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Synthesis of new thioxanthenes by organocatalytic intramolecular Friedel–Crafts reaction

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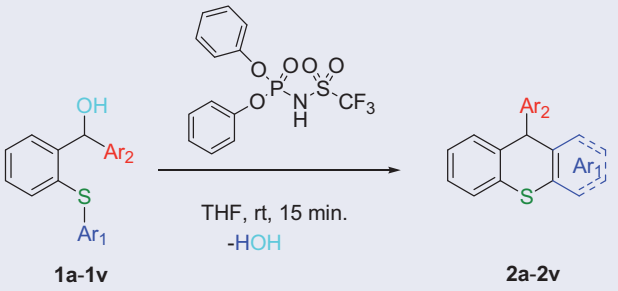
ABSTRACT

An efficient organocatalytic route has been developed to synthesize novel substituted thioxanthenes (**2a**–**2v**) starting from diaryl thioether alcohols (**1a**–**1v**) using the intramolecular Friedel–Crafts reaction. The starting materials were obtained in two stages via a coupling reaction followed by the Grignard reaction. In this study, we tried for the first time to use some organic Brønsted acids as organocatalysts (**3a**–**3h**) in the intramolecular Friedel–Crafts cyclization reaction of thioether alcohols. The synthesis of original substituted thioxanthenes was achieved within 15 minutes by using *N*-triflylphosphoramide (**3h**) with quantitative yields in THF at room temperature.

GRAPHICAL ABSTRACT



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Brønsted acid catalyst; Friedel–Crafts reaction; intramolecular cyclization; N-triflylphosphoramide; thioxanthenes

Introduction

Thioxanthenes are a significant part of diarylannulated heterocycles, in which the oxygen atom in xanthene is replaced by a sulfur atom. Thioxanthene compounds and their derivatives have valuable biological properties, such as antiparasitic,[1] anti-cancer[2] and antitumor,[3] antimicrobial,[4] anti-inflammatory, and antioxidant activities.[5] In addition to these important properties, these substances are used in the development of neuroleptic and antidepressive drugs. These compounds are utilized in a broad spectrum

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of applications in medicinal chemistry. For example, they are antipsychotic drugs which are used in the treatment of schizophrenia and other psychotic disorders.[6] This type of drugs has also other valuable effects, such as antihistaminic, anesthetic, antinausea, and antiemetic activities.[7] Moreover, these compounds, found in certain plants, are also conventional medicines used in the treatment of common conditions, such as fever, colds, ulcers, diarrhea, itching, and abdominal illnesses.[8]

Several methods for synthesis of thioxanthene derivatives have been reported. The most conventional approach based on the synthesis of the thioxanthone derivatives and their reduction.[8,9] The classical way of synthesis of thioxanthones is through the condensation of thiosalicylic acids with benzene derivatives, followed by cyclization of the formed thioether in the presence of sulfuric acid,[10] phosphoric acid,[11] or Lewis acids such as $AlCl_3$.[3b] However, due to the low yields obtained after the use of sulphuric acid, the lack of regioselectivity, and the long reaction times, these traditional methods have not been preferred in recent years.

A different route to obtain thioxanthenes is cross-coupling between an aromatic thioether and aryl halide in the presence of transition metal catalysts, such as Pd or Cu, and subsequent cyclization.[12] The intramolecular cyclization of biaryls, including ortho-substituted sulfur-containing functional groups, has been reported as another pathway for the synthesis of thioxanthenes.[13]

Recently, we reported obtaining 9-arylxanthenes through intramolecular Friedel–Crafts alkylation (FCA) of appropriate alcohols *via* the use of an organocatalyst.[14] It is noteworthy that the route based on arylation using an FCA protocol has recently demonstrated new developments. In particular, arylation that does not use any metals has attracted considerable research interest due to its potential to prevent the disadvantages of organometallic chemistry, including the high cost, application of toxic materials, and difficult purification.[15] These novel methods have significant advantages, such as using moderate reaction conditions and inexpensive and less poisonous catalysts.[16] Alcohols have recently been reported to be exceedingly useful reagents that can be utilized in Friedel–Crafts alkylation in contrast to organohalides, which are more toxic and require harsh conditions.[17] To the best of our knowledge, Panda et al. are the only research group that used an intramolecular FCA procedure to synthesize some substituted 9-arylthioxanthenes *via* Lewis acid ($FeCl_3$)-catalysis.[18]

