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Intramolecular Friedel–Crafts Reaction with Trifluoroacetic Acid: Synthesizing Some New Functionalized 9-Aryl/Alkyl Thioxanthenes

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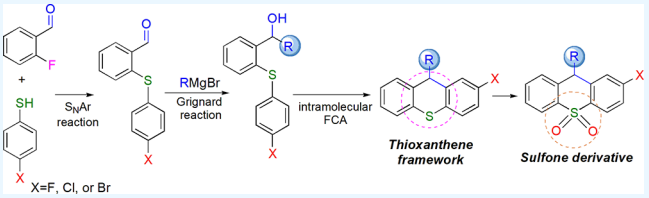
ABSTRACT: In this study, a series of halogen-substituted thioxanthenes were synthesized because the most important and biologically active derivatives of xanthenes are thioxanthenes. In order to obtain new thioxanthene derivatives, first, the starting molecules were synthesized by the appropriate reaction methods in two steps. The intramolecular Friedel–Crafts alkylation (FCA) method was used to convert the prepared three aromatic substituted starting alcohol compounds to their corresponding thioxanthenes by cyclization. For the intramolecular FCA reaction of secondary alcohols, which are the starting compounds (**1a–1t**), organic Brønsted acids, which require more innovative, easier, and suitable reaction conditions, were used instead of halide reagents with corrosive effects as classical FCA catalysts. Trifluoroacetic acid was determined to be the organocatalyst with the best yield. Therefore, some original 9-aryl/alkyl thioxanthene derivatives (**2a–2t**) were synthesized using the optimized FCA method. In addition, a new sulfone derivative of thioxanthene **3i** was prepared by performing the oxidation reaction with one of the obtained new thioxanthene **2i**. Thioxanthenes and their derivatives are important heterocyclic structures that contain pharmacologically valuable sulfur and are used in the treatment of psychotic diseases such as Alzheimer's or schizophrenia, as well as a number of potent biological activities.



INTRODUCTION

The synthesis of xanthenes, especially thioxanthenes, has increased remarkably in recent years due to their wide range of biological and pharmacological properties. As an example of its biological and pharmacological properties, anticancer,[1−4] antitumor,[5−7] antiviral,[8] antimicrobial,[9−11] antibacterial,[12−15] and anti-inflammatory[16] activities can be cited. Moreover, some types are also used as materials in dye technology,[17,18] sensor,[19,20] and organic light-emitting diodes (OLEDs)[21−25] due to the conjugation and heteroring in their structures, ensuring optical and electrochemical properties. In addition to these activities, the most noticeable biological activities of thioxanthenes are their use as drugs in many neurological diseases.[26−31]

Thioxanthene-class drugs are effective in the systematic treatment of psychoses. They are effectively used in the treatment of schizophrenia, organic psychoses, and other idiopathic psychotic diseases.[32] The use of such drugs is very useful in the treatment of patients with severe depression, psychotic features, and organic psychotic disorders. The most important thioxanthene derivative drugs (Figure 1) used as medicine are zuclopenthixol,[33−35] its cis-isomer clopenthixol,[36,37] flupentixol,[11,38,39] chlorprothixen,[12,40] and thiothixene.[3,41,42] However, these drugs have other clinically useful properties such as antiemetic, antinausea, and antihistamine effects, as well as the ability to potentiate analgesics, sedatives, and general anesthetic actions.[43] In addition, some plants, including thioxanthene derivatives, are also traditional drugs

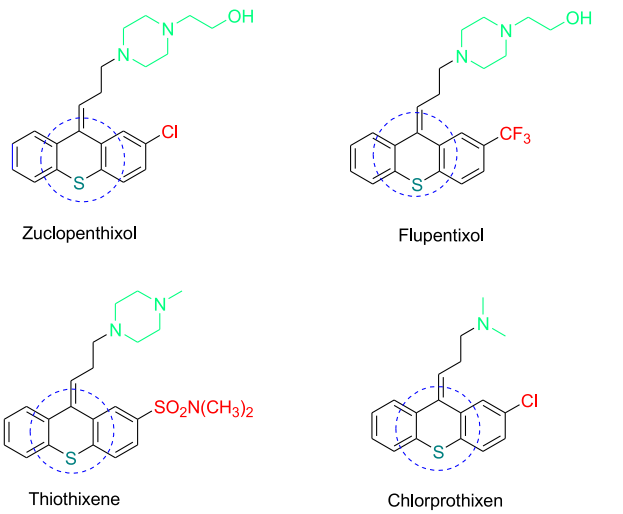


Figure 1. Structures of some thioxanthene derivative drugs used in the treatment of neurological diseases.

