A Novel, Convenient Synthesis of 2-Aryl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazines

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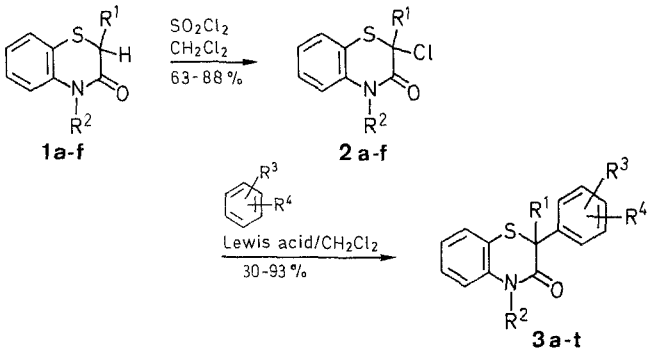
A novel method for the synthesis of 2-aryl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazines consists of a Friedel–Crafts type reaction of substituted benzenes with 2-chloro-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazines. This method is convenient by virtue of its simplicity and the good yields.

In the course of our synthetic work[1] on novel calcium antagonists, we prepared 3-oxo-2-phenyl-3,4-dihydro-2*H*-1,4-benzothiazines **3** which are methoxy- or hydroxy-substituted on the phenyl group at C-2. 3-Oxo-2-phenyl-3,4-dihydro-2*H*-1,4-benzothiazines have earlier been prepared[2–5] by condensation of α-bromophenylacetic acid derivatives and 2-aminothiophenol. However, this method has the drawback that already the preparation of the starting α-bromophenylacetic acids requires several steps.[6–11] We now applied the known[12–15] Friedel–Crafts reaction of substituted benzenes with 1-chloro-2-oxoalkyl sulfides to the synthesis of compounds **3** from the *C*-chloroheterocycles **2** and thus established a convenient synthetic method for **3** (Scheme **A**).

The starting compounds **2** were obtained by treatment of 3-oxo-3,4-dihydro-2*H*-1,4-benzothiazines **1**[16–21] with an equimolecular amount or a slight excess (1.0–1.2 equiv) of sulfuryl chloride in dichloromethane under various conditions which depend on the solubility of **1** and the bulkiness of the alkyl group at C-2. Secondary chloro compounds (**2a**,[18] **b**,[18] **e,f**) precipitated as crystals in nearly pure form when the solvent was concentrated *in vacuo* or the reaction mixture was stirred at 0 °C; these compounds were used in the next step without further purification because of their instability toward moisture. Tertiary chloro compounds (**2c, d**), which are less stable than the secondary compounds, were submitted to the next reaction step without isolation to avoid decomposition.

The Friedel–Crafts reaction of methoxybenzenes with compounds **2a, b, e, f** was carried out in dichloromethane using an equimolecular amount of aluminum chloride (10 min) and gave products **3a–f, i, j** in good yields. The reaction of benzene, used as a solvent, with **2b** gave product **3g**[22] in 75% yield. The reaction of chlorobenzene with **2b** afforded products **3h** and **4** in 54% and 15% yields, respectively. The formation of by-product **4** can be explained by higher reactivity of the benzene ring in **3h**



1, 2	R^1	R^2	1, 2	R^1	R^2
a	H	H	**d**	*i*-C_3H_7	CH_3
b	H	CH_3	**e**	H	$(CH_2)_3NMe_2 \cdot HCl$
c	CH_3	CH_3	**f**	H	CH_2CO_2H

3	R^1	R^2	R^3	R^4
a	H	H	4′-OCH_3	H
b	H	H	3′-OCH_3	4′-OCH_3
c	H	H	2′-OCH_3	5′-OCH_3
d	H	CH_3	4′-OCH_3	H
e	H	CH_3	3′-OCH_3	4′-OCH_3
f	H	CH_3	2′-OCH_3	5′-OCH_3
g	H	CH_3	H	H
h	H	CH_3	4′-Cl	H
i	H	$(CH_2)_3NMe_2$	4′-OCH_3	H
j	H	CH_2CO_2H	4′-OCH_3	H
k	H	CH_3	4′-OH	H
l	H	CH_3	2′-OH	H
m	H	CH_3	2′-OH	5′-OCH_3
n	H	CH_3	2′-OCH_3	5′-OH
o	H	CH_3	2′-OH	5′-NO_2
p	CH_3	CH_3	4′-OH	H
q	CH_3	CH_3	2′-OH	5′-OCH_3
r	CH_3	CH_3	2′-OCH_3	5′-OH
s	*i*-C_3H_7	CH_3	2′-OH	5′-OCH_3
t	*i*-C_3H_7	CH_3	2′-OCH_3	5′-OH

