Radical-mediated cyclization reactions leading to spiro and [6,6]-fused heterocycles

K.C. Majumdar, P. Debnath, A.K. Pal, S.K. Chattopadhyay, and A. Biswas

Abstract: Regiochemical study of $^{n}Bu_3SnH$–AIBN-mediated aryl-radical cyclization of different 3-(2-bromophenylsulfenylmethyl)coumarins, 3-(2-bromophenylsulfonyl-methyl)coumarins, and 6-[(2-bromophenoxy)methyl]-4-methoxypyran-2-ones have been investigated with the formation of different [6,6]-fused and spirocylic heterocycles. The sulfides and ethers were prepared from 3-chloromethyl coumarin and 6-(bromomethyl)-4-methoxy pyran-2-one with different 2-bromothiophenol and 2-bromophenols under classical alkylation condition. The corresponding sulfones were prepared by oxidation of the sulfides with *m*-CPBA.

Key words: aryl-radical cyclization, coumarin and pyrone derivatives, 5-exo-trig, 5-endo-trig, $^{n}Bu_3SnH$, sulfur heterocycles.

Résumé : On a effectué des réactions de cyclisation radicalaires aryliques, catalysées par le Bu_3SnH–AIBN, de diverses 3-(2-bromophénylsulfénylméthyl)coumarines, de 3-(2-bromophénylsulfonylméthyl)coumarines et de 6-[(2-bromophénoxy)méthyl]–4-méthoxypyran-2-ones et on a étudié leur régiochimie par rapport à la formation d'hétérocycles divers spirocycliques ou à fusion [6,6]. On a préparé les sulfures et les éthers de la 3-chlorométhylcoumarine et de la 6-(6-bromométhyl)-4-méthoxypyran-2-one à l'aide de divers 2-bromothiophénols et de 2-bromophénols, dans des conditions d'alkylation classique. Les sulfones correspondantes ont été préparées par oxydation des sulfures à l'aide d'acide *m*-chloroperbenzoïque.

Mots-clés : cyclisation radicalaire arylique, dérivés de la coumarine et des pyrones, 5-exo-trig, 6-endo-trig, Bu_3SnH, hétérocycles sulfurés.

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Introduction

Recently, free-radical cyclizations have been regarded as a versatile route for the construction of carbocycles as well as heterocycles (1). In particular, the synthesis of sulfur heterocycles by radical pathway presents a major challenge in organic synthesis. A survey of the literature revealed a few reports on the preparation of sulfur heterocycles by free-radical pathways, which include the cyclizations where the sulfur functionality either constitute the part of the hexenyl chain (2) or is placed outside (3) the 5-hexenyl system. Intramolecular homolytic substitution by an alkyl or aryl radical at the sulfur atom in the alkyl sulfides and sulfoxides have also been widely acceptable for the construction of sulfur heterocycles (4). To the best of our knowledge, no reports on the construction of benzothiophene and benzothiopyran heterocycles by free-radical methodology, employing 2-bromothiophenol as aryl-radical precursor, are available in literature.

We previously reported the synthesis of several novel five- and six-membered sulfur heterocycles by the application of sigmatropic rearrangement (5). Recently, we were successful in synthesizing quinolone-annulated (6) [6,6]-fused sulfur heterocycles by $^{n}Bu_3SnH$-mediated radical cyclization where small amount of β-scission (6, 7) product was formed along with 5-endo cyclization. It has been recognized that a stereoelectronically favored 5-exo cyclization is generally preferred over a 5-endo ring closure in those system, having an alkenic bond at the 5 position relative to the radical center. This regiochemical preference can be altered by the attachment of a suitable stabilizing group to the acceptor double bond (8). An extensive investigation by Della and Graney (2*f*) on the 5-hexenyl radical, where the sulfur functionality is in the α position to the radical center, revealed a dramatic effect on the regiochemistry of radical cyclization. Therefore, we studied the radical cyclization of 3-(2-bromo phenylsulfenylmethyl)coumarins, 3-(2-bromophenylsulfinyl methyl)coumarins, and 3-(2-bromophenylsulfonyl methyl)-coumarins. Here, we report the results of our investigation.

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K.C. Majumdar,[1] P. Debnath, A.K. Pal, S.K. Chattopadhyay, and A. Biswas. Department of Chemistry, University of Kalyani, Kalyani 741235, West Bengal, India

[1]Corresponding author (e-mail: kcm_ku@yahoo.co.in).

Results and discussion

The precursors 3-(2-bromophenylsulfenylmethyl)coumarins (**3a**–**3c**) were prepared in 82%–95% yield by treating 3-chloromethyl coumarin (**1**) with 2-bromothiophenol (**2**) in refluxing acetone (dry) in the presence of anhyd. potassium carbonate for 8 h (Scheme 1). The corresponding sulfones **4a**–**4c** and sulfoxide **5a** were synthesized in 85%–94% and 86% yields, respectively, from the sulfides **3a**–**3c** by the oxidation with *m*-CPBA (Scheme 1). Compounds **3a**–**3c** and