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used in the treatment of common diseases, such as coryza, fever, diarrhea, ulcers, stomachaches, and itching.[44]

The most common method involves the reduction of thioxanthone derivatives.[45,46] Thioxanthones are traditionally made by condensing thiosalicylic acids with benzene derivatives, then cycling the resulting thioether in the presence of sulfuric acid, phosphoric acid, or Lewis acids like $AlCl_3$.[47] However, these conventional techniques have not been favored in recent years due to the low yields obtained with the use of sulfuric acid, the absence of regioselectivity, and the lengthy reaction durations. In the recent years, many acid-catalyzed cyclization methods have been developed by organic chemists to form new functionalized aromatic and heteroaromatic skeletons.[48−51] Due to their novel and useful structure, many methods have been developed in recent years for the synthesis of thioxanthenes.[52] Cross-coupling between an aromatic thioether and an aryl halide in the presence of transition metal catalysts, such as Pd or Cu, and subsequent cyclization is another method for obtaining thioxanthenes.[53,54] The Friedel−Crafts reactions and the addition of Grignard reagents to carbonyl compounds followed by intramolecular cyclization are two more intriguing ways to access these frameworks.[55−59]

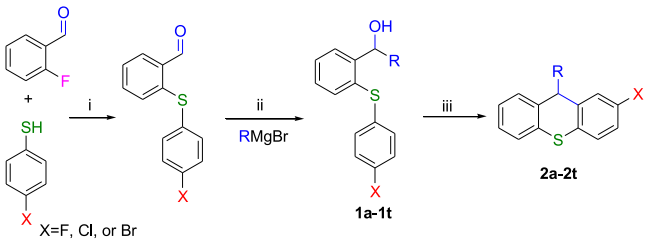
In this study, the synthesis of halogen-substituted 9-aryl/alkyl thioxanthene compounds was accomplished for the first time. For this purpose, first, starting compounds in structures suitable for ring closure were synthesized. The synthesis of the starting materials was carried out in two steps. First, nucleophilic aromatic substitution (S_NAr) reactions of 2-fluorobenzaldehyde with different thiophenol compounds were carried out. Then, by addition of aryl or alkyl magnesium bromide compounds to the aldehyde group in the obtained binding molecules, new secondary alcohols were synthesized (**1a−1t**). Of the 20 starting compounds synthesized, 14 were original. Then, the syntheses of the original 9-aryl/alkyl thioxanthenes were made by the intramolecular FCA method of the starting compound secondary alcohols prepared for our purpose. This method was previously developed by us[60] and has been reoptimized in this study and adapted to the synthesis of specific 9-aryl/alkyl thioxanthenes with halogen linked, especially at their second carbon. The reason for this is that the yields of halogen-substituted thioxanthenes in our previously developed method are lower than other derivatives. After the optimization experiments carried out in this work, it was observed that higher yields were obtained when trifluoroacetic acid (TFA) was used as a catalyst and dichloromethane (DCM) was used as a solvent. In addition, groups such as cyanobenzene, thiophene, and pyridine, which were not previously included in the thioxanthene ring and thought to increase the biological properties of the compounds, were added to the ring as the aryl group. The reason halogens are preferred as substituents is to allow very different groups to be attached to the thioxanthene ring by using halogens.

As a result, 19 thioxanthene derivatives (**2a−2t**) were synthesized by the intramolecular FCA method using TFA as a catalyst in this study. Four of these compounds (**2b**, **2c**, **2d**, and **2e**) were synthesized in our previous study;[60] their yields were further increased in this work. The other 15 compounds were synthesized for the first time, and their structures were elucidated by spectroscopic methods. Moreover, in this study, thioxanthene **2i** was also oxidized and converted into a sulfone derivative (**3i**). Cyclic sulfoxides and sulfones are important pharmacophores with a wide range of pharmacological activities due to their various mechanisms of action.[61,62]

RESULTS AND DISCUSSION

Initially, using a metal-free nucleophilic aromatic substitution (S_NAr) reaction[58,60,63−66] and a Grignard reaction, we synthesized starting chemicals in two steps (Scheme 1).

