+$, 199.0582; found, 199.0574.

*9H-Thioxanthen-9-one (**20c**).*[23] White solid; yield 42.7% (90 mg); mp: 214−216 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66−8.59 (m, 2H), 7.66−7.54 (m, 4H), 7.53−7.44 (m, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 180.1, 137.4, 132.4, 130.0, 129.3, 126.4, 126.1; HRMS (ESI): *m*/*z* calcd for $C_{13}H_9OS$ [M + H]$^+$, 213.0374; found, 213.0367.

*12H-Benzo[a]thioxanthene (**21b**).*[24] Gray solid; yield 40.1% (99 mg); mp: 114−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.3 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.54−7.39 (m, 4H), 7.23 (s, 2H), 4.29 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 135.6, 134.1, 132.7, 131.5, 131.4, 130.7, 129.0, 128.4, 126.8, 126.8, 126.7, 126.7, 126.6, 125.3, 125.3, 122.6, 33.6; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{13}S$ [M + H]$^+$, 249.0738; found, 249.0731.

*12H-Benzo[a]thioxanthen-12-one (**21c**).* Yellow crystal; yield 45.8% (120 mg); mp: 127−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.90 (d, *J* = 8.8 Hz, 1H), 8.66 (d, *J* = 7.9 Hz, 1H), 7.99 (d, *J* = 8.7 Hz, 1H), 7.89 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.79−7.72 (m, 1H), 7.65−7.51 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 182.3, 140.1, 135.2, 133.7, 132.9, 132.5, 132.3, 131.6, 130.0, 129.3, 128.7, 127.0, 126.9, 126.8, 125.4, 124.2, 123.9; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{11}OS$ [M + H]$^+$, 263.0531; found, 263.0521.

*2-Ethyl-9H-thioxanthene (**22b**).* Yellow wax; yield 42.0% (95 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46−7.42 (m, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.34−7.29 (m, 1H), 7.23−7.15 (m, 3H), 7.04 (dd, *J* = 7.9, 1.9 Hz, 1H), 3.84 (s, 2H), 2.64 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 143.1, 136.5, 136.4, 134.3, 130.7, 128.0, 127.7, 127.0, 126.9, 126.6, 126.6, 126.3, 39.4, 28.6, 15.9; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}S$ [M + H]$^+$, 227.0895; found, 227.0889.

*2-Ethyl-9H-thioxanthen-9-one (**22c**).* Yellow solid; yield 48.2% (115 mg); mp: 111−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, *J* = 9.5 Hz, 1H), 8.46 (s, 1H), 7.64−7.54 (m, 2H), 7.55−7.43 (m, 3H), 2.79 (q, *J* = 7.6 Hz, 2H), 1.32 (t, *J* = 7.7 Hz, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 180.2, 142.9, 137.6, 134.5, 132.8, 132.2, 130.0, 129.3, 129.2, 128.6, 126.2, 28.8, 15.6; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{13}OS$ [M + H]$^+$, 241.0687; found, 241.0677.

*2-Methoxy-9H-thioxanthene (**23b**).*[25] White solid; yield 39.3% (90 mg); mp: 104−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46−7.40 (m, 1H), 7.38−7.27 (m, 2H), 7.24−7.14 (m, 2H), 6.91 (d, *J* = 2.7 Hz, 1H), 6.76 (dd, *J* = 8.5, 2.7 Hz, 1H), 3.83 (s, 2H), 3.81 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.1, 138.1, 136.4, 134.7, 128.0, 127.8, 127.0, 126.6, 125.0, 114.0, 112.4, 55.6, 39.8; HRMS (ESI): *m*/*z* calcd for $C_{14}H_{13}OS$ [M + H]$^+$, 229.0687; found, 229.0670.

*2-Methoxy-9H-thioxanthen-9-one (**23c**).*[7] Pale white solid; yield 40.8% (99 mg); mp: 131−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (dd, *J* = 8.7, 0.9 Hz, 1H), 8.09 (d, *J* = 2.9 Hz, 1H), 7.65−7.56 (m, 2H), 7.53−7.43 (m, 2H), 7.30−7.26 (m, 1H), 3.95 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 179.9, 158.6, 137.7, 132.2, 130.4, 130.0, 129.3, 128.8, 127.5, 126.3, 126.2, 122.9, 110.5, 55.9; HRMS (ESI): *m*/*z* calcd for $C_{14}H_{11}O_2S$ [M + H]$^+$, 243.0474; found, 243.0478.