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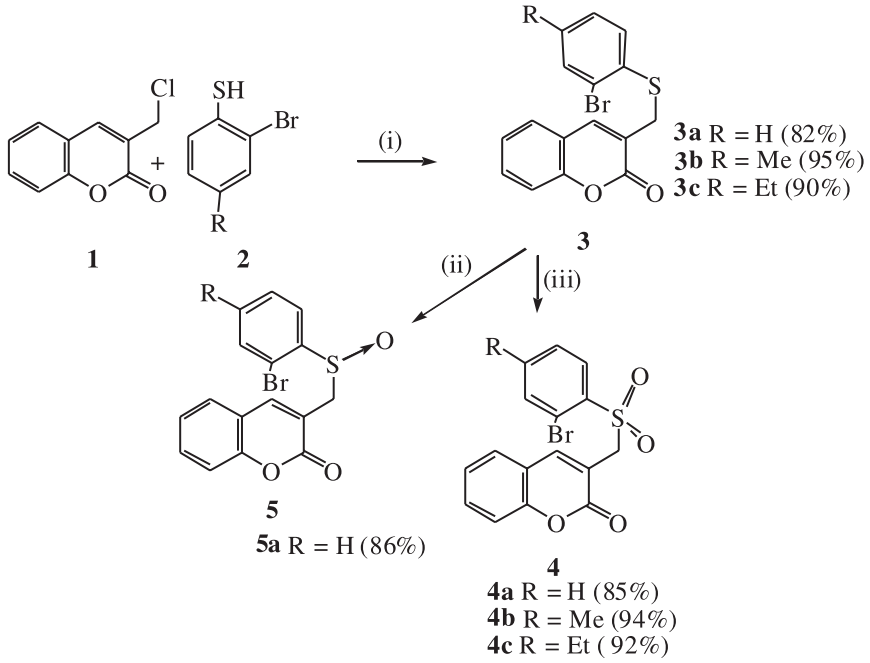
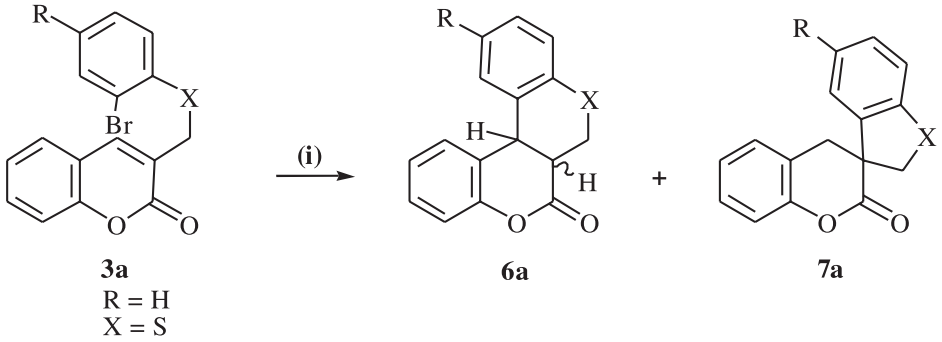
Scheme 1. Reagents and conditions: (*i*) anhyd. K_2CO_3, dry acetone, 8 h, and reflux; (*ii*) *m*-CPBA (1 equiv.), CH_2CL_2, 0 °C, and 1 h; (*iii*) *m*-CPBA (excess), CH_2Cl_2, and 0 °C to reflux.



Scheme 2. Reagents and conditions: (*i*) $^nBu_3SnH$, AIBN, toluene, N_2, 55–60 °C, and 1 h.



4a–**4c** were characterized by elemental analysis and spectroscopic data.

We initiated our study on the radical cyclization with the sulfide **3a**. Compound **3a**, when heated for 1 h at 55–60 °C with $^nBu_3SnH$ in dry degassed toluene in the presence of a catalytic amount of AIBN, afforded the two cyclized products **6a** and **7a** in 72% and 20% yield, respectively (Scheme 2).

Similarly, other sulfides **3b**–**3c** were treated to give the cyclic products **6b**–**6c** and **7b** in 85%–88% and 5% yields, respectively (Table 1). Sulfones **4a**–**4c**, when subjected to radical cyclization under similar conditions as the previously described, furnished the spirocyclic compounds **8a**–**8c** in 76%–85% yield, exclusively (Table 1), instead of the expected 5-endo cyclized product **9** (Scheme 3). The structure of the compounds **6a**–**6c**, **7a**–**7b**, and **8a**–**8c** were established from their elemental analysis and spectroscopic data. We observed that compounds **3** and **4**, when subjected to radical cyclization under refluxing conditions, underwent extensive decomposition without giving any cyclized products. To extend the scope of this reaction, we also attempted a similar radical reaction with 3-(2-bromophenylsulfinylmethyl)coumarins (**5a**), employing similar reaction condition. Unfortunately, we were unable to obtain any cyclized products, as the starting material decomposed under the reaction conditions.

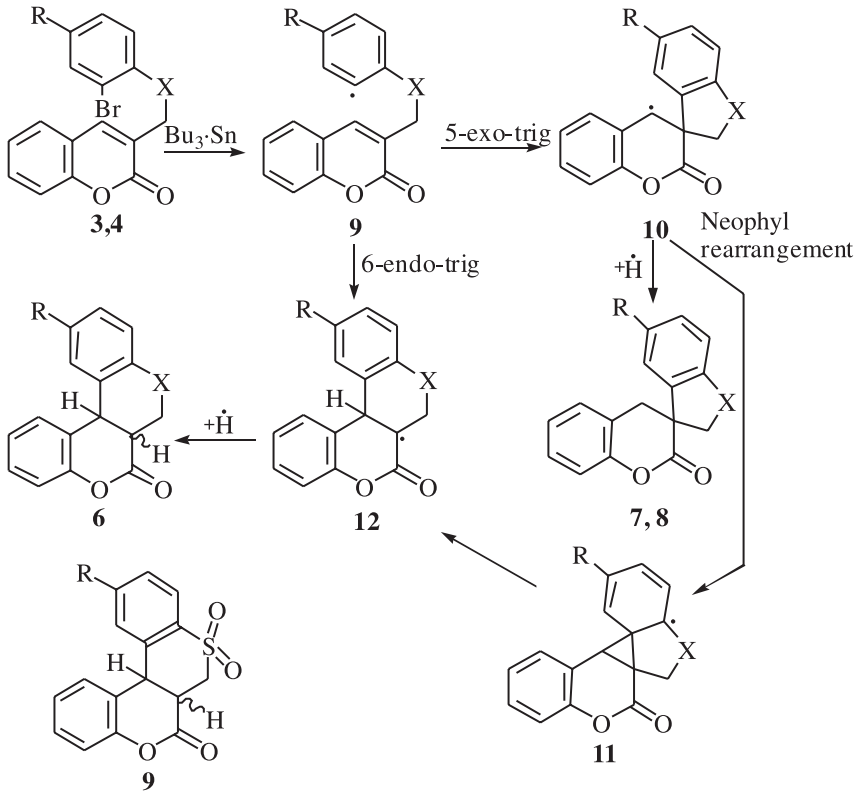
The mechanistic rationalization for the formation of products **6a**–**6c** and **7a**–**7b** can be explained by assuming a 5-endo followed by a 5-exo cyclization of the aryl radical onto the double bond of a coumarin moiety, as depicted in Scheme 3. An alternative pathway, via 5-exo cyclization followed by neophyl rearrangement (9), has also been considered for the formation of products **6a**–**6c**. In the case of phenylsulfonylmethyl congener **4a**–**4c**, the generated aryl radicals undergo 5-exo cyclization exclusively to produce the spirocylic products **8a**–**8c**. However, 5-exo cyclization with subsequent neophyl rearrangement pathway is highly unlikely with the present system. The stability and nonnucleophilicity (10) of the intermediate benzylic radical, attributed to the excellent overlapping (11) of a p orbital of the radical center with the adjacent aromatic π system, might prevent further attack, and hence, the production of the intermediate cyclohexadienyl radical **11**.