Scheme A

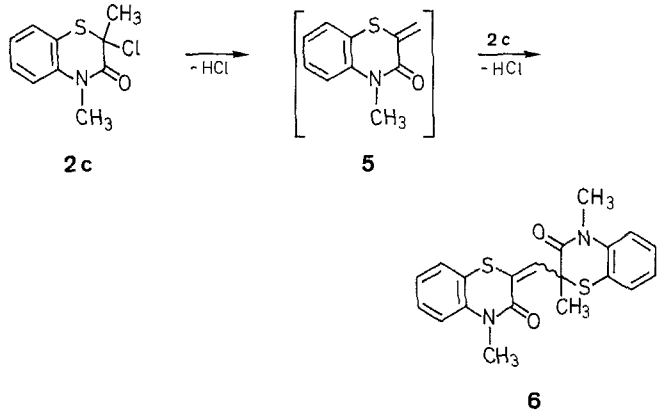
Table 1. Chlorination of 3-Oxo-3,4-dihydro-2*H*-1,4-benzothiazines **1a–f**

Substrate	SO_2Cl_2 (equiv)	Reaction Temperature and Time	Product	Yield[a] (%)	mp[b] (°C)	IR (KBr) $\nu_{C=O}$ (cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS) δ, *J*(Hz)
1a[16,17]	1.0	r.t., 5 h	**2a**[18]	86	198–210 (dec) (221–223)[18]	1663	6.19 (s, 1H); 6.87–7.67 (m, 4H); 10.80–11.37 (br, 1H)
1b[18]	1.0	r.t., 15 min	**2b**[18]	88	93–95 (dec) (95–97)[18]	1635	3.37 (s, 3H); 6.21 (s, 1H); 6.83–7.57 (m, 4H)
1c[19]	1.1	0 °C, 30 min	**2c**	[c]	[c]	[c]	[c]
1d	1.2	r.t., 30 min	**2d**	[c]	[c]	[c]	[c]
1e[20]	1.0	r.t., 15 min	**2e**	63	176–180 (dec)	1646	1.82–2.32 (m, 2H); 2.70 (d, 6H, *J* = 4.5); 2.87–3.35 (m, 2H); 3.73–4.34 (m, 2H); 6.27 (s, 1H); 6.96–7.70 (m, 4H); 10.83–11.57 (br, 1H)
1f[21]	1.0	r.t., 15 min	**2f**	78	149–151 (dec)	1660	4.57 (d, 1H, *J* = 18); 4.77 (d, 1H, *J* = 18); 6.28 (s, 1H); 6.95–7.65 (m, 4H); 7.75–9.18 (br, 1H)

[a] Yield of isolated product.
[b] Melting point of crude product.
[c] Chlorinated compound was not isolated because of its instability.

as compared to that of chlorobenzene. The reaction of phenol, 4-methoxyphenol, or 4-nitrophenol with **2b, c, d** proceeded in the presence of Lewis acid in dichloromethane to give products **3k–t**. Only **2b** reacted with phenol and 4-methoxyphenol in the absence of Lewis acid (short reaction time) to give **3k, l** and **3m, n**, respectively.

The reaction of phenol or 4-methoxyphenol with **2c** without Lewis acid yielded **3p** and dimer **6** as a by-product, or **3q** and **6**, respectively. Compound **6** was considered to be produced via electrophilic substitution of **2c** by **5**, the dehydrochlorination product of **2c** (Scheme **B**).



Scheme **B**

Table 3. Reaction of 2-Chloro-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazines **2b–d** with Phenol or Substituted Phenols

Substrate	ArH	Lewis acid	Reaction Temperature and Time	Product: Yield[a] (%)
2b	phenol	$AlCl_3$	0 °C, 10 min	**3k:** 77, **3l:** 5
2b	phenol	–	r.t., 10 min	**3k:** 77, **3l:** 10
2b	4-methoxyphenol	$AlCl_3$	0 °C, 10 min	**3m:** 60, **3n:** 21
2b	4-methoxyphenol	–	r.t., 10 min	**3m:** 85, **3n:** 4
2b	4-nitrophenol	$AlCl_3$	r.t., 10 h	**3o:** 74
2c	phenol	$AlCl_3$	0 °C, 30 min	**3p:** 78
2c	phenol	–	r.t., 3 h	**3p:** 50, **6:** 26
2c	4-methoxyphenol	$AlCl_3$	0 °C, 30 min	**3q:** 52, **3r:** 9
2c	4-methoxyphenol	–	