*2-Bromo-9H-thioxanthene (**24b**).* White solid; yield 41.5% (114 mg); mp: 103−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (s, 1H), 7.43 (dd, *J* = 7.0, 1.7 Hz, 1H), 7.34−7.16 (m, 5H), 3.82 (s, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 138.5, 135.5, 133.5, 133.3, 130.9, 129.6, 128.3, 128.2, 127.0, 126.9, 120.4, 39.0; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{10}SBr$ [M + H]$^+$, 276.9687; found, 276.9684.

*2-Bromo-9H-thioxanthen-9-one (**24c**).* Pale white solid; yield 45.0% (130 mg); mp: 165−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, *J* = 2.2 Hz, 1H), 8.61 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.72 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.68−7.61 (m, 1H), 7.61−7.55 (m, 1H), 7.53−7.48 (m, 1H), 7.47 (d, *J* = 8.6 Hz, 1H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 179.0, 137.0, 136.1, 135.4, 132.8, 132.6, 130.6, 130.2, 128.0, 127.7, 126.8, 126.2, 120.4; HRMS (ESI): *m*/*z* calcd for $C_{13}H_8OSBr$ [M + H]$^+$, 290.9479; found, 290.9462.

Telescoped Procedure for the Synthesis of Xanthene (1b). To a solution of corresponding substrate **1a** (198 mg, 1.0 mmol 1 equiv.) in DCM (5 mL) was added $TiCl_4$ (1 M solution in DCM, 4 mL, 4 equiv.) at room temperature, and the mixture was stirred at room temperature for 24 h, then with added Et_3SiH (465 mg, 4.0 mmol, 4 equiv.) for another 12 h. The reaction was quenched by the addition of H_2O (10 mL), then was extracted three times with DCM (20 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (PE/EA = 10:1) to afford the desired product **1b** (155 mg, 85%).

Procedure for the Synthesis of Xanthone (1c). To a solution of corresponding substrate **1a** (198 mg, 1.0 mmol, 1 equiv.) in DCM (5 mL) was added $TiCl_4$ (1 M solution in DCM, 4 mL, 4 equiv.) at room temperature, and the mixture was stirred at room temperature for 24 h. The reaction was quenched by the addition of H_2O (10 mL), then was extracted three times with DCM (20 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude products were treated to acetonitrile (5 mL), which dissolved H_5IO_6 (399 mg, 1.75 mmol, 1.75 equiv.) and CrO_3 (2.5 mg, 0.025 mmol, equiv. 2.5%) for 1 h. The residue was extracted with DCM (20 mL) three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (PE/EA = 10:1) to afford the desired product **1c** (168 mg, 86%).

Procedure for the Synthesis of Pranoprofen. *Ethyl 2-(4-((3-Formylpyridin-2-yl)oxy)phenyl)propanoate (**25**).* To a solution of 2-fluoronicotinaldehyde (309 mg, 2.47 mmol, 1 equiv.) and ethyl 2-(4-hydroxyphenyl)propanoate (400 mg, 2.06 mmol, 1.2 equiv.) in 4 mL of DMF, K_2CO_3 (284 mg, 2.06 mmol, 1 equiv.) was added. The mixture was heating at 100 °C for 2 h (oil bath). After cooling to room temperature, water was added to the reaction mixture and extracted with AcOEt. The combined organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel flash column chromatography (PE/EA = 10:1) to afford **25** (566 mg, 92%).

Oil; yield 92.0% (566 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (dd, *J* = 4.6, 1.6 Hz, 1H), 8.25 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.22−7.03 (m, 3H), 4.24−4.01 (m, 2H), 3.75 (q, *J* = 7.1 Hz, 1H), 1.54 (t, *J* = 11.6 Hz, 4H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 188.8, 174.4, 164.0, 153.1, 152.1, 138.2, 137.6, 128.9, 121.5, 119.6, 119.1, 60.8, 45.0, 18.7, 14.1; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{18}O_4N$ [M + H]$^+$, 300.1230; found, 300.1227.

*Ethyl 2-(5H-Chromeno[2,3-b]pyridin-7-yl)propanoate (**26**).*[12] To a solution of **25** (500 mg, 1.67 mmol, 1 equiv.) in DCM (5 mL) was added $TiCl_4$ (1 M solution in DCM, 6.69 mL, 4 equiv.) at room temperature, and the mixture was stirred at room temperature for 24 h, then with added Et_3SiH (1.07 mL, 6.69 mmol, 4 equiv.) for another 3 h. The reaction was quenched by the addition of H_2O (10 mL), then was extracted three times with DCM (20 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (PE/EA = 10:1) to afford **26** (335 mg, 71%).