As $^nBu_3SnH$-mediated cyclization of the substrates de-

Table 1. Radical cyclization of sulfides and sulfones

Entry	Precursor	X	R	Product 5-exo/6-endo	Yield (%) 5-exo/6-endo
1	**3a**	S	H	**7a/6a**	20/72
2	**3b**	S	CH_3	**7b/6b**	5/85
3	**3c**	S	CH_2CH_3	**–/6c**	–/88
4	**4a**	SO_2	H	**8a/–**	76/–
5	**4b**	SO_2	CH_3	**8b/–**	78/–
6	**4c**	SO_2	CH_2CH_3	**8c/–**	85

Scheme 3.



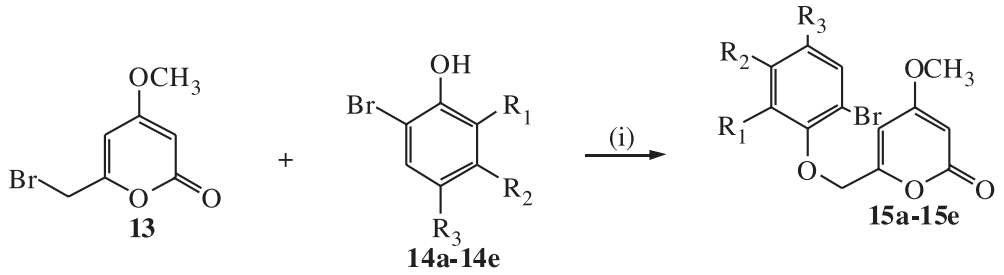
rived from benzo[1]pyran-2-ones afforded a mixture of [6,6]-fused and (or) spiro heterocycles, we wanted to examine the radical cyclization of the substrates containing pyran-2-one moiety. For this purpose, 6-[(2-bromophenoxy)methyl]-4-methoxypyran-2-ones (**15a**–**15e**) were synthesized in 77%–89% yields from 6-(bromomethyl)-4-methoxy pyran-2-one (**13**) and 2-bromophenols (**14a**–**14e**) (Scheme 4). Substrates **15a**–**15e** were characterized from their spectral data.

We then carried out the ^{n}Bu$_3$SnCl-mediated cyclization of compound **15a**. We applied the optimal reaction conditions used earlier (12), i.e., ^{n}Bu$_3$SnCl, Na(CN)BH$_3$, AIBN, in dry toluene, and under nitrogen atmosphere at 80 °C for 5 h. Surprisingly, intramolecular cyclization occurred to give only 11% of the cyclized product **16a**, and 76% of the starting material **15a** was recovered. However, changing the solvent, reagents, and raising the temperature of this reaction improved the yield. The best result was achieved by carrying out the reaction in toluene at 110 °C and using ^{n}Bu$_3$SnH instead of ^{n}Bu$_3$SnCl, which furnished **16a** in 79% yield. Similarly, compounds **15b**–**15e** afforded **16b**–**16e** in 68%–76% yields (Scheme 5).

The exclusive formation of five-membered spiro heterocycles **16a**–**16e** from **15a**–**15e** may easily be explained by the generation of the aryl radical **17** followed by a 5-exo-trig cyclization to give the allyl-radical intermediate **18**, which in turn abstracts the hydrogen from ^{n}Bu$_3$SnH to afford the spiro heterocycles **16a**–**16e**. The exclusive formation of five-membered heterocyclic compounds **16a**–**16e** from the substrates **15a**–**15e** may be attributed to the stability of the intermediate allylic radical **18.** There are precedents of Michael-type addition of a radical to the substrates containing Michael acceptors, giving Michael-type addition products; otherwise, α-*oxo* radical would be expected (13) (Scheme 6).

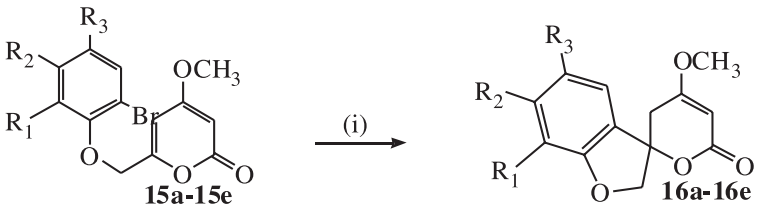
Although a stereoelectronically favored 5-exo-trig ring

Scheme 4. Reagents and conditions: (*i*) dry acetone, K_2CO_3, and reflux 3–4 h.



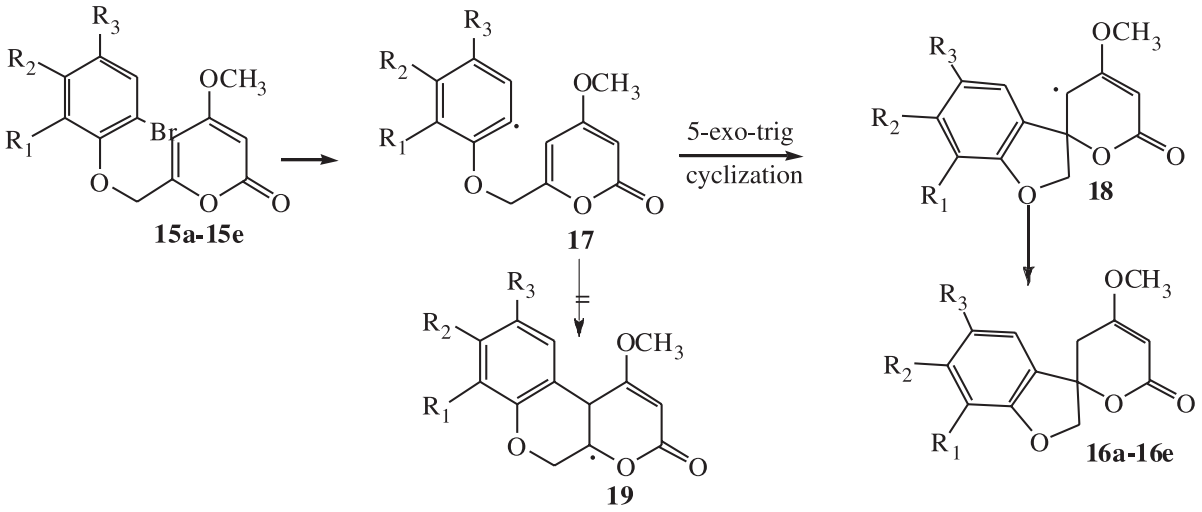
	R_1	R_2	R_3	Yield (%)
15a	H	H	H	82
b	Me	H	H	85
c	H	Me	H	81
d	Me	H	Me	77
e	H	H	OCH_3	89

Scheme 5. Reagents and conditions: (*i*) $^nBu_3SnH$, AIBN, dry toluene, reflux, 3–4 h, and N_2 atmosphere.



