Ammonium Chloride-Catalyzed Three-Component Reaction for the Synthesis of Fused 4*H*-Chromene Derivatives in Aqueous Medium

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This work is dedicated to Professor Gautam Barua, former Director of the Indian Institute of Technology, Guwahati for his immense contribution in setting up and developing the Science Department of IIT Guwahati.

Abstract: An efficient one-pot process was developed to synthesize 4*H*-chromene derivatives using a three-component reaction involving salicylaldehydes, cyclic 1,3-diketones, and thiols in an aqueous medium at room temperature. This protocol was accomplished using the inexpensive and readily available catalyst NH_4Cl. The attractive features of this protocol are: use of inexpensive catalyst NH_4Cl, good yields, and mild and environmentally benign reaction conditions.

Key words: 4*H*-chromenes, salicylaldehydes, cyclic 1,3-diketones, thiols, ammonium chloride, aqueous medium, multicomponent reactions (MCRs)

Multicomponent reaction (MCR) offers a remarkable handy protocol to construct new heterocyclic molecules with relevant biological activity.[1] Water is truly the nature's reaction medium playing a crucial role in various life-sustaining processes. Needless to say, water is found in high abundance, hence cost-effective, and is a green solvent in organic transformations[2] owing to its nonflammable and nontoxic nature. Further, it exhibits unique properties like high dielectric constant, and its cohesive energy density puts an extraordinary effect on reaction rates with unique selectivity and reactivity.[3] Designing MCRs using water as the reaction medium to synthesize heterocyclic scaffolds with medicinal traits is one of the trending research amongst synthetic organic chemists in view of green chemistry.[4]

The chromene scaffold and its derivatives exhibit useful biological and pharmacological activities such as antibacterial,[5] antitumor,[6] anticancer,[7] anticonvulsant,[8] apoptosis inducers,[9] Chk1-inhibitors,[10] and anti-anaphylactic activities.[11] Some of them are found as natural products, for example, the antibacterial rhodomyrtone (**I**)[12] and the gastric antisecretory agent **II**[13] as shown in Figure 1.

Literature search reveals that salicylaldehyde reacts with an active methylene compound such as cyclic 1,3-diketones[14] or malononitrile[15] to form a Knoevenagel product, which can react with a suitable nucleophile such as thiols, indoles, benzotriazoles, and 4-hydroxycoumarins followed by ring-closure reaction leading to the formation of 4*H*-chromene compounds. The other methods available for the synthesis of 4*H*-chromene derivatives are cycloaddition of propargylic alcohols,[16a] or ketones[16b] with phenols, reactions of allenic esters and ketones with salicyl-*N*-tosylimines,[17] ring-closing metathesis reaction of aryl vinyl ethers,[18] copper-catalyzed intra-[19a] and intermolecular[19b] coupling of aryl bromides with 1,3-dicarbonyl compounds, tetrahydrothiophene-catalyzed ylide annulation reaction,[20] organocatalytic sequential one-pot reaction of 1,3-diones with salicylaldehydes,[21] and tandem benzylation and cyclization of 1,3-dicarbonyl compounds using benzylic alcohols.[22] A survey of the literature shows that the majority of the strategies for the synthesis of 4*H*-chromene derivatives involve either expensive catalysts,[16a,b,18,21] or multistep sequences,[18,20] prolonged reaction time,[19b] and harsh reaction conditions.[18,19,22] Consequently, there is a need to develop a synthetic method using inexpensive and environmentally benign catalyst.

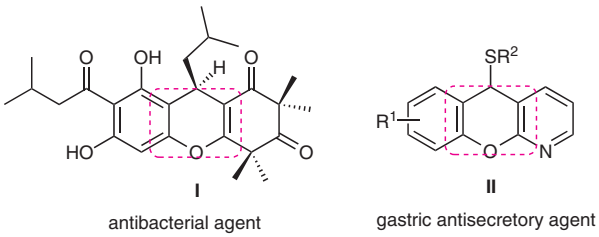

Figure 1 Some natural compounds containing chromene skeleton

Ammonium chloride is readily available and is an inexpensive catalyst. In aqueous medium, it is a good proton source, which can activate the carbonyl group through hydrogen bonding.[23] Moreover, it can react with carbonyl groups in the presence of amines to form imines, which can act as dienophiles in Diels–Alder reactions.[24] Thus, NH_4Cl was considered to be a promising catalyst in view of its remarkable ability to catalyze a manifold of organic transformations by way of multicomponent reactions for the synthesis of pyrrolo[3,4-*b*]pyridin-5-ones,[23a] di- and tetrapeptides,[25a] 3,4-dihydropyrimidin-2-(1*H*)-ones,[25b] spirochromenes,[25c] 4-imino-4*H*-3,1-benzoxazines,[25d] tetrahydrofuro[2,3-*c*]pyridine,[25e] and tetrahydrobenzo[α]xanthen-11-one derivatives.[25f]