Oil; yield 92.0% (335 mg); ^{1}H NMR (400 MHz, CD_3OD): δ 8.09 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.80−7.69 (m, 1H), 7.24−7.13 (m, 3H), 7.05 (d, *J* = 9.1 Hz, 1H), 4.22−4.02 (m, 4H), 3.73 (q, *J* = 7.1 Hz, 1H), 1.49−1.42 (m, 3H), 1.22−1.15 (m, 3H); ^{13}C {^{1}H} NMR (150 MHz, CD_3OD): δ 176.2, 159.6, 151.8, 146.9, 140.8, 138.1, 129.0, 128.3, 121.5, 121.3, 117.8, 117.7, 62.0, 28.6, 19.0, 14.5; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{18}O_3N$ [M + H]$^+$, 284.1281; found, 284.1281.

Pranoprofen.[12] Compound **26** (320 mg, 1.13 mmol, 1 equiv.) was diluted with THF/H_2O = 3:1 (v/v) (4 mL); then, LiOH (135 mg, 5.56 mmol, 5 equiv.) was added, and the reaction was stirred at room temperature for 3 h. Then, water was added to the reaction mixture and extracted with CH_2Cl_2. The combined organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel flash column chromatography (PE/EA = 5:1−1:1) to afford pranoprofen (259 mg, 90%).

https://dx.doi.org/10.1021/acs.joc.0c02694
J. Org. Chem. 2021, 86, 3334−3343

White solid; yield 90.0% (259 mg); mp: 180−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25−8.14 (m, 1H), 7.61−7.49 (m, 1H), 7.18 (dd, J = 8.4, 2.2 Hz, 1H), 7.12 (dd, J = 10.3, 5.2 Hz, 2H), 7.04 (dd, J = 7.4, 4.9 Hz, 1H), 4.09 (s, 2H), 3.85−3.60 (m, 1H), 1.51 (d, J = 7.2 Hz, 3H); ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 179.3, 158.3, 150.9, 146.5, 138.6, 135.4, 127.6, 127.4, 119.9, 119.7, 117.4, 115.4, 44.6, 28.1, 18.3; HRMS (ESI): m/z calcd for $C_{15}H_{14}O_3N$ $[M + H]^+$, 256.0968; found, 256.0966.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02694.

^{1}H and ^{13}C spectra of all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Qiong Xiao − *Department of Medicinal Chemistry, State Key Laboratory of Bioactive Substance and Function of Natural Medicines & Beijing Key Laboratory of Active Substances Discovery and Drugability Evaluation, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, China*; orcid.org/0000-0001-7881-1362; Email: xiaoqiong@imm.ac.cn

Authors

Zeyu Shi − *Department of Medicinal Chemistry, State Key Laboratory of Bioactive Substance and Function of Natural Medicines & Beijing Key Laboratory of Active Substances Discovery and Drugability Evaluation, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, China*

Si Chen − *Department of Medicinal Chemistry, State Key Laboratory of Bioactive Substance and Function of Natural Medicines & Beijing Key Laboratory of Active Substances Discovery and Drugability Evaluation, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, China*

Dali Yin − *Department of Medicinal Chemistry, State Key Laboratory of Bioactive Substance and Function of Natural Medicines & Beijing Key Laboratory of Active Substances Discovery and Drugability Evaluation, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02694

Author Contributions

†Z.Y.S. and S.C. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the National Key R&D Program of China (no. 2018YFC1706403), Drug Innovation Major Project (no. 2018ZX09711-001-005, China), CAMS Innovation Fund for Medical Sciences (no. 2017-I2M-2-004, China), and Disciplines Construction Project (no. 201920200802, China).

■ REFERENCES

(1) (a) Wezeman, T.; Bräse, S.; Masters, K.-S. Xanthone dimers: A compound family which is both common and privileged. *Nat. Prod. Rep.* **2015**, *32*, 6−28. (b) Preres, V.; Nagem, T. J.; de Oliveira, F. F. Tetraoxygenated naturally occurring xanthones. *Phytochemistry* **2000**, *55*, 683−710.