	R_1	R_2	R_3	Yield (%)
16a	H	H	H	79
b	Me	H	H	74
c	H	Me	H	68
d	Me	H	Me	71
e	H	H	OCH_3	76

Scheme 6.



closure is preferred for α-sulfenyl-5-hexenyl and α-sulfonyl-5-hexenylsystem, a significant amount of 5-endo-trig product is also formed, because of the longer C–S bond (8), to facilitate the easier approach of the radical center to accommodate the 5-endo transition state. This is quite evident for compounds **3a**–**3c** where products **6a**–**6c** were formed predominantly along with a small amount of the 5-membered products **7a**–**7b**. The stabilization of the intermediate tertiary radical **12** by the adjacent carbonyl group may also be responsible for the formation of the 5-endo product. However, this longer C–S bond for the facile 5-endo ring closure will no longer hold for the sulfones **4a**–**4c**. The presence of the two oxygen atoms attached to sulfur may be expected to favor the stereoelectronically favored 5-exo attack with the formation of highly stable spiro heterocyclic radical intermediate, which, by abstracting H-radicals, produces spirocyclic compounds **8a**–**8c** in excellent yield. However, in the case of compound **15**, the stabilization of the radical intermediate **18** by extended conjugation with the enone part might be responsible for the exclusive formation of the spiro product.

Interestingly, we found that the ratios of the spirocyclic to [6,6]-fused products from compounds **3a**–**3c** were different, depending on the group attached to the thiophenol. However, this ratio is increased by the presence of an activating group attached to the thiophenol moiety. With the *p*-ethyl-substituted phenylsulfenyl precursor, the [6,6]-fused product was produced exclusively. In contrast, this substituent effect on the mode of ring closure was completely absent for the precursors **4** and also from compound **15**. The explanation of the effect of the activating substituent, attached to the thiophenol moiety, is quite unknown. However, this study revealed that the choice of suitable precursors can be utilized for the selective formation of spirocyclic or [6,6]-fused sulfur heterocycles.

Conclusion

In summary, we have described $^{n}Bu_3SnH$-mediated mild and efficient synthesis of coumarin and pyrone-annulated heterocycles. All the reactions were clean with moderate to good yield. The use of 2-bromothiophenol provides an easy access to benzothiophene as well as benzothiopyran derivatives, which are of synthetic utility in organic synthesis.

Experimental

Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded on a PerkinElmer L120–000A spectrometer (ν_{max} in cm^{-1}) using KBr discs. UV-absorption spectra were recorded in EtOH on a Shimadzu UV-2401PC spectrophotometer (λ_{max} in nm). ^1H NMR (300 MHz, 400 MHz, and 500 MHz) and ^{13}C NMR (75.5 MHz and 125 MHz) spectra were recorded on a Bruker DPX-300, Varian-400 MHz FTNMR, and Bruker DPX-500 spectrometer in $CDCl_3$ (chemical shifts in δ) with TMS as internal standard. Silica gel (60–120 mesh; Spectrochem, India) was used for chromatographic separation. Silica gel G (E-Merck, India) was used for TLC. Petroleum ether refers to the fraction boiling between 60 °C and 80 °C.

General procedure for the preparation of 3-(2-bromophenylsulfenylmethyl)coumarins

To a solution of 3-chloromethylcoumarin (**1**) (1 g, 5.15 mmol) in dry acetone (100 mL), 2-bromothiophenol (**2a**–**2c**) (5.15 mmol) and anhyd. potassium carbonate (2 g) were added, and the reaction mixture was refluxed for 8 h. The reaction mixture was then cooled, filtered, and the solvent was removed. The residual mass was extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was washed with 5% Na_2CO_3 solution (2 × 10 mL), then with water (3 × 10 mL), and finally with brine (10 mL). After the removal of the solvent, the residue was subjected to column chromatography over silica gel. Elution of the column with 25% ethyl acetate in petroleum ether afforded 3-(2-bromophenylsulfenylmethyl)coumarins (**3a**–**3c**). All compounds were recrystalized from chloroform – petroleum ether (60–80 °C).

Compound 3a

Yield: 82%. Colourless crystalline solid; mp 100 °C. IR (KBr) ν_{max} (cm^{-1}): 1715, 1604, 743. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.07 (s, 2H, $-SCH_2$), 7.02–7.07 (m, 1H, ArH), 7.18–7.25 (m, 3H, ArH), 7.31 (d, 1H, *J* = 8.28 Hz, ArH), 7.36 (d, 1H, *J* = 7.5 Hz, ArH), 7.47–7.51 (m, 1H, ArH), 7.54 (d, 1H, *J* = 7.87 Hz, ArH), 7.57 (s, 1H, =CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 33.2, 116.9, 119.4, 124.6, 124.9, 125.3, 128.1, 128.2, 128.4, 130.5, 131.8, 133.6, 136.6, 140.5, 153.6, 161.4. MS *m*/*z*: 346, 348 [M^+]. Anal. calcd. for $C_{16}H_{11}O_2SBr$: C 55.33, H 3.17; found: C 55.55, H 3.27.

Compound 3b

Yield: 95%. Colourless crystalline solid; mp 98 °C. IR (KBr) ν_{max} (cm^{-1}): 1712, 1603, 756. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.27 (s, 3H, $ArCH_3$), 4.03 (s, 2H, $-SCH_2$), 6.99 (d, 1H, *J* = 7.78 Hz, ArH), 7.14 (d, 1H, *J* = 7.9 Hz, ArH), 7.21 (d, 1H, *J* = 7.4 Hz, ArH), 7.31–7.36 (m, 2H, ArH), 7.40 (s, 1H, ArH), 7.46 (d, 1H, *J* = 7.4 Hz, ArH), 7.5 (s, 1H, =CH). MS *m*/*z*: 360, 362 [M^+]. Anal. calcd. for $C_{17}H_{13}O_2SBr$: C 56.51, H 3.60; found: C 56.26, H 3.47.