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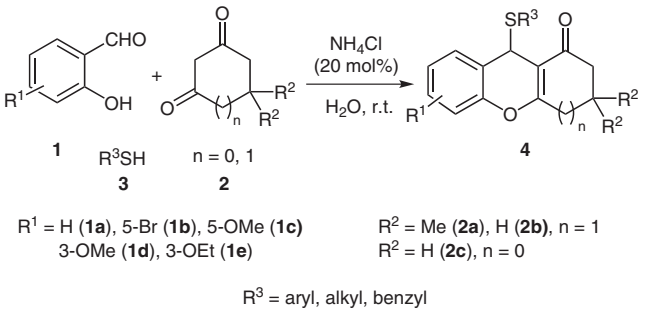
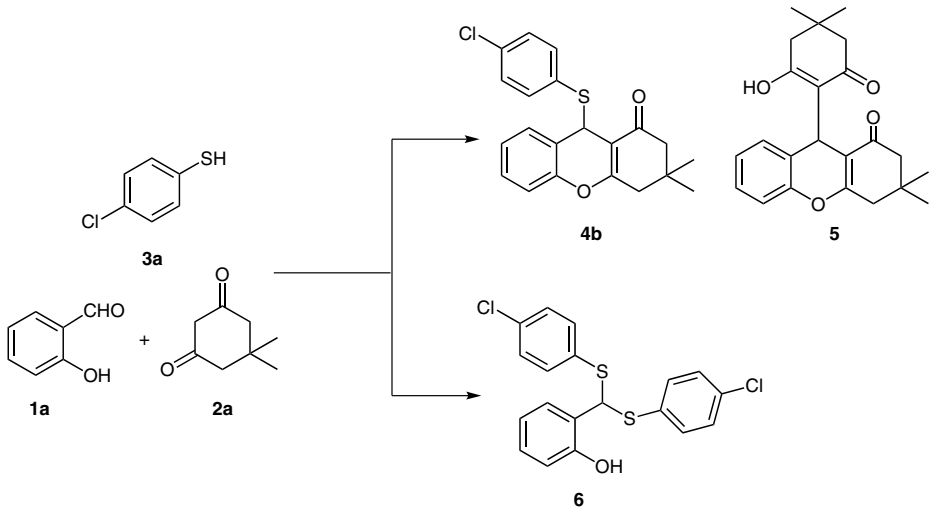
In continuation of our investigations on the synthesis of novel heterocyclic compounds under aqueous conditions,[26] we conceived to investigate the synthesis of 4*H*-chromene compounds using more environmentally benign reaction conditions. We report herein a new, convenient, and highly efficient greener protocol for the synthesis of 4*H*-chromenes **4** via three-component condensation of salicylaldehydes **1**, cyclic 1,3-dicarbonyl compounds **2**, and aromatic or aliphatic thiols **3** catalyzed by ammonium chloride in water at room temperature as shown in Scheme 1.



Scheme 1 One-pot three-component synthesis of 4*H*-chromene derivatives

In our initial efforts to synthesize 4*H*-chromene derivative **4b**, a reaction was carried out with an equimolar mixture of salicylaldehyde (**1a**), dimedone (**2a**), and 4-chlorothiophenol (**3a**) in water in the absence of catalyst at room temperature. The reaction did not proceed to completion even after 12 hours and resulted in the isolation of product 4*H*-chromene derivative **4b** and 1-oxohexahydroxanthene derivative **5**[27] in 22% and 48% yield (Table 1, entry 1), respectively, which was confirmed from IR and ^{1}H NMR

Table 1 Optimization of Reaction Conditions for the Synthesis of 3,3-Dimethyl-9-(4-chlorophenylthio)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**4b**)[a]



Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[b]		
				4b	**5**	**6**
1	none	H_2O	12	22	48	–
2	NH_4Cl (10)	H_2O	12	67	7	–
3	NH_4Cl (20)	H_2O	5	78	trace	–
4	NH_4Cl (30)	H_2O	5	74	trace	–
5	NH_4Cl (20)	EtOH	5	29	14	17
6	NH_4Cl (20)	neat	16	46	8	–
7	NH_4Br (20)	H_2O	6	74	trace	–
8	TBAB (20)	H_2O	12	37	36	26
9	TBAI (20)	H_2O	16	38	26	20
10	BETAC (20)	H_2O	12	42	22	24
11	TBATB (20)	H_2O	12	38	18	42

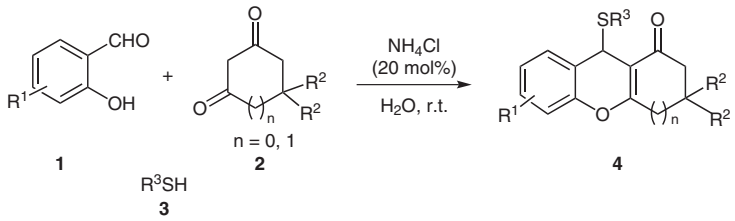
[a] Reaction conditions: salicylaldehyde (**1a**), dimedone (**2a**), and 4-chlorothiophenol (**3a**) were taken in a 1:1:1 ratio at r.t.
[b] Isolated yields after column chromatography.

spectra. The same reaction was also carried out in the presence of 10 mol% of NH_4Cl in water, which afforded the product **4b** along with the formation of a trace amount of compound **5** in 67% and 7% yield (Table 1, entry 2), respectively. To reduce the formation of the by-products as well to increase the yield of the desired 4*H*-chromene **4b**, a similar reaction was executed using 20 and 30 mol% of NH_4Cl to afford compound **4b** in 78% and 74% yield, respectively. It was noted that the yield of the product **4b** had increased from 67 to 78% by increasing the amount of catalyst from 10% to 20% with the formation of only a trace amount of product **5**, which also shortened the reaction time significantly (Table1, entry 3). However, increasing the amount of catalyst from 20% to 30% did not improve the yield of the product (Table 1, entry 4). The reactions were very sluggish and incomplete even after 16 hours, when the same reaction was carried out in the presence of 20 mol% of NH_4Cl under solvent-free conditions (Table 1, entry 6).