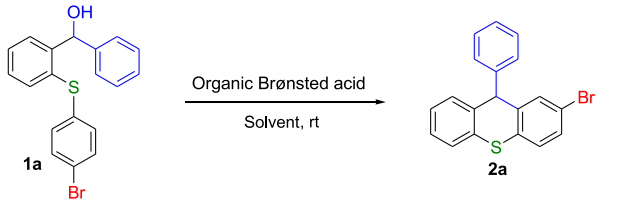
Scheme 1. (i) S_NAr Reaction; (ii) Grignard Reaction; and (iii) Intramolecular FCA



Then, with good yields (95−100%), we produced the required diaryl secondary alcohols with a thioether group as reagents (**1a−1t**). Since most of the synthesized starting compounds (between **1f** and **1t**) were original and synthesized for the first time, the structures were elucidated by spectroscopic methods. While the synthesis of **1b**, **1c**, **1d**, and **1e** was obtained in our previous study,[60] **1a** was synthesized in another study.[67]

Then, suitable reaction conditions were determined to synthesize new halogenated thioxanthene derivatives via the intramolecular FCA reaction using organocatalysts. In order to obtain the best yield, some organic Bronsted acid catalysts and solvents were tested for intramolecular FCA of a halogen-substituted secondary aryl alcohol compound **1a**. As organic Bronsted acids, N-triphyllylphosphoramide (NTPA), TFA, *p*-toluenesulfonic acid (p-TSA), and diphenyl hydrogen phosphate (DPP) were tested, as shown in Table 1.

Table 1. Comparison of Catalysts and Solvents for the Intramolecular FCA Reaction of 1a[a]



entry	catalyst	solvent	time (h)	conv. (%)[b]
1	TFA	THF	24	70
2	NTPA	THF	24	65
3	DPP	THF	24	0
4	*p*-TSA	THF	24	25
5	TFA	MeOH	24	5
6	TFA	EtAc	24	20
7	TFA	toluene	24	51
8	TFA	DMF	24	4
9	TFA	$CHCl_3$	24	38
10	TFA	DCM	24	80
11	TFA	MeCN	24	70
12	TFA	DCM	3	85
13	**TFA**	**DCM**	**12**	**92**

[a]Condition: **1a** (0.1 mmol) and organic Brønsted acid (10% equiv) in solvent (2.5 mL) were stirred at room temperature. [b]The % conversions were determined by GC−MS.