Compound 3c

Yield: 90%. Colourless crystalline solid; mp 85–86 °C. IR (KBr) ν_{max} (cm^{-1}): 1702, 1607, 751. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.15 (t, 3H, *J* = 7.5 Hz, $-CH_2CH_3$), 2.53 (q, 2H, *J* = 7.5 Hz, $-CH_2CH_3$), 4.03 (s, 2H, $-SCH_2$), 7.01 (d, 1H, *J* = 7.1 Hz, ArH), 7.1 (d, 1H, *J* = 7.98 Hz, ArH), 7.21 (d, 1H, *J* = 7.43 Hz, ArH) 7.31–7.35 (m, 2H, ArH), 7.41 (s, 1H, ArH), 7.46 (d, 1H, *J* = 7.4 Hz, ArH), 7.49 (s, 1H, =CH). MS *m*/*z*: 374, 376 [M^+]. Anal. calcd. for $C_{18}H_{15}O_2SBr$: C 57.60, H 4.00; found: C 57.67, H 4.12.

General procedure for the preparation of 3-(2-bromophenylsulfonylmethyl)coumarins

To a stirred solution of compound 3-(2-bromophenylsulfenylmethyl)coumarin (**3a**–**3c**) (1.44 mmol) in CH_2Cl_2 (10 mL), a solution of *m*-CPBA (77%, 621 mg, 1.79 mmol, 2.5 equiv.) was added over a period of 1 h. After the addition of *m*-CPBA, the reaction mixture was refluxed for another 2 h for complete conversion (TLC observation). The mixture was then cooled and washed with satd. sodium carbonate (3 × 10 mL) and brine (10 mL) and dried (Na_2SO_4). The mixture was then concentrated, and the crude mass obtained was purified by column chromatography using 20% ethyl acetate in petroleum ether as eluant to afford 3-(2-bromophenylsulfonylmethyl)coumarins (**4a**–**4c**), which were recrystalized from chloroform – petrolium ether (60–80 °C).

Compound 4a

Yield: 85%. Colourless crystalline solid; mp 148 °C. IR (KBr) ν_{max} (cm^{-1}): 1722, 1318, 749. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.71 (s, 2H, $-SO_2CH_2$), 7.25–7.29 (m, 2H, ArH), 7.39–7.56 (m, 4H, ArH), 7.79 (d, 1H, *J* = 7.9 Hz, ArH), 7.95 (s, 1H, =CH), 7.98 (d, 1H, *J* = 7.6 Hz, ArH). MS *m*/*z*: 378, 380 [M^+]. Anal. calcd. for $C_{16}H_{11}O_4SBr$: C 50.66, H 2.90; found C 50.74, H 2.84.

Compound 4b

Yield: 94%. Colourless crystalline solid; mp 151 °C. IR (KBr) ν_{max} (cm^{-1}): 1722, 1313, 763. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.39 (s, 3H, $ArCH_3$), 4.68 (s, 2H, $-SO_2CH_2$), 7.18 (d, 1H, *J* = 7.98 Hz, ArH), 7.27–7.31 (m, 2H, ArH), 7.50–7.56 (m, 2H, ArH), 7.61 (s, 1H, ArH), 7.83 (d, 1H, *J* = 8.08 Hz, ArH), 7.95 (s, 1H, =CH). MS *m*/*z*: 392, 394 [M^+]. Anal. calcd. for $C_{17}H_{13}O_4SBr$: C 51.91, H 3.31; found: C 52.07, H 3.39.

Compound 4c

Yield: 92%. Colourless crystalline solid; mp 160 °C. IR (KBr) ν_{max} (cm^{-1}): 1726, 1313, 766. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.22 (t, 3H, *J* = 7.5 Hz, $-CH_2CH_3$), 2.66 (q, 2H, *J* = 7.4 Hz, $-CH_2CH_3$), 4.69 (s, 2H, $-SO_2CH_2$), 7.21(d, 1H, *J* = 8.3 Hz, ArH), 7.27–7.31 (m, 2H, ArH), 7.50–7.56 (m, 2H, ArH), 7.62 (s, 1H, ArH), 7.88 (d, 1H, *J* = 8.1 Hz, ArH), 7.95 (s, 1H, =CH). MS *m*/*z*: 406, 408 [M^+]. Anal. calcd. for $C_{18}H_{15}O_4SBr$: C 53.07, H 3.69; found: C 53.28, H 3.81.

General procedure for the preparation of 3-(2-bromophenylsulfinylmethyl)coumarin

To a stirred solution of 3-(2-bromophenylsulfenylmethyl)coumarin (**3a**) (1.44 mmol) in CH_2Cl_2 (10 mL) at 0 °C, a solution of *m*-CPBA (77%, 249 mg, 1.44 mmol) was added over a period of 1 h. After the complete addition of *m*-CPBA, the reaction was stirred for another 1 h for complete conversion (TLC observation). The mixture was then washed with satd. solution of sodium carbonate (3 × 10 mL) and brine (10 mL) and dried (Na_2SO_4). The mixture was then concentrated, and the crude mass obtained was purified by column chromatography using 25% ethyl acetate in petroleum ether as eluant to afford 3-(2-bromophenylsulfinylmethyl)coumarin (**5a**), which was recrystallized from chloroform – petrolium ether (60–80 °C).

Compound 5a

Yield: 92%. Colourless crystalline solid; mp 170–172 °C. IR (KBr) ν_{max} (cm^{-1}): 1709, 1057, 756. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.09 (d, 1H, *J* = 12.85 Hz, $–SOCH_2$), 4.28 (d, 1H, *J* = 12.85 Hz, $–SOCH_2$), 7.27–7.32 (m, 2H, ArH), 7.35–7.42 (m, 2H, ArH), 7.48–7.56 (m, 3H, ArH), 7.57–7.60 (m, 1H, ArH), 7.72 (s, 1H, =CH). MS *m*/*z*: 362, 364 [M^+]. Anal. calcd. for $C_{16}H_{11}O_3SBr$: C 52.91, H 3.05; found C 53.06, H 3.14.