Although hydroarylation reaction of activated alkenes using FCA was previously employed with certain Brønsted acids, such as diphenyl hydrogen phosphate as a catalyst,[19] no report exists of intramolecular FCA using organic Brønsted acids as a catalyst instead of Lewis acids except our newly published work.[14] According to recent studies, non-chiral, organic Brønsted acids are better than Lewis or inorganic Brønsted acids.[20] Recently, new Brønsted acids containing $-NSO_2CF_3$ or $-NSO_2F$ groups were synthesized to form a new catalyst species named super-acid. These groups, especially the triflate groups, significantly increased acidity.[21] Because *N*-triflate groups have lower pK_a values compared to natural organic acids, more acidic *N*-triflate groups can catalyze reactions leading to a generally higher yield in a shorter time.[22] More specifically, *N*-triflylphosphoramide (**3h**) (Fig. 1) was used as an organic Brønsted acid as described in previous reports.[23]

In this work, due to the crucial importance of thioxanthenes as biologically active compounds, we applied our organocatalytic method for the synthesis of novel

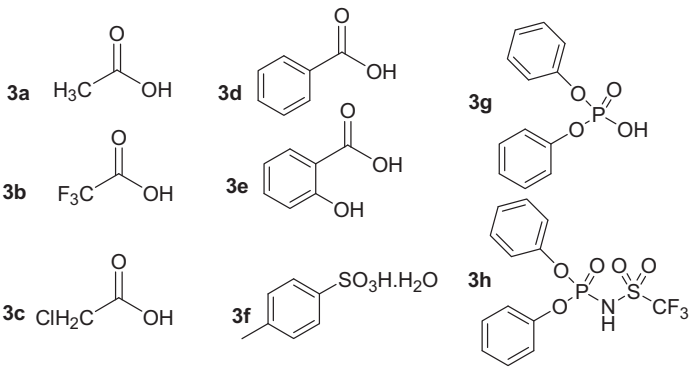


Figure 1. Organic Brønsted acids used for intramolecular FCA.

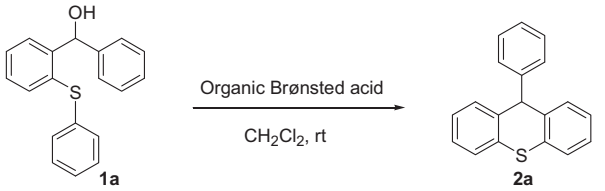
thioxanthenes. For this purpose, we modified the technique through new optimization studies and determined the best reaction conditions for intramolecular cyclization of thioxanthenes. Importantly, using *N*-triflylphosphoramide (**3h**), we synthesized sixteen original 9-arylthioxanthenes (**2b**, **2c**, **2e**, **2f**, **2i**, and **2k**–**2v**) with excellent yields.

Based on our previous findings, we first synthesized starting compounds in two steps through a metal-free coupling reaction[24] and Grignard reaction. Then, we obtained the desired diaryl alcohols containing a thioether group as reagents (**1a**–**1v**) with excellent yields (95%–100%). All starting materials synthesized in this study are also novel except **1a**, **1g**, and **1j**.

Thioether alcohol **1a** was used for intramolecular FCA, and different acid catalysts were examined as initial optimization tests. Next, certain organic Brønsted acids were investigated as catalysts for the intramolecular FCA reaction of **1a.** Specifically, acetic acid (**3a**), trifluoroacetic acid (**3b**), chloroacetic acid (**3c**), benzoic acid (**3d**), salicylic acid (**3e**), *p*-toluenesulfonic acid (**3f**), diphenyl hydrogen phosphate (**3g**), and *N*-triflylphosphoramide (**3h**) were used as organocatalysts. To determine the best catalyst, **1a** and organic Brønsted acids (**3a**–**3h**) were dissolved in dichloromethane. Furthermore, the mixture was stirred at room temperature until the starting thioether alcohol was spent. Finally, the new organocatalysts that catalyzed the intramolecular FCA reaction of thioether alcohols were identified and compared.