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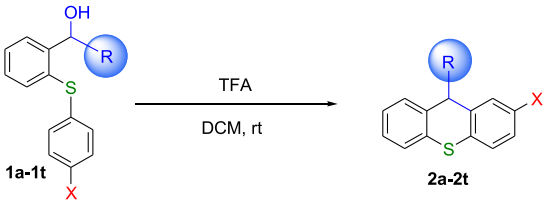
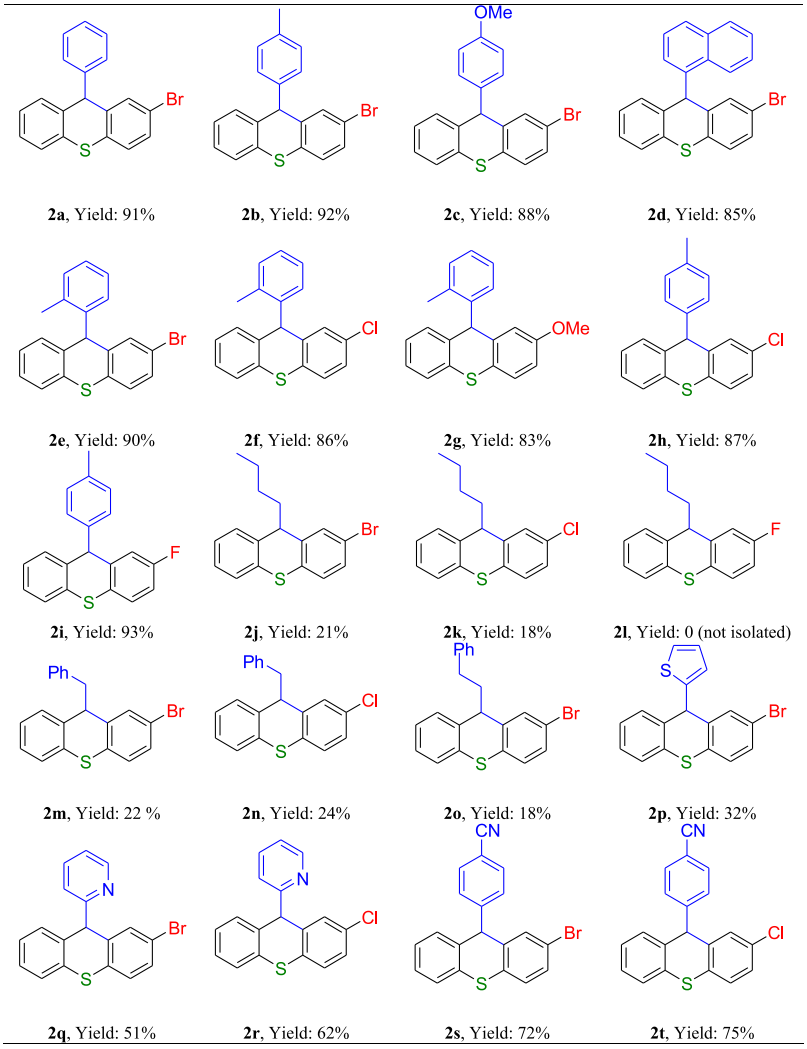
Table 2. Structures and Yields of New Thioxanthenes Synthesized by Intramolecular FCA Reaction[a,b]





[a]Condition: compound **1a−1t** (0.1 mmol) and TFA (10% mmol) in DCM (2.5 mL) were stirred at room temperature. [b]The % yields of isolated products.

In reactions with acid catalysts, samples were taken at certain times, and their conversions were determined by GC−MS (Table 1). According to these results, it was observed that the best yield was obtained with TFA after 24 h (entry 1). After the determination of TFA as the best catalyst, various solvents were tested for the FCA method (entries 5−13).

In the solvent research, it was determined that the solvent with the highest yield was DCM. Then, the reaction time and the amount of catalyst were tested using the best solvent and catalyst. Considering the reaction times, it was observed that 92% yield was obtained with DCM after 12 h (Table 1, entry 13). Different equivalents of the catalyst were tested, but the best yield was obtained when 0.10 equiv of catalyst was used.

Due to the deactivating effects of halogen groups, it causes low yields in the intramolecular FCA reaction. However, as a result of the optimization studies, medium to high yields were obtained, even in halogen-substituted compounds (Table 2). Many new 9-aryl/alkyl thioxanthene syntheses have been achieved by using different substituents with the method we developed, which takes place under easy conditions and does not require expensive and corrosive catalysts such as transition metals.

Different aromatic and aliphatic groups, indicated by R, were added to halogen-containing thioether compounds by the Grignard reaction, and starting compounds with different structures, most of which were original, were obtained (Scheme 1). Thus, we also examined the effect of groups such as aryl, alkyl, heteroaryl, and benzyl represented by R on the cyclization reaction. Looking at the results (Table 2), high yields were obtained with phenyl, methyl, and methoxy