These results show that the catalyst NH_4Cl has a remarkable effect in suppressing the formation of by-products and controlling the reaction selectivity in water. To examine the efficacy of the catalyst, several reactions were also performed in the presence of other mild acid catalyst such as TBAB, TBAI, BETAC, and TBATB under identical reaction conditions, but all of them delivered poorer results in terms of yield and selectivity toward **4b** (Table 1, entries 8–11) and gave 2-{bis[(4-chlorophenyl)thio]methyl}phenol (**6**) as another by-product. It is worthwhile to mention that the same reaction gave comparatively similar yields when 20 mol% of NH_4Br was used in water (Table 1, entry 7). Since the yield has not increased significantly and cost of the NH_4Br is higher as compared to NH_4Cl, all the reactions were performed using 20 mol% of NH_4Cl in water.

The above observations indicate that the reaction proceeds well in the presence of 20 mol% of NH_4Cl in aqueous media. The mild reaction conditions and clean TLC pattern are the main advantages of the present reaction in

Table 2 Substrate Scope for the Synthesis of 4*H*-Chromene Derivatives **4**[a]



Entry	**1**	**2**	R^3	Time (h)	Product	Yield (%)[b]
1	**1a**	**2a**	Ph	5.0	**4a**	79
2	**1a**	**2a**	4-ClC_6H_4	5.0	**4b**	78
3	**1a**	**2a**	4-BrC_6H_4	4.5	**4c**	76
4	**1a**	**2a**	4-MeC_6H_4	4.0	**4d**	71
5	**1a**	**2a**	4-$MeOC_6H_4$	4.0	**4e**	74
6	**1a**	**2a**	2-naphthyl	6.0	**4f**	70
7	**1a**	**2a**	Et	5.0	**4g**	77
8	**1a**	**2a**	Pr	4.5	**4h**	75
9	**1b**	**2b**	Bn	5.0	**4i**	55
10	**1c**	**2b**	4-MeC_6H_4	4.0	**4j**	62
11	**1c**	**2a**	4-ClC_6H_4	4.0	**4k**	75
12	**1d**	**2a**	Pr	3.0	**4l**	71
13	**1d**	**2a**	Ph	4.0	**4m**	79
14	**1e**	**2a**	Ph	4.0	**4n**	77
15	**1a**	**2c**	Ph	3.0	**4o**	72
16	**1b**	**2c**	Ph	3.0	**4p**	69

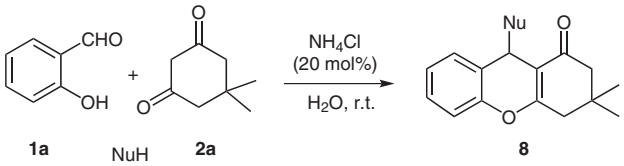
[a] Reaction conditions: salicylaldehyde **1**, 1,3-cyclic ketone **2**, and thiol **3** were taken in a 1:1:1 ratio in the presence of 20 mol% of NH_4Cl in 5 mL of H_2O at r.t.; entries 15 and 16 were conducted at reflux.
[b] Isolated yields.

water. With the optimized conditions in hand, we next embarked on an investigation of the substrate scope of the present multicomponent reaction for the synthesis of 4*H*-chromene derivatives **4** with different salicylaldehydes **1**, cyclic 1,3-diketones **2**, and thiols **3**. Performing the reaction with a mixture of salicylaldehyde, dimedone, and thiophenol under identical conditions, the desired product **4a** was obtained in 79% yield (Table 2, entry 1). To explore the synthetic scope and the generality of the present protocol, various reactions were performed with a wide variety of aromatic thiols containing different substituents in the aromatic ring such as Br, Me, and OMe with salicylaldehyde and dimedone. The reaction time and percentage yield of the products **4c**–**f** are shown in Table 2 (entries 3–6). Likewise, aliphatic thiols such as ethane thiol and propane thiol were tested under identical reaction condition to provide the desired 4*H*-chromene products **4g**,**h** in good yields (entries 7 and 8, Table 2).

For verifying the generality of the present method, other substituted salicylaldehyde derivatives bearing Br, MeO, and OEt substituent in the ring were also examined with dimedone and different aliphatic or aromatic thiols under identical reaction conditions to provide the desired 4*H*-chromene products **4i**–**n** in moderate to good yields (Table 2, entries 9–14). Furthermore, the reactions with other cyclic 1,3-diketones such as cyclohexa-1,3-dione and cyclopenta-1,3-dione with salicylaldehydes and thiophenol were also performed to give the desired products **4i**,**j** and **4o**,**p** (entries 9, 10 and 15, 16). It was observed that the similar transformation failed in the case of acyclic 1,3-diketone such as acetylacetone and also for malononitrile.

The present protocol was further examined by carrying out two consecutive reactions with salicylaldehyde (**1a**), dimedone (**2a**), and with a nucleophile such as indole (**7a**) and β-naphthol (**7b**), and the desired products **8a** and **8b** were isolated in 81% and 58% yield, respectively, as shown in Table 3.

Table 3 Substrate Scope for the Synthesis of 4*H*-Chromene Derivatives **8**[a]



1a NuH **7** **2a** **8**

Entry	NuH **7**	Time (h)	Product	Yield (%)[b]
1	indole	5.0	**8a**	81
2	2-naphthol	6.0	**8b**	58

[a] Reaction conditions: salicylaldehyde (**1a**), dimedone (**2a**), and nucleophile **7** were taken in a 1:1:1 ratio in the presence of 20 mol% of NH_4Cl in 5 mL of H_2O. For entry 1, the reaction was carried out at r.t., whereas in the case of entry 2 the reaction mixture was refluxed.
[b] Isolated yields.