As can be seen in Table 1, benzoic acid (**3d**) did not catalyze the intramolecular Friedel–Crafts reaction of **1a** (Entry 5). Meanwhile, acetic acid (**3a**), chloroacetic acid (**3c**), salicylic acid (**3e**), and diphenyl hydrogen phosphate (**3g**) produced meager yields in the reaction although it lasted 24 h (Entries 2, 4, 6, and 8). In contrast, *p*-toluenesulfonic acid (**3f**) generated a moderate yield (55%), and excellent yields of 88% and 92% were obtained by the use of trifluoroacetic acid (**3b**) and *N*-triflylphosphoramide (**3h**) for 2 h (Entries 3 and 9). When the pKa values of the organic Brønsted acids used are compared, we can see that the lowest values of pKa in water are with trifluoroacetic acid and *p*-toluenesulfonic acid. However, while Brønsted acids are deprotonated, anions forming may be stabilized more efficiently by some solvents. Eventually, the pKa values may be measured differently in different solutions. For example, while the pKa value of salicylic acid is 2.97 in water, it is 8.23[25] in DMF and 6.6[26] in DMSO. In acetonitrile,

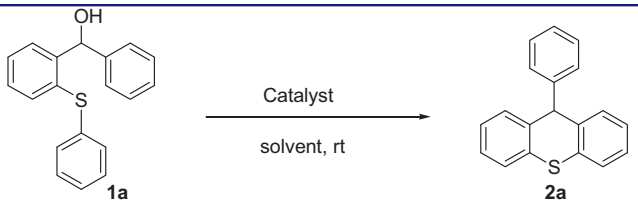
Table 1. Screening of organic Brønsted acids for intramolecular FCA of **1a**.[a]



Entry	Organic Brønsted acid (10% equiv.)	Time	Conv. (%)[b]
1	None	24 h	0
2	**3a**	24 h	6
3	**3b**	2 h	88
4	**3c**	24 h	10
5	**3d**	24 h	0
6	**3e**	24 h	5
7	**3f**	24 h	55
8	**3g**	24 h	4
9	**3h**	2 h	92

[a]Condition: **1a** (0.1 mmol) and organic Brønsted acid (10 % equiv.) in CH_2Cl_2 (2.5 mL) were stirred at room temperature.
[b]The conversion in GC–MS.

Table 2. Screening of solvents for intramolecular FCA of **1a**.[a]



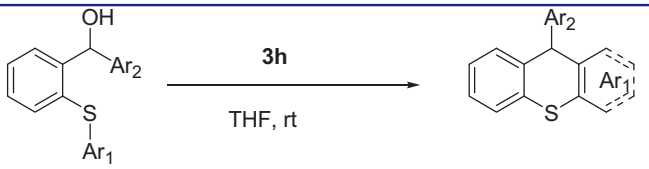
Entry	Catalyst	Solvent	Cat. Amount (mol%)	Time	Conv. (%)[b]
1	**3h**	CH_2Cl_2	10	2 h	92
2	**3h**	Benzene	10	2 h	91
3	**3h**	Toluene	10	2 h	93
4	**3h**	$CHCl_3$	10	2 h	91
5	**3h**	THF	10	15 min	>99
6	**3h**	CH_3CN	10	15 min	96
7	**3h**	DMSO	10	5 h	57
8	**3h**	THF	5	15 min	93
9	**3b**	THF	10	15 min	95

[a]Condition: **1a** (0.1 mmol) and catalyst (10% mmol) in solvent (2.5 mL) were stirred at room temperature.
[b]The conversion in GC–MS.

N-triflylphosphoramides have a pKa value of within the range 6–7,[27] but the pKa value of benzoic acid is 20.7.[28] Our results indicate that *N*-triflylphosphoramides are much more acidic than benzoic acid in acetonitrile. Therefore, *N*-triflylphosphoramide (**3h**) is the best acidic catalyst for the intramolecular FCA reaction of **1a** because of its stability and high acidity in organic solvents. The second best catalyst is trifluoroacetic acid (**3b**), but it may not be preferred because of its strongly corrosive nature and certain side reactions occurring in the long term.