General procedure for the radical-cyclization reactions

A suspension of the compounds **3a**–**3c** and **4a**–**4c** (0.430 mmol), $^nBu_3SnH$ (0.174 mL, 0.648 mmol), and AIBN (20 mg) in dry degassed toluene (10 mL) was stirred at 55–60 °C for 1 h under N_2. The solvent was removed under reduced pressure. Water (10 mL) was added to the residue, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with water (2 × 10 mL) and brine (10 mL) and dried (Na_2SO_4). Evaporation of the solvent furnished a crude material, which was then subjected to column chromatography over silica gel. The column was eluted with 8% and 25% ethyl acetate in petroleum ether to give the cyclized products **6a**–**6c**, **7a**, **7b**, and **8a–8c**. All compounds were recrystalized from chloroform – petrolium ether (60–80 °C).

Compounds 6a

Yield: 72%. Colourless crystalline solid; mp 128 °C. IR (KBr) ν_{max} (cm^{-1}): 1758, 1455, 1148. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.12 (dd, 1H, *J* = 5.9 and 12.6 Hz, $–SCHH_a$), 3.30–3.31 (m, 1H, $–C–H_c$), 3.51 (dd, 1H, *J* = 5.7 and 13.0 Hz, $–SCHH_b$), 4.35 (d, 1H, *J* = 4.9 Hz, $–C–H_d$), 6.86 (d, 1H, *J* = 7.6 Hz, ArH), 7.04–7.20 (m, 5H, ArH), 7.18(d, 1H, *J* = 7.3 Hz, ArH), 7.32–7.36 (m, 1H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.68, 39.15, 39.75, 117.24, 124.57, 124.89, 125.16, 127.70, 128.10, 129.0, 129.19, 129.70, 131.41, 133.20, 150.60, 168.51. MS *m*/*z*: 268 [M^+]. Anal. calcd. for $C_{16}H_{12}O_2S$: C 71.64, H 4.48; found: C 71.73, H 4.53.

Compounds 6b

Yield: 85%. Colourless crystalline solid; mp 130 °C. IR (KBr) ν_{max} (cm^{-1}): 1756, 1610, 1142.^1H NMR (400 MHz, $CDCl_3$) δ: 2.22 (s, 3H, $ArCH_3$), 3.09 (dd, 1H, *J* = 6.28 and 13.0 Hz, $–SCHH_a$), 3.29–3.34 (m, 1H, $–C–H_c$), 3.49 (dd, 1H, *J* = 6.02 and 13.3 Hz, $–SCHH_b$), 4.31 (d, 1H, *J* = 5.17 Hz, $–C–H_d$), 6.65 (s, 1H, ArH), 6.99 (d, 1H, *J* = 7.0 Hz, ArH), 7.08–7.20 (m, 4H, ArH), 7.44–7.46 (m, 1H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.42, 25.24, 39.65, 40.45, 117.61, 124.94, 125.29, 128.11, 129.41, 129.45, 129.57, 130.07, 130.56, 132.02, 135.51, 151.04, 169.14. MS *m*/*z*: 282 [M^+]. Anal. calcd. for $C_{17}H_{14}O_2S$: C 72.34, H 4.96; found: C 72.26, H 5.03.

Compounds 6c

Yield: 88%. Colourless crystalline solid; mp 192 °C. IR (KBr) ν_{max} (cm^{-1}): 1763, 1612, 1140.^1H NMR (400 MHz, $CDCl_3$) δ: 1.09 (t, 3H, *J* = 7.8 Hz, $–CH_2CH_3$), 2.49 (q, 2H, *J* = 7.5 Hz, $–CH_2CH_3$), 3.08 (dd, 1H, *J* = 6.0 and 12.6 Hz, $–SCHH_a$), 3.26–3.32 (m, 1H, $–C–H_c$), 3.49 (dd, 1H, *J* = 5.7 and 13.7 Hz, $–SCHH_b$), 4.34 (d, 1H, *J* = 5.12 Hz, $–C–H_d$), 6.69 (s, 1H, ArH), 7.03–7.20 (m, 5H, ArH), 7.32–7.38 (m, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.90, 25.11, 28.75, 39.62, 40.36, 117.59, 125.0, 125.31, 128.09, 128.20, 129.39, 129.54, 129.67, 130.20, 131.69, 141.88, 150.99, 169.17. MS *m*/*z*: 296 [M^+]. Anal. calcd. for $C_{18}H_{16}O_2S$: C 72.97, H 5.41; found: C 73.11, H 5.36.

Compound 7a

Yield: 20%. Colourless crystalline solid; mp 126 °C. IR (KBr) ν_{max} (cm^{-1}): 1759, 1458, 1143. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.13 (d, 1H, *J* = 11.52 Hz, –SCH), 3.21 (d, 1H, *J* = 16.12 Hz, ArCH), 3.26 (d, 1H, *J* = 16.08 Hz, ArCH), 3.88 (d, 1H, *J* = 11.48 Hz, –SCH), 6.97–7.03 (m, 2H, ArH), 7.09–7.15 (m, 3H, ArH), 7.17–7.22 (m, 2H, ArH), 7.30–7.34 (m, 1H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 34.6, 40.7, 55.9, 116.5, 121.1, 122.8, 124.6, 124.8, 124.9, 128.8, 128.9, 129.1, 139.0, 140.5, 151.4, 169.3. MS *m*/*z*: 268 [M^+]. Anal. calcd. for $C_{16}H_{12}O_2S$: C 71.64, H 4.48; found: C 71.86, H 4.60.

Compound 7b

Yield: 5%. Colourless crystalline solid; mp 108 °C. IR (KBr) ν_{max} (cm^{-1}): 1766, 1457, 1167. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.22 (s, 3H, $ArCH_3$), 3.12 (d, 1H, *J* = 11.4 Hz, –SCH), 3.20 (d, 1H, *J* = 16.32 Hz, ArCH), 3.24 (d, 1H, *J* = 16.4 Hz, ArCH), 3.79 (d, 1H, *J* = 11.40 Hz, –SCH), 6.84 (s, 1H, ArH), 6.98–7.0 (m, 1H, ArH), 7.07–7.16 (m, 4H, ArH), 7.29–7.33 (m, 1H, ArH). MS *m*/*z*: 282 [M^+]. Anal. calcd. for $C_{17}H_{14}O_2S$: C 72.34, H 4.96; found: C 72.18, H 5.10.