All the synthesized compounds were characterized by IR, NMR, and elemental analysis. The products **4a**–**p** exhibited a diagnostic signal in the range of δ = 4.96–5.38 assignable to H-9 at the point of attachment of 4*H*-chromene to the thiol moiety depending on the nature of the substituent in salicylaldehydes and thiols. Finally, the structure of one of the representative compounds such as 9-[(4-chlorophenyl)thio]-7-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**4k**) was confirmed unambiguously by single crystal X-ray diffraction analysis (Figure 2) (see Supporting Information).

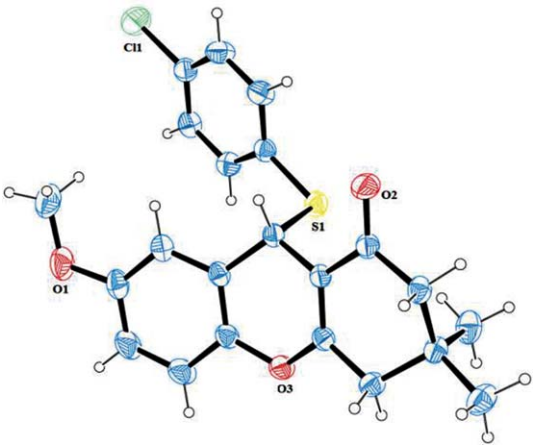
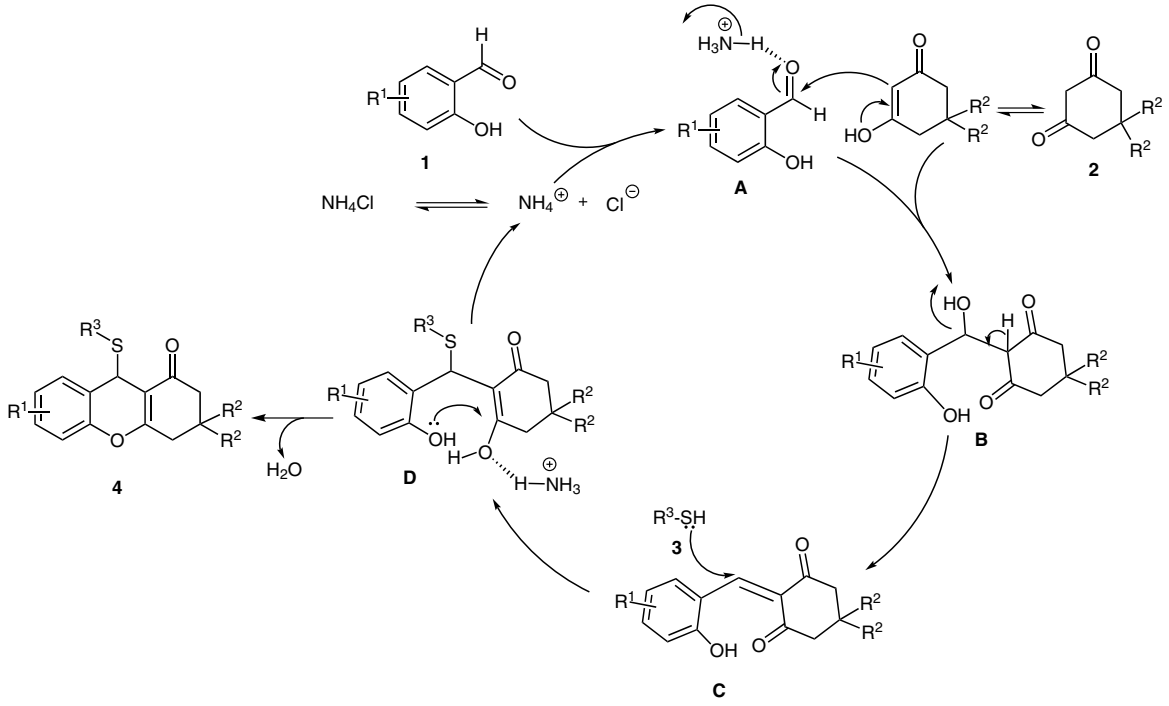


Figure 2 X-ray crystal structure of 4*H*-chromene **4k**[28]

The formation of the product may be explained as follows: The first step is believed to be the condensation reaction between salicylaldehyde **1** with cyclic 1,3-diketone **2** to give a Knoevenagel product **C**, which can act as a suitable Michael acceptor. The role of ammonium chloride is a source of proton, which activates carbonyl group through hydrogen bonding. Then a nucleophile such as thiol reacts at the exocyclic benzylidene double bond of the Knoevenagel product **C** to form the intermediate **D**, which further undergoes intramolecular ring-closure reaction followed by dehydration to give the desired 4*H*-chromene compounds **4** as shown in Scheme 2.

In conclusion, we have demonstrated an efficient and eco-friendly protocol for the synthesis of 4*H*-chromene derivatives by employing the environmentally benign catalyst NH_4Cl via one-pot three-component condensation reaction from wide variety of salicylaldehydes, cyclic 1,3-diketones, and aromatic or aliphatic thiols employing water as the reaction medium. This new method is endowed with advantages such as green reaction medium, environmentally benign reaction conditions with good yields, superior atom economy, the easy accessibility of the catalyst, and its cost effectiveness.

Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on PerkinElmer 281 IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Varian 400 spectrometer with TMS as internal reference; chemical shifts (δ scale) are reported in parts per million (ppm). ^1H NMR spectra are reported in the order: multiplicity, coupling constant



Scheme 2 Proposed NH_4Cl-catalyzed formation of 4*H*-chromene derivatives **4**

(*J* value) in hertz (Hz) and number of protons. Standard abbreviations were used to denote signal multiplicities. Mass spectrometry data was collected on Agilent Technologies 6520 Accurate-Mass Q-TOF LC/MS spectrometer. Elemental analyses were carried out using PerkinElmer 2400 Series II CHNS/O analyzer at the Department of Chemistry, Indian Institute of Technology, Guwahati. The X-ray crystal structure was determined with a Siemens P-4 diffractometer.

4*H*-Chromene Derivatives 4a–p; General Procedure

A mixture of salicylaldehyde **1** (1 mmol), cyclic 1,3-diketone **2** (1 mmol), aliphatic or aromatic thiol **3** (1 mmol), and NH_4Cl (0.2 mmol) in H_2O (5 mL) was stirred at r.t. for 3–6 h in a 25 mL round-bottomed flask. The progress of the reaction was monitored by TLC (eluent: EtOAc–hexane, 1:9). After the completion of the reaction, the crude reaction mixture was extracted with EtOAc (2 × 10 mL), the combined organic layers were washed with H_2O (10 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was chromatographed on silica gel (60–120 mesh, eluent: EtOAc–hexane, 1:9) to afford the pure products in 55–79% yields (Table 1).

Compounds **4a** and **4b** have been previously reported.[15b] The data for the by-products **5** and **6** obtained in the screening reactions are also described below.

9-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (5) (Table 1, Entry 1)

Yield: 0.175 g (48%); white solid; mp 219–221 °C.

IR (KBr): 3208, 2954, 1645 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.46 (s, 1 H), 7.17–7.14 (m, 1 H), 7.13–6.99 (m, 3 H), 4.66 (s, 1 H), 2.60 (d, *J* = 17.6 Hz, 1 H), 2.47 (d, *J* = 17.6 Hz, 1 H), 2.38–2.32 (m, 4 H), 1.99 (d, *J* = 16.8 Hz, 1 H), 1.93 (d, *J* = 8 Hz, 1 H), 1.12 (s, 3 H), 1.03 (s, 3 H), 0.99 (s, 3 H), 0.98 (s, 3 H).

Anal. Calcd for $C_{23}H_{26}O_4$ (366.45): C, 75.38; H, 7.15. Found: C, 75.44; H, 7.12.

2-{Bis[(4-chlorophenyl)thio]methyl}phenol (6) (Table 1, Entry 8)

Yield: 0.101 g (26%); brown liquid.

IR (film): 3446, 2924, 1641, 1474, 1092 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.25 (m, 4 H), 7.20–7.12 (m, 6 H), 6.81 (d, *J* = 7.6 Hz, 2 H), 5.71 (s, 1 H).

Anal. Calcd for $C_{19}H_{14}Cl_2OS_2$ (393.35): C, 58.02, H, 3.59. Found: C, 58.08; H, 3.56.

9-(4-Bromophenylsulfanyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (4c)

Yield: 0.315 g (76%); orange liquid.

IR (film): 3061, 2958, 2871, 1668, 1645, 1582, 1485, 1470, 1384, 1235, 1177, 1144, 1090, 1067, 1010, 925, 872, 820 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 1 H), 7.19–7.08 (m, 3 H), 6.90 (dd, *J* = 8.4, 1.6 Hz, 2 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 5.28 (s, 1 H), 2.40–2.27 (m, 4 H), 1.15 (s, 3 H), 1.06 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5, 166.2, 150.5, 137.5 (2 C), 131.3, 131.2 (2 C), 129.3, 128.2, 125.0, 123.3, 122.2, 116.1, 109.5, 50.7, 41.2, 40.9, 31.9, 28.3, 28.2.

Anal. Calcd for $C_{21}H_{19}BrO_2S$ (415.34): C, 60.73; H, 4.61. Found: C, 60.83; H, 4.66.

3,3-Dimethyl-9-(*p*-tolylthio)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (4d)

Yield: 0.248 g (71%); orange liquid.

IR (film): 3020, 2958, 2926, 2875, 1662, 1644, 1582, 1486, 1460, 1383, 1293, 1235, 1177, 1019, 910, 873, 809, 751, 663 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 7.6 Hz, 2 H), 7.18–7.09 (m, 2 H), 6.96 (d, *J* = 8 Hz, 2 H), 6.93 (d, *J* = 8 Hz, 1 H), 6.81 (d, *J* = 8.4 Hz, 1 H), 5.26 (s, 1 H), 2.38–2.35 (m, 4 H), 2.31 (s, 3 H), 1.17 (s, 3 H), 1.07 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.9, 166.3, 150.6, 136.4 (2 C), 128.0, 129.5, 129.1 (2 C), 128.5, 128.2, 125.0, 122.8, 116.1, 109.8, 50.9, 41.3, 40.7, 32.1, 28.5, 28.4, 21.3.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{22}O_2S$ + Na: 373.1233; found: 373.1358.

Anal. Calcd for $C_{22}H_{22}O_2S$ (350.47): C, 75.39; H, 6.33. Found: C, 75.46; H, 6.28.

9-[(4-Methoxyphenyl)thio]-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (4e)
Yield: 0.270 g (74%); orange solid; mp 107–108 °C.