In the next step, we investigated the effect of the solvent on the cyclization reaction of **1a** by using the best catalysts we had established (Table 2). We achieved encouraging

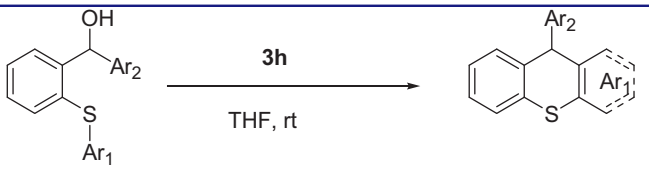
Table 3. Effect of the functional groups on Ar_1 used for intramolecular FCA of thioether alcohols.[a]



Entry	Product	Ar_1	Ar_2	Yield (%)[b]
1	**2a**	C_6H_5	C_6H_5	99
2	**2b**	4-$MeOC_6H_4$	C_6H_5	99
3	**2c**	4-MeC_6H_4	4-$MeOC_6H_4$	98
4	**2d**	4-ClC_6H_4	C_6H_5	35
5	**2e**	4-BrC_6H_4	4-MeC_6H_4	65
6	**2f**	4-FC_6H_4	C_6H_5	40

[a]Condition: Thioether alcohol (0.1 mmol) and **3h** in THF (2.5 mL) were stirred at room temperature.
[b]Yield of isolated product.

Table 4. Effect of the functional groups on Ar_2 for intramolecular FCA of thioether alcohols.[a]



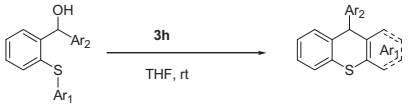
Entry	Product	Ar_1	Ar_2	Yield (%)[b]
1	**2a**	C_6H_5	C_6H_5	99
2	**2g**	C_6H_5	4-$MeOC_6H_4$	99
3	**2h**	C_6H_5	1-Np	70
4	**2i**	C_6H_5	2-MeC_6H_4	76
5	**2j**	C_6H_5	4-MeC_6H_4	96
6	**2k**	C_6H_5	2-Thienyl	98

[a]Condition: Thioether alcohol (0.1 mmol) and **3h** (10% mmol) in THF (2.5 mL) were stirred at room temperature.
[b]Yield of isolated product.

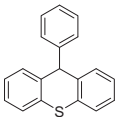
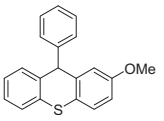
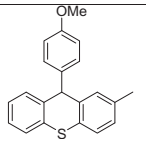
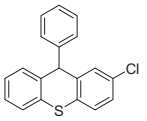
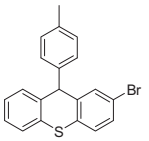
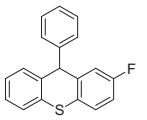
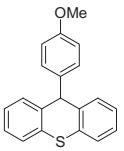
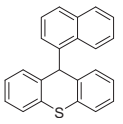
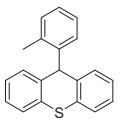
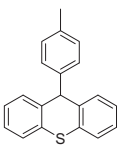
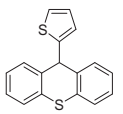
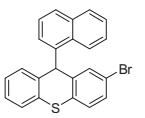
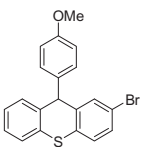
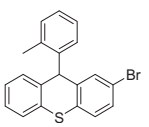
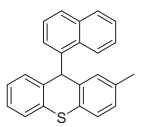
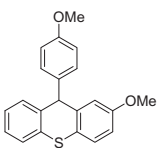
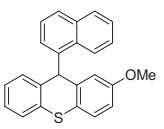
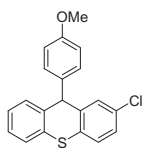
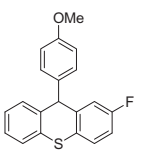
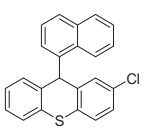
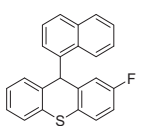
results in this part as the intramolecular FCA reaction of thioether alcohol **1a** produced excellent yields with CH_2Cl_2, benzene, toluene, and $CHCl_3$ after a two-hour reaction with catalyst **3h**. Interestingly, however, the best yield of 99% was obtained with THF in just 15 min without any side reaction using 10 mol% of the catalyst **3h** (Entry 5). Also, when we used CH_3CN as a solvent, the reaction was completed in 15 min with a yield of 96% (Entry 6). In addition, the second best catalyst **3b** was also examined in THF, but the yield was lower than the catalyst **3h**. Furthermore, a lower yield was obtained when we used 5 mol% of catalyst **3h** in the reaction (Entry 8).