Compound 8a

Yield: 76%. Colourless crystalline solid; mp 120 °C. IR (KBr) ν_{max} (cm^{-1}): 1756, 1310, 1149. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.42 (d, 1H, *J* = 13.4 Hz, $–SO_2CH$), 3.43 (d, 1H, *J* = 16.17 Hz, ArCH), 3.49 (d, 1H, *J* = 16.2 Hz, ArCH), 4.00 (d, 1H, *J* = 13.4 Hz, $–SO_2CH$), 7.17–7.23 (m, 4H, ArH), 7.36–7.41 (m, 1H, ArH), 7.55–7.61 (m, 2H, ArH), 7.78–7.80 (m, 1H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 37.6, 48.15, 58.0, 117.2, 122.3, 125.9, 126.5, 129.5, 129.9, 130.7, 131.0, 134.5, 137.7, 138.6, 151.5, 167.3. MS *m*/*z*: 300 [M^+]. Anal. calcd. for $C_{16}H_{12}O_4S$: C 64.00, H 4.00; found: C 64.21, H 4.08.

Compound 8b

Yield: 78%. Colourless crystalline solid; mp 92–93 °C. IR (KBr) ν_{max} (cm^{-1}): 1756, 1310, 1149. ^1H NMR (500 MHz,

$CDCl_3$) δ: 2.36 (s, 3H, $ArCH_3$), 3.38 (d, 1H, *J* = 13.08 Hz, –SO_2CH), 3.43 (d, 1H, *J* = 15.97 Hz, ArCH), 3.50 (d, 1H, *J* = 16.02 Hz, ArCH), 3.90 (d, 1H, *J* = 13.32 Hz, –SO_2CH), 6.83(s, 1H, ArH), 7.18–7.38 (m, 5H, ArH), 7.65–7.66 (m, 1H, ArH). MS *m/z*: 314 [M^+]. Anal. calcd. for $C_{17}H_{14}O_2S$: C 64.97, H 4.46; found: C 65.19, H 4.55.

Compound 8c

Yield: 85%. Colourless crystalline solid; mp 78 °C. IR (KBr) ν_{max} (cm^{-1}): 1766, 1302, 1121. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.09 (t, 3H, *J* = 7.6 and 15.0 Hz, –CH_2CH_3), 2.60 (q, 2H, *J* = 7.5 and 14.8 Hz, –CH_2CH_3), 3.39 (d, 1H, *J* = 13.4 Hz, –SO_2CH), 3.40 (d, 1H, *J* = 16.17 Hz, ArCH), 3.46 (d, 1H, *J* = 16.2 Hz, ArCH), 3.99 (d, 1H, *J* = 13.38 Hz, –SO_2CH), 6.97 (s, 1H, ArH), 7.16–7.20 (m, 3H, ArH), 7.36–7.39 (m, 2H, ArH), 7.66–7.68 (m, 1H, ArH). MS *m/z*: 328 [M^+]. Anal. calcd. for $C_{18}H_{16}O_4S$: C 65.85, H 4.88; found: C 65.99, H 4.98.

General procedure for the preparation of 15a–15e

6-(Bromomethyl)-4-methyl-2*H*-pyran-2-one (**13**) (1.05 g, 4.82 mmol) and different *o*-bromophenols (**14a–14e**) (4.82 mmol) were refluxed in dry acetone (100 mL) in the presence of anhyd. potassium carbonate (3 g) for 3–4 h. The reaction mixture was then cooled, filtered, and the solvent was removed. Residual mass was extracted with CH_2Cl_2 (3 × 50 mL), and the extract was washed with water (3 × 30 mL) and then with brine (30 mL) and dried (Na_2SO_4). The residual mass after the removal of the solvent was subjected to column chromatography over silica gel (60–120 mesh). The column was eluted with petroleum ether – chloroform (1:9) to give compounds **15a**–**15e**. Attempts to recrystallize the products from different solvents, such as methanol, chloroform – petroleum ether (60–80 °C), benzene – petroleum ether (60–80 °C), acetonitrile–methanol, failed to give any crystalline compounds. All compounds were found to be amorphous in nature and hence white as paper.

Compound 15a

Yield: 82%. White amorphous solid; mp 117 °C. IR (KBr) ν_{max} (cm^{-1}): 2951, 1740, 1259, 1033. ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.83 (s, 3H), 4.85 (d, *J* = 0.90 Hz, 2H), 5.47 (d, *J* = 2.25 Hz, 1H), 6.33–6.35 (m, 1H), 6.87–6.94 (m, 2H), 7.28–7.31(m, 1H), 7.56 (dd, *J* = 1.59 and 7.83 Hz, 1H). MS *m/z*: 310, 312 [M^+]. Anal. calcd. for $C_{13}H_{11}BrO_4$: C 50.18, H 3.56; found: C 50.43, H 3.63.

Compound 15b

Yield: 85%. White amorphous solid; mp 109–110 °C. IR (KBr) ν_{max} (cm^{-1}): 2920, 1732, 1260, 1049. ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.29 (s, 3H), 3.83 (s, 3H), 4.64 (s, 2H), 5.49 (d, *J* = 1.88 Hz, 1H), 6.29 (s, 1H), 7.24–7.53 (m, 3H). MS *m/z*: 324, 326 [M^+]. Anal. calcd. for $C_{14}H_{13}BrO_4$: C 51.71, H 4.03; found: C 51.66, H 4.21.

Compound 15c

Yield: 81%. White amorphous solid; mp 121 °C. IR (KBr) ν_{max} (cm^{-1}): 2920, 1730, 1260, 1033. ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.54 (s, 3H), 3.82 (s, 3H), 4.73 (s, 2H), 5.49 (d, *J* = 2.04 Hz, 1H), 6.37 (t, *J* = 0.94 Hz, 1H), 6.94 (d, *J* = 8.21 Hz, 1H), 7.39 (d, *J* = 8.16 Hz, 1H), 7.75 (s, 1H). MS *m/z*: 324, 326 [M^+]. Anal. calcd. for $C_{14}H_{13}BrO_4$: C 51.71, H 4.03; found: C 51.88, H 4.12.