IR (KBr): 2954, 1659, 1640, 1589, 1462, 1380, 1232, 1172, 1030, 758, 533 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.26 (m, 2 H), 7.17–7.12 (m, 1 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 6.79 (dd, *J* = 8, 1.6 Hz, 1 H), 6.67 (d, *J* = 8.8 Hz, 2 H), 5.22 (s, 1 H), 3.78 (s, 3 H), 2.39–2.28 (m, 4 H), 1.18 (s, 3 H), 1.07 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.4, 165.8, 160.1, 150.4, 137.8 (2 C), 129.3, 127.7, 124.6, 122.3, 121.9, 115.7, 113.5 (2 C), 109.3, 54.9, 50.5, 40.9, 40.5, 31.7, 28.2, 28.1.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{22}O_3S$ + Na: 389.1182; found: 389.1198.

Anal. Calcd for $C_{22}H_{22}O_3S$ (366.47): C, 72.10; H, 6.05. Found: C, 72.18; H, 6.10.

3,3-Dimethyl-9-(naphthalen-2-ylthio)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (4f)
Yield: 0.270 g (70%); orange liquid.

IR (film): 2956, 2926, 1665, 1643, 1581, 1498, 1460, 1381, 1266, 1176, 1143, 1129, 1031, 1013, 943 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.2 Hz, 1 H), 7.69–7.58 (m, 2 H), 7.54 (s, 1 H), 7.52–7.41 (m, 2 H), 7.28–7.23 (m, 1 H), 7.21–7.09 (m, 3 H), 6.73 (d, *J* = 7.8 Hz, 1 H), 5.39 (s, 1 H), 2.47–2.31 (m, 4 H), 1.15 (s, 3 H), 1.06 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.0, 166.4, 150.6, 136.1, 133.2, 133.0, 132.7, 129.5, 129.4, 128.2, 127.7, 127.6, 126.6, 126.5, 126.2, 125.1, 122.8, 116.1, 109.7, 50.8, 41.3, 41.0, 32.0, 28.6, 28.3.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{22}O_2S$ + Na: 409.0233; found: 409.0143.

Anal Calcd for $C_{25}H_{22}O_2S$ (386.51): C, 77.69; H, 5.74. Found: C, 77.74; H, 5.78.

9-(Ethylthio)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthene-1-one (4g)
Yield: 0.221 g (77%); orange solid; mp 63–64 °C.

IR (KBr): 2960, 1662, 1645, 1458, 1380, 1235, 1176, 1141, 1017, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.27–7.15 (m, 2 H), 7.03 (dd, *J* = 8, 1.2 Hz, 1 H), 5.04 (s, 1 H), 2.59–2.47 (m, 2 H), 2.45–2.27 (m, 4 H), 1.17 (s, 3 H), 1.13 (s, 3 H), 1.10 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.0, 165.8, 150.5, 129.4, 127.9, 125.1, 122.6, 116.0, 110.7, 50.5, 41.2, 34.8, 31.8, 29.2, 27.1, 23.5, 13.9.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{20}O_2S$ + Na: 311.1076; found: 311.1143.

Anal. Calcd for $C_{17}H_{20}O_2S$ (288.40): C, 70.80; H, 6.99. Found: C, 70.86; H, 6.92.

3,3-Dimethyl-9-(propylthio)-2,3,4,9-tetrahydro-1*H*-xanthene-1-one (4h)
Yield: 0.226 g (75%); orange liquid.

IR (film): 2959, 1662, 1645, 1582, 1457, 1379, 1291, 1234, 1176, 1144, 1012, 871, 754, 701, 663, 542 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 7.6 Hz, 1 H), 7.21 (d, *J* = 7.6 Hz, 1 H), 7.16 (d, *J* = 8.4 Hz, 1 H), 7.02 (d, *J* = 7.6 Hz, 1 H), 5.02 (s, 1 H), 2.59–2.46 (m, 2 H), 2.40–2.19 (m, 4 H), 1.48–1.41 (m, 2 H), 1.17 (s, 3 H), 1.13 (s, 3 H), 0.85 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.3, 165.2, 150.2, 129.1, 127.6, 124.7, 122.4, 115.7, 110.4, 50.1, 40.8, 34.4, 31.4, 31.2, 28.9, 26.6, 22.0, 13.2.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{22}O_2S$ + Na: 325.1200; found: 325.1286.

Anal. Calcd for $C_{18}H_{22}O_2S$ (302.43): C, 71.48; H, 7.33. Found: C, 71.55; H, 7.38.

9-(Benzylthio)-7-bromo-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (4i)
Yield: 0.220 g (55%); colorless liquid.

IR (film): 2928, 1659, 1640, 1473, 1410, 1377, 1231, 1166, 1130, 995, 703 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.18 (m, 7 H), 6.88 (d, *J* = 8.8 Hz, 1 H), 4.96 (s, 1 H), 3.61 (s, 2 H), 2.43–2.29 (m, 4 H), 1.19–1.18 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.4, 167.1, 149.8, 138.5, 132.7, 131.4, 129.0 (2 C), 128.5 (2 C), 127.1, 124.7, 118.0, 117.7, 111.8, 36.8, 35.1 (2 C), 27.7, 20.0.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{17}BrO_2S$ + Na: 425.0025; found: 425.0139.

Anal. Calcd for $C_{20}H_{17}BrO_2S$ (401.32): C, 59.86; H, 4.27. Found: C, 59.92: H, 4.33.