Therefore, we developed a new route for intramolecular FCA cyclization of thioether alcohols using 10 mol% **3h** in THF at room temperature for 15 min to synthesize substituted thioxanthene derivatives with excellent results. Then, we examined the influence of the different groups of thioether alcohols on the reaction. For this purpose, differently substituted thiophenols were used in the first step of the preparation of the starting

Table 5. Scope of substrates for intramolecular FCA of 1a-1v and their yields.



1a-1v **2a-2v**

 **2a** 99%	 **2b** 99%	 **2c** 98%
 **2d** 35%	 **2e** 65%	 **2f** 40%
 **2g** 99%	 **2h** 70%	 **2i** 76%
 **2j** 96%	 **2k** 98%	 **2l** 45%
 **2m** 31%	 **2n** 55%	 **2o** 85%
 **2p** 82%	 **2r** 80%	 **2s** 72%
 **2t** 73%	 **2u** 87%	 **2v** 68%

materials. Varying substituted thiophenols (Ar_1) having Me, MeO, Br, Cl, or F groups were utilized in the experiments for the coupling reaction step. We reached this decision because in the electrophilic aromatic substitution reactions, especially the Friedel-Crafts reactions, electron-attracting and donating groups attached to the ring considerably affect the yield of the reaction. To understand the effect of the Ar_1 group on the intramolecular FCA, different substituted Ar_1 units were used while the other aromatic ring (Ar_2) was kept as a phenyl or a substituted phenyl ring. The results of the impacts of the screening reactions of the different functional groups on the aromatic thioether (Ar_1) are presented in Table 3.

As can be seen in Table 3, electron-donating groups activating the ring, such as methoxy- and methyl-substituted phenyl and phenyl groups (Table 3, entries 1–3), increased the yield of the electrophilic aromatic substitution. On the other hand, the units that slightly deactivated the ring, such as halogen-substituted phenyl rings (Entries 4–6) reduced the yield of the intramolecular FCA of thioether alcohols.

Furthermore, we used different arylmagnesium bromides (Ar_2) in the Grignard reaction. However, as known, the range of substituents that can be used in the Grignard reaction is limited. When Ar_1 was kept as a phenyl group, and Ar_2 group was replaced by different groups and in varying positions (Table 4), we observed that the phenyl or 4-Me and 4-MeO that substituted the phenyl and thenyl groups generated excellent yields within the range 96%–99% (Entries 1, 2, 5, and 6). However, the 2-Me substituted phenyl, and 1-naphthyl groups produced slightly lower yields of 70% and 76% (Entries 3 and 4), which was likely due to the possible steric hindrance. As a result, the Ar_1 group was more active than the Ar_2 group in the electrophilic aromatic substitution reaction because the Ar_1 group plays an essential role in the mechanism of the reaction. As known, the mechanism of the reaction is the electrophilic aromatic substitution mechanism, and the proposed mechanism was shown in our previous report[14] about the synthesis of xanthene derivatives by an intramolecular Friedel-Crafts reaction. Moreover in recent works, when it was looked at the similar reaction mechanism with chiral Brønsted acids, it is shown that an ortho-quinone methide (o-QM) intermediate may occur in acidic medium.[29]

Conclusion

Herein, we applied an organocatalytic method we had previously developed for the syntheses of novel substituted thioxanthenes via intramolecular Friedel–Crafts cyclisation starting from thioether diaryl alcohol compounds in the absence of transition-metal catalysts. In this study, we investigated new reaction conditions to synthesize thioxanthenes and obtained excellent yields. Furthermore, the function of certain organic Brønsted-acids as catalysts was explored. Importantly, *N*-triflylphosphoramide (**3h**) was established as the best organocatalyst among the studied ones.