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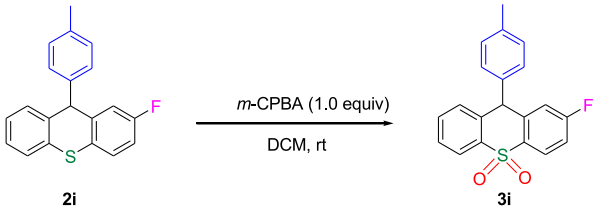
substituted phenyl and naphthyl groups (**1a**−**1i**), as expected. However, lower yields were obtained with heteroaromatic, alkyl, and cyano-substituted phenyl groups. Among them, very low yields were observed in the intramolecular FCA reaction of the compounds to which butyl (**1j** and **1k**), benzyl (**1m** and **1n**), and Ph−CH_2CH_2− (**1o**) groups were attached, while no products could be isolated with **1l**. This is due to the rearrangement of the carbocation formed during the reaction as an intermediate and the formation of byproducts. While low yields were obtained with the thiophene-bonded substrate from the heteroaryl groups (**2p**), average yields were provided with the pyridine substrates (**1q** and **1r**). Average yields were also obtained with **1s** and **1t** containing cyano, an electron withdrawing group.

In this study, to demonstrate that thioxanthenes (**2i**) can be converted into different and useful derivatives, one of the synthesized thioxanthenes was oxidized to a sulfone derivative using *meta*-chloro peroxy benzoic acid (*m*-CPBA). This derivatization reaction is shown in Scheme 2.

Scheme 2. Thioxanthene Derivatization Reaction



CONCLUSIONS

In this research, a novel set of thioxanthene derivatives substituted with halogens at the 9-aryl/alkyl position was synthesized. These compounds exhibit a high likelihood of belonging to the class of thioxanthenes, known for their effectiveness in treating schizophrenia, organic psychoses, and other idiopathic psychotic disorders. The synthesis of 2-halo-9-aryl/alkyl thioxanthene derivatives employed a reoptimized version of a previously developed method. Initially, starting compounds with a new functionalized alcohol structure conducive to cyclization were synthesized. Subsequently, the obtained starting alcohols (**1a**−**1t**) were transformed into novel thioxanthene derivatives through an optimized intramolecular Friedel−Crafts alkylation (FCA). In this way, the synthesis of new halogen-substituted thioxanthenes (**2a**−**2t**) with high yields was achieved using TFA as an organocatalyst under mild conditions. Besides, we demonstrated that thioxanthenes can be turned into useful sulfone derivatives.

Halogenated thioxanthenes have potential applications in drug synthesis, particularly as amine analogs of thioxanthenes like zuclopenthixol and chlorprotixen. These drugs are commonly used to treat various psychoses, with a focus on schizophrenia and Alzheimer's disease. Future research may explore the attachment of new groups to thioxanthenes using halogen groups, aiming to introduce novel functionalities that enhance their biological activity and address gaps identified in the existing literature.

EXPERIMENTAL SECTION

General Information. The majority of the chemicals used in this work were commercially available from Merck or Aldrich. The starting carbinols **1a**−**1t** were prepared by the coupling reaction of 2-fluorobenzaldehyde and substituted thiophenols and then the Grignard reaction of 2-thioether-benzaldehydes and some arylmagnesium bromides. All substrates were purified by crystallization or column chromatography and were characterized by IR, ^{1}H NMR, ^{13}C NMR, elemental analysis, and GC−MS. All novel products were characterized by IR, ^{1}H NMR, ^{13}C NMR, elemental analysis, and GC−MS. The reactions were monitored by TLC using silica gel plates, and the products were purified by flash column chromatography on silica gel (Merck; 230−400 mesh), eluting with hexane-ethyl acetate (v/v 9:1). NMR spectra were recorded at 500 MHz for ^{1}H and 125 MHz for ^{13}C using Me_4Si as the internal standard in $CDCl_3$. GC−MS were recorded on a Shimadzu/QP2010 Plus. IR spectra were recorded on a Bruker Vertex 70 IR spectrometer.

General Procedure for Intramolecular FCA. To a stirred solution of a starting alcohol compound (**1a**−**1t**) (0.1 mmol) in dry DCM (2.5 mL) was added TFA (10 mol %) at room temperature, and the reaction was stirred until the spot of the starting compound disappeared in TLC (12−24 h). After the completion of the reaction, the mixture was concentrated in a vacuum and extracted with ethyl acetate. The product was charged on silica gel after the usual reaction workup and concentration.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c07150.

Experimental details, general procedures, experimental characterization data (IR, NMR, MS, and elemental analysis), and spectra of ^{1}H, ^{13}C nuclear magnetic resonance of all products (PDF)

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Notes

The authors declare no competing financial interest.

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