(2) (a) Franklin, G.; Conceição, L. F. R.; Kombrink, E.; Dias, A. C. P. Xanthone biosynthesis in Hypericum perforatum cells provides antioxidant and antimicrobial protection upon biotic stress. *Phytochemistry* **2009**, *70*, 60−68. (b) Tanaka, N.; Kashiwada, Y.; Kim, S.-Y.; Sekiya, M.; Ikeshiro, Y.; Takaishi, Y. Xanthones from Hypericum chinense and their cytotoxicity evaluation. *Phytochemistry* **2009**, *70*, 1456−1461. (c) Ryu, H. W.; Curtis-Long, M. J.; Jung, S.; Jin, Y. M.; Cho, J. K.; Ryu, Y. B.; Lee, W. S.; Park, K. H. Xanthones with neuraminidase inhibitory activity from the seedcases of Garcinia mangostana. *Bioorg. Med. Chem.* **2010**, *18*, 6258−6264. (d) Carr, A. A.; Grunwell, F. J.; Sill, D. A.; Donald, R. M.; William, S. F.; Joseph, S. B.; Martin, G. J.; Robert, W. F.; Gerald, D. M. Bis-basic-substituted polycyclic aromatic compounds. A new class of antiviral agents. 7. bisalkamine esters of 9-oxoxanthene-2, 7-dicarboxylic acid, 3, 6-bis-basic ethers of xanthen-9-one, and 2, 7-bis (aminoacyl) xanthen-9-ones,-xanthenes, and-thioxanthenes. *J. Med. Chem.* **1976**, *19*, 1142−1148.

(3) (a) Sousa, M.; Pinto, M. Synthesis of xanthones: an overview. *Curr. Med. Chem.* **2005**, *12*, 2447−2479. (b) Resende, D. I. S. P.; Durães, F.; Maia, M.; Sousa, E.; Pinto, M. M. M. Recent advances in the synthesis of xanthones and azaxanthones. *Org. Chem. Front.* **2020**, *7*, 3027−3066.

(4) (a) Davies, J. S. H.; Lamb, F.; Suschitzky, H. 367. Studies in the xanthone series. Part II. preparation and reactions of 1-formyl-2-hydroxyxanthone. *J. Chem. Soc.* **1958**, 1790−1793. (b) Gobbi, S.; Rampa, A.; Bisi, A.; Belluti, F.; Valenti, P.; Caputo, A.; Zampiron, A.; Carrara, M. Synthesis and antitumor activity of new derivatives of xanthen-9-one-4-acetic acid. *J. Med. Chem.* **2002**, *45*, 4931−4939.

(5) Zhang, H.; Shi, R.; Gan, P.; Liu, C.; Ding, A.; Wang, Q.; Lei, A. Palladium-catalyzed oxidative double C-H functionalization/carbonylation for the synthesis of xanthones. *Angew. Chem., Int. Ed.* **2012**, *51*, 5204−5207.

(6) (a) Wertz, S.; Leifert, D.; Studer, A. Cross dehydrogenative coupling via base-promoted homolytic aromatic substitution (BHAS): synthesis of fluorenones and xanthones. *Org. Lett.* **2013**, *15*, 928−931. (b) Wang, P.; Rao, H.; Hua, R.; Li, C.-J. Rhodium-catalyzed xanthone formation from 2-aryloxybenzaldehydes via cross-dehydrogenative coupling (CDC). *Org. Lett.* **2012**, *14*, 902−905.

(7) Rao, H.; Ma, X.; Liu, Q.; Li, Z.; Cao, S.; Li, C.-J. Metal-free oxidative coupling: xanthone formation via direct annulation of 2-aryloxybenzaldehyde using tetrabutylammonium bromide as a promoter in aqueous medium. *Adv. Synth. Catal.* **2013**, *355*, 2191−2196.

(8) Verma, S. K.; Prajapati, A.; Saini, M. K.; Basak, A. K. Lewis acid catalyzed reductive cyclization of 2-aryloxybenzaldehydes and 2-(arylthio)benzaldehydes to unsubstituted 9H-xanthenes and thioxanthenes in diisopropyl ether. *Adv. Synth. Catal.* **2020**, DOI: 10.1002/adsc.202000836.

(9) Yamazaki, S. Chromium (VI) oxide-catalyzed benzylic oxidation with periodic acid. *Org. Lett.* **1999**, *1*, 2129−2132.

(10) Shi, Z.; Xiao, Q.; Yin, D. Synthesis of tetrahydroisoquinolines through $TiCl_4$-mediated cyclization and Et_3SiH reduction. *Chin. Chem. Lett.* **2020**, *31*, 729−732.