Therefore, we, for the first time to our knowledge, developed a new intramolecular FCA route for the synthesis of certain novel substituted arylthioxanthenes in the presence of **3 h** as an organocatalyst with excellent yields. This new protocol does not require inert reaction conditions or any protection. The novel substituted thioxanthenes **2a**–**2v** (Table 5) may be used as bioactive compounds in the pharmaceutical chemistry

or as photoelectric materials in material chemistry. Nevertheless, further research is required of their pharmacological and photoelectric effects and activities.

Experimental details

The majority of the chemicals used in this work were commercially available from Merck or Aldrich. The starting carbinols **1a**–**1v** were prpared by coupling reaction of 2-fluorobenzaldehyde and substituted thiophenols and then Grignard reaction of 2-thioetherbenzaldehydes and some arylmagnesium bromides. All substrates were purified by crystallization or column chromatography and were characterized by IR, ^{1}H NMR, ^{13}C NMR, elementel analysis and GC-MS. **2a**,[18] **2d**,[30] **2g**,[18] **2h**,[31] and **2j**[32] were synthesized and characterized before with different procedures. All novel products were characterized by IR, ^{1}H NMR, ^{13}C NMR, elementel 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 Shimadzu/QP2010 Plus. IR spectra were recorded on a Bruker Vertex 70 IR spectrometer.

General procedure for intramolecular Friedel Crafts cyclization

To a stirred solution of a starting alcohol compound (**1a**–**1v**) (0.1 mmol) in dry THF (2.5 mL) was added *N*-triflylphosphoramide (**3h**) (10 mol%) at room temperature and the reaction was stirred for 15 min. After the completion of the reaction as observed on TLC, the mixture was concentrated in vacuo and was extracted with ethylacetate. After usual reaction workup and concentration, the product was charged on silica gel.

Spectral data for selected products

9-(4-Methoxy-phenyl)-2-methyl-9H-thioxanthene 2c

98% Yield as colorless oily. **IR** (cm^{-1}) ν 3057, 3028, 2959, 2836, 1606, 1579, 1246, 1180, 1060, 806, 742. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46-7.41 (m, 2H), 7.35 (d, 1H, $J = 10$ Hz), 7.29–7.22 (m, 3H), 7.08 (d, 1H, $J = 9.5$ Hz), 6.97 (d, 2H, $J = 8.5$ Hz), 6.76 (d, 2H, $J = 9$ Hz), 5.26 (s, 1H), 3.75 (s, 3H), 2.33 (s, 3H), 2.38 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 158.1, 137.8, 137.5, 136.4, 133.4, 133.1, 130.1, 129.6, 129.4, 128.8, 127.6, 127.1, 127.0, 126.6, 124.4, 113.5, 55.1, 52.8, 21.1. **MS** (m/z) = 41, 63, 77, 92, 113, 129, 152, 165, 178, 211, 241, 259, 273, 287, 303, 318 (M^+). Anal. Calcd. for $C_{21}H_{18}OS$: C, 79.21; H, 5.70; S, 10.07. Found: C, 79.32; H, 5.83; S, 9.96.

9-Thiophen-2-yl-9H-thioxanthene 2k

98% Yield as yellow oily. **IR** (cm^{-1}) ν 3104, 3058, 2922, 2869, 1670, 1581, 1475, 1365, 1023, 733, 687. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30-7.24 (m, 2H), 7.18–7.08 (m, 7H), 6.80 (dd, $J_1 = 3.5$ Hz, $J_2 = 5.5$ Hz, 1H), 6.73 (ddd, $J_1 = J_2 = 1.0$ Hz, $J_3 = 3.5$ Hz, 1H), 5.19 (s, 1H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 147.3, 144.6, 136.3, 133.9, 132.5, 129.9, 129.2,

129.1, 128.6, 128.5, 127.3, 126.7, 126.6, 125.4, 125.3, 125.2, 45.8. **MS** (m/z) = 45, 51, 69, 75, 88, 101, 123, 152, 165, 197, 205, 231, 234, 247, 280 (M^+). Anal. Calcd. for $C_{17}H_{12}S_2$: C, 72.82; H, 4.31; S, 22.87. Found: C, 72.93; H, 4.46; S, 22.60.

Supplementary information

Experimental details, analytical data for all compounds and copies of ^{1}H NMR, 13C NMR spectra, GC-MS and elemental analysis are provided.

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Disclosure statement

No potential conflict of interest was reported by the author.

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