Compound 15d

Yield: 77%. White amorphous solid; mp 126 °C. IR (KBr) ν_{max} (cm^{-1}): 2920, 1733, 1259, 1035. ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.25 (s, 3H), 2.27 (s, 3H), 3.83 (s, 3H), 4.63 (d, *J* = 0.94 Hz, 2H), 5.49 (d, *J* = 2.44 Hz, 1H), 6.32–6.34 (m, 1H), 6.93 (s, 1H), 7.05 (s, 1H). MS *m/z*: 338, 340 [M^+]. Anal. calcd. for $C_{15}H_{15}BrO_4$: C 53.12, H 4.46; found: C 52.90, H 4.52.

Compound 15e

Yield: 89%. White amorphous solid; mp 132 °C. IR (KBr) ν_{max} (cm^{-1}): 2921, 1733, 1259, 1053. ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.75 (s, 3H), 3.81 (s, 3H), 4.77 (s, 2H), 5.45 (d, *J* = 2.0 Hz, 1H), 6.30 (s, 1H), 6.78–6.85 (m, 2H), 7.11 (d, *J* = 2.68 Hz, 1H). MS *m/z*: 340, 342[M^+]. Anal. calcd. for $C_{14}H_{13}BrO_5$: C 49.29, H 3.84; found: C 49.38, H 3.70.

General procedure for the radical cyclization of compound 15a–15e

The appropriate compound **15a**–**15e** (0.32 mmol) was dissolved in dry toluene (10 mL), and the solution was purged with nitrogen for 30 min. AIBN (26 mg) and $^nBu_3SnH$ (0.104 mL, 0.38 mmol) were added, and the reaction mixture was refluxed for 3–4 h under nitrogen atmosphere. The reaction mixture was allowed to cool down to room temperature, and the solvent was removed under reduced pressure. Water (10 mL) was added to the residual mass, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 solution was stirred with 10% KF solution (10 mL) for 1 h. The organic phase was washed with water (2 × 20 mL) and then brine (1 × 20 mL) and dried (Na_2SO_4). The solvent was distilled off, and the crude solid was purified by column chromatography over silica gel (230–400 mesh). Elution of the column with petroleum ether – ethyl acetate (4:1) gave pure solids **16a**–**16e**. Attempts to recrystallize the products from different solvents, such as methanol, chloroform – petroleum ether (60–80 °C), benzene – petroleum ether (60–80 °C), and acetonitrile–methanol, failed to give any crystalline compounds. All compounds were found to be amorphous in nature and hence white as paper

Compound 16a

Yield: 79%. White amorphous solid; mp 152–154 °C. IR (KBr) ν_{max} (cm^{-1}): 2998, 1697, 1261, 1015. ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.78 (d, *J* = 17.18 Hz, 1H), 3.05 (d, *J* = 17.19 Hz, 1H), 3.83 (s, 3H), 4.37 (d, *J* = 10.6 Hz, 1H), 4.71 (d, *J* = 10.60 Hz, 1H), 5.30 (s, 1H), 6.87–7.38 (m, 4H). ^{13}C NMR (125 MHz) δ: 36.5, 56.8, 81.4, 85.7, 91.3, 111.5, 121.6, 124.3, 126.8, 132.1, 160.9, 165.8, 171.5. MS *m/z*: 232 [M^+]. Anal. calcd. for $C_{13}H_{12}O_4$: C 67.23, H 5.21; found: C 67.45, H 5.08.

Compound 16b

Yield: 74%. White amorphous solid; mp 147 °C. IR (KBr) ν_{max} (cm^{-1}): 2922, 1714, 1238, 1060. ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.19 (s, 3H), 2.78 (d, *J* = 17.18 Hz, 1H), 2.98 (d, *J* = 17.23 Hz, 1H), 3.82 (s, 3H), 4.36 (d, *J* = 10.72 Hz, 1H), 4.72 (d, *J* = 10.74 Hz, 1H), 5.29 (s, 1H), 7.19–7.29 (m,

3H). MS *m*/*z*: 246 [M^+]. Anal. calcd. for $C_{14}H_{14}O_4$: C 68.28, H 5.73; found: C 68.11, H 5.62.

Compound 16c

Yield: 68%. White amorphous solid; mp 162 °C. IR (KBr) ν_{max} (cm^{-1}): 2920, 1720, 1240, 1035. ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.33 (s, 3H), 2.77 (d, *J* = 17.16 Hz, 1H), 3.03 (d, *J* = 17.18 Hz, 1H), 3.83 (s, 3H), 4.36 (d, *J* = 10.58 Hz, 1H), 4.67 (d, *J* = 10.66 Hz, 1H), 5.29 (s, 1H), 6.69–6.75 (m, 2H), 7.24 (s, 1H). MS *m*/*z*: 246 [M^+]. Anal. calcd. for $C_{14}H_{14}O_4$: C 68.28, H 5.73; found: C 68.55, H 5.65.

Compound 16d

Yield: 71%. White amorphous solid; mp 143–144 °C. IR (KBr) ν_{max} (cm^{-1}): 2928, 1716, 1230, 1025. ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.17 (s, 3H), 2.24 (s, 3H), 2.74 (d, *J* = 17.22 Hz, 1H), 3.03 (d, *J* = 17.21 Hz, 1H), 3.82 (s, 3H), 4.33 (d, *J* = 10.60 Hz, 1H), 4.68 (d, *J* = 10.64 Hz, 1H), 5.28 (s, 1H), 6.92 (s, 1H), 6.97 (s, 1H). MS *m*/*z*: 260 [M^+]. Anal. calcd. for $C_{15}H_{16}O_4$: C 69.22, H 6.20; found: C 69.07, H 6.43.

Compound 16e

Yield: 76%. White amorphous solid; mp 166–167 °C. IR (KBr) ν_{max} (cm^{-1}): 2922, 1717, 1266, 1026. ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.76 (d, *J* = 17.18 Hz, 1H), 3.03 (d, *J* = 17.18 Hz, 1H), 3.74 (s, 3H), 3.82 (s, 3H), 4.36 (d, *J* = 10.52 Hz, 1H), 4.68 (d, *J* = 10.51 Hz, 1H), 5.28 (s, 1H), 6.78–6.90 (m, 3H). MS *m*/*z*: 262 [M^+]. Anal. calcd. for $C_{14}H_{14}O_5$: C 64.12, H 5.38; found: C 64.03, H 5.43.

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