(11) Abrego, G.; Alvarado, H.; Souto, E. B.; Guevara, B.; Bellowa, L. H.; Parra, A.; Calpena, A.; Garcia, M. L. Biopharmaceutical profile of pranoprofen-loaded PLGA nanoparticles containing hydrogels for ocular administration. *Eur. J. Pharm. Biopharm.* **2015**, *95*, 261−270.

(12) (a) Li, Q.; Li, J.; Wang, S. Synthetic method for pranoprofen. CN 103864804 A, 2014. (b) Deng, J.; Ye, Q.; Luo, R.; Huang, C.; Xiong, W.; Tan, Z. A kind of preparation method of new pranoprofen. CN 109942589 A, 2019.

(13) Sai, M. An efficient $Ga(OTf)_3$/isopropanol catalytic system for direct reduction of benzylic alcohols. *Adv. Synth. Catal.* **2018**, *360*, 4330−4335.

(14) Tang, J.; Zhao, S.; Wei, Y.; Quan, Z.; Huo, C. CBr_4 promoted intramolecular aerobic oxidative dehydrogenative arylation of

aldehydes: application in the synthesis of xanthones and fluorenones. *Org. Biomol. Chem.* **2017**, *15*, 1589−1592.
(15) Han, Y.; Barany, G. Novel S-xanthenyl protecting groups for cysteine and their applications for the N^{α}-9-fluorenylmethyloxycarbonyl (Fmoc) strategy of peptide synthesis [1-3]. *J. Org. Chem.* **1997**, *62*, 3841−3848.
(16) Böss, E.; Hillringhaus, T.; Nitsch, J.; Klussmann, M. Lewis acid-catalysed one pot synthesis of substituted xanthenes. *Org. Biomol. Chem.* **2011**, *9*, 1744−1748.
(17) JOJIMA, T.; TAKESHIBA, H.; KINOTO, T. Pyridazines. III. intramolecular cycloaddition of 3-substituted-6-(2-allylphenoxy) pyridazines. *Chem. Pharm. Bull.* **1976**, *24*, 1588−1595.
(18) Zhou, K.; Yu, Y.; Lin, Y.-M.; Gong, L. Copper-catalyzed aerobic asymmetric cross- dehydrogenative coupling of $C(sp^3)$−H bonds driven by visible light. *Green Chem.* **2020**, *22*, 4597−4603.
(19) Bao, H.; Hu, X.; Zhang, J.; Liu, Y. Cu(0)/Selectfluor system-catalyzed intramolecular Csp^2-H/Csp^2-H cross-dehydrogenative coupling (CDC). *Tetrahedron* **2019**, *75*, 130533.
(20) Yates, P.; Bichan, D. J. Bridged xanthenes. I. an intermolecular cycloaddition route. *Can. J. Chem.* **1975**, *53*, 2045−2053.
(21) Hu, J.; Adogla, E. A.; Ju, Y.; Fan, D.; Wang, Q. Copper-catalyzed ortho-acylation of phenols with aryl aldehydes and its application in one-step preparation of xanthones. *Chem. Commun.* **2012**, *48*, 11256−11258.
(22) Wang, M.; Fan, Q.; Jiang, X. Transition-metal-free diarylannulated sulfide and selenide construction via radical/anion-mediated sulfur-iodine and selenium-iodine exchange. *Org. Lett.* **2016**, *18*, 5756−5759.
(23) Shen, Z.; Pan, D.; Wang, Y.; Li, M.; Hu, X.; Sun, N.; Jin, L.; Hu, B. Visible-light-induced aerobic oxidation of benzylic $C(sp^3)$-H of alkylarenes promoted by DDQ, tert-butyl nitrite, and acetic acid. *Synlett* **2019**, *30*, 218−224.
(24) Wang, M.; Wei, J.; Fan, Q.; Jiang, X. Cu(II)-catalyzed sulfide construction: both aryl groups utilization of intermolecular and intramolecular diaryliodonium salt. *Chem. Commun.* **2017**, *53*, 2918−2921.
(25) Bhanuchandra, M.; Yorimitsu, H.; Osuka, A. Synthesis of spirocyclic diarylfluorenes by one-pot twofold SNAr reactions of diaryl sulfones with diarylmethanes. *Org. Lett.* **2016**, *18*, 384−387.

https://dx.doi.org/10.1021/acs.joc.0c02694
J. Org. Chem. 2021, 86, 3334−3343