7-Methoxy-9-(*p*-tolylthio)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (4j)
Yield: 0.218 g (62%); orange solid; mp 145–146 °C.

IR (KBr): 2952, 2927, 1654, 1637, 1493, 1459, 1339, 1260, 1225, 1198, 1033, 998, 874, 808, 753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (d, *J* = 8 Hz, 2 H), 6.93 (d, *J* = 8.4 Hz, 2 H), 6.75–6.72 (m, 3 H), 5.25 (s, 1 H), 3.77 (s, 3 H), 2.41–2.37 (m, 4 H), 2.32 (s, 3 H), 2.01–2.04 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.2, 168.3, 156.7, 144.9, 139.2, 137.0 (2 C), 129.1 (2 C), 128.1, 123.6, 117.0, 115.3, 112.4, 109.9, 55.8, 41.2, 37.0, 27.7, 21.4, 20.4.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{20}O_3S$ + Na: 375.1025; found: 375.1018.

Anal. Calcd for $C_{21}H_{20}O_3S$ (352.45): C, 71.56; H, 5.72. Found: C, 71.60; H, 5.78.

9-[(4-Chlorophenyl)thio]-7-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (4k)
Yield: 0.300 g (75%); orange solid; mp 112–113 °C.

IR (KBr): 2955, 1659, 1643, 1497, 1380, 1216, 1038, 824 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8.4 Hz, 2 H), 7.02 (d, *J* = 8 Hz, 2 H), 6.80–6.73 (m, 2 H), 6.69 (d, *J* = 2.8 Hz, 1 H), 5.28 (s, 1 H), 3.76 (s, 3 H), 2.40–2.31 (m, 4 H), 1.15 (s, 3 H), 1.08 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.9, 166.7, 156.6, 144.9, 137.5 (2 C), 135.2, 130.7, 128.5 (2 C), 123.0, 117.3, 115.3, 112.3, 108.8, 55.7, 50.9, 41.7, 41.4, 32.1, 28.6, 28.4.

Anal. Calcd for $C_{22}H_{21}ClO_3S$ (400.92): C, 65.91; H, 5.28. Found: C, 65.89: H, 5.34.

5-Methoxy-3,3-dimethyl-9-(propylthio)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (4l)
Yield: 0.235 g (71%); orange solid; mp 128–129 °C.

IR (KBr): 3009, 2955, 1655, 1639, 1612, 1582, 1485, 1381, 1271, 1228, 1124, 1094, 764, 734, 544 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (t, *J* = 8 Hz, 1 H), 6.98 (dd, *J* = 7.6, 1.2 Hz, 1 H), 6.81 (dd, *J* = 8.0, 1.2 Hz, 1 H), 5.01 (s, 1 H),

3.91 (s, 3 H), 2.66 (d, *J* = 17.2 Hz, 1 H), 2.56 (d, *J* = 17.6 Hz, 1 H), 2.41–2.19 (m, 4 H), 1.48–1.39 (m, 2 H), 1.17 (s, 3 H), 1.13 (s, 3 H), 0.86 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.8, 165.3, 147.1, 140.2, 124.7, 123.5, 120.7, 110.4, 109.9, 55.8, 50.5, 41.1, 34.7, 31.8, 31.3, 29.1, 27.0, 22.2, 13.5.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{24}O_3S$ + Na: 355.1338; found: 355.1335.

Anal. Calcd for $C_{19}H_{24}O_3S$ (332.46): C, 68.64; H, 7.28. Found: C, 68.72; H, 7.36.

5-Methoxy-3,3-dimethyl-9-(phenylthio)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (4m)
Yield: 0.289 g (79%); orange solid; mp 102–105 °C.

IR (KBr): 3055, 2958, 1670, 1645, 1583, 1470, 1385, 1274, 1228, 1186, 1124, 1093, 954, 841, 789, 737, 665 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.27 (m, 1 H), 7.16 (t, *J* = 7.2 Hz, 2 H), 7.11–7.02 (m, 3 H), 6.85 (d, *J* = 7.8 Hz, 1 H), 6.76 (d, *J* = 7.8 Hz, 1 H), 5.30 (s, 1 H), 3.82 (s, 3 H), 2.48–2.28 (m, 4 H), 1.15 (s, 3 H), 1.06 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.8, 166.0, 147.4, 140.5, 136.1 (2 C), 131.9, 128.8, 128.2 (2 C), 124.7, 123.5, 120.9, 110.5, 109.6, 56.1, 50.8, 41.3, 40.8, 32.0, 28.4 (2 C).

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{22}O_3S$ + Na: 389.1182; found: 389.1198.

Anal. Calcd for $C_{22}H_{22}O_3S$ (366.47): C, 72.10; H, 6.05. Found: C, 72.18; H, 6.10.

5-Ethoxy-3,3-dimethyl-9-(phenylthio)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (4n)
Yield: 0.292 g (77%); orange liquid.

IR (film): 2957, 1664, 1645, 1582, 1473, 1438, 1383, 1275, 1226, 1189, 1083, 750, 692 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 6.6 Hz, 1 H), 7.17 (t, *J* = 7.8 Hz, 2H), 7.13–7.09 (m, 2 H), 7.02 (t, *J* = 7.8 Hz, 1 H), 6.80 (d, *J* = 7.8 Hz, 1 H), 6.75 (d, *J* = 8.1 Hz, 1 H), 5.29 (s, 1 H), 4.14–3.92 (m, 2 H), 2.48–2.32 (m, 4 H), 1.38 (t, *J* = 6.9 Hz, 3 H), 1.16 (s, 3 H), 1.07 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.9, 166.2, 146.6, 140.8, 136.1 (2 C), 132.1, 128.6, 128.2 (2 C), 124.6, 123.6, 120.9, 112.3, 109.6, 64.8, 50.8, 41.2, 40.9, 32.1, 28.4, 28.3, 14.7.

MS (ESI): [M + Na]$^+$ calcd for $C_{23}H_{24}O_3S$ + Na: 403.1338; found: 403.1375.

Anal. Calcd for $C_{23}H_{24}O_3S$ (380.49): C, 72.60; H, 6.36. Found: C, 72.68; H, 6.44.

9-(Phenylthio)-2,3-dihydrocyclopenta[*b*]chromen-1(9*H*)-one (4o)
Yield: 0.211 g (72%); brown liquid.

IR (film): 2923, 1704, 1651, 1574, 1438, 1393, 1249, 1163, 1119, 744, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.49 (m, 1 H), 7.31–7.27 (m, 1 H), 7.25–7.20 (m, 2 H), 7.14 (t, *J* = 7.2 Hz, 2 H), 6.94 (d, *J* = 8 Hz, 2 H), 6.85–6.83 (m, 1 H), 5.13 (s, 1 H), 2.57–2.36 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.5, 179.9, 151.3, 136.8 (2 C), 131.0, 130.9, 129.2, 128.8, 128.4 (2 C), 125.8, 122.2, 116.6, 114.0, 40.5, 33.6, 25.3.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{14}O_2S$ + Na: 317.0607; found: 317.0610.

Anal. Calcd for $C_{18}H_{14}O_2S$ (294.37): C, 73.44; H, 4.79. Found: C, 73.53; H, 4.82.

7-Bromo-9-(phenylthio)-2,3-dihydrocyclopenta[*b*]chromen-1(9*H*)-one (4p)
Yield: 0.257 g (69%); brown solid; mp 182–183 °C.

IR (KBr): 2920, 1700, 1649, 1470, 1437, 1384, 1245, 1194, 1160, 1119, 1014, 823, 740, 697 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 2.4 Hz, 1 H), 7.36–7.31 (m, 2 H), 7.19 (t, *J* = 7.8 Hz, 2 H), 7.00 (d, *J* = 8.4, 1.2 Hz, 2 H), 6.75 (d, *J* = 9.0 Hz, 1 H), 5.07 (s, 1 H), 2.62–2.51 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1, 179.5, 150.3, 136.8 (2 C), 133.5, 131.7, 130.4, 129.5, 128.6 (2 C), 124.3, 118.3, 118.1, 113.7, 40.1, 33.6, 25.3.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{13}BrO_2S$ + Na: 396.9692; found: 396.9662.

Anal. Calcd for $C_{18}H_{13}BrO_2S$ (373.26): C, 57.92; H, 3.51. Found: C, 57.98; H, 3.55.

9-(1*H*-Indol-3-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (8a)
Yield: 0.277 g (81%); orange solid; mp 200–202 °C.

IR (KBr): 3329, 1643, 1467, 1421, 1375, 1228, 1179 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (s, 1 H), 7.39 (d, *J* = 7.5 Hz, 2 H), 7.32–7.22 (m, 2 H) 7.20–7.05 (m, 3 H), 6.96 (d, *J* = 4.5 Hz, 2 H), 5.32 (s, 1 H), 2.64–2.15 (m, 4 H), 1.11 (s, 3 H), 1.04 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.4, 164.3, 149.4, 136.5, 130.1, 127.3, 125.5, 125.2, 124.8, 122.4, 121.4, 120.1, 119.1, 118.9, 116.1, 112.6, 111.2, 50.8, 41.4, 32.0, 29.4, 29.0, 27.5.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{21}NO_2$ + Na: 366.1455; found: 366.1467.

Anal. Calcd for $C_{23}H_{21}NO_2$ (343.15): C, 80.44; H, 6.16. Found: C, 80.47; H, 6.18.

9-(2-Hydroxynaphthalen-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (8b)
Yield: 0.214 g (58%); white solid; mp 229–231 °C.

IR (KBr): 3204, 2960, 1655, 1634, 1484, 1431, 1382, 1182, 1143 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.27 (s, 1 H), 7.79 (d, *J* = 9 Hz, 2 H), 7.66 (d, *J* = 7.5 Hz, 1 H), 7.37 (q, *J* = 5.7 Hz, 3 H), 7.01 (s, 2 H), 6.60 (s, 2 H), 5.77 (s, 1 H), 2.61 (s, 2 H), 2.39 (d, *J* = 5.7 Hz, 2 H), 1.15 (s, 3 H), 0.99 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.6, 166.8, 152.7, 147.7, 132.6, 131.4, 131.0, 129.0, 128.7, 128.1, 127.8, 127.4, 125.2, 123.3, 121.4, 118.7, 117.3, 116.5, 113.8, 50.1, 41.5, 32.3, 28.9, 27.9, 27.1.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{22}O_3$: 371.1642; found: 371.1642.

Anal. Calcd for $C_{25}H_{22}O_3$ (370.15): C, 81.06; H, 5.99. Found: C, 81.09; H, 5.94.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are X-ray crystallographic data (CIF files) of **4k**, spectral data of all compounds and copies of ^{1}H, ^{13}C NMR, and MS spectra of products.

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(28) Complete crystallographic data of **4k** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 926004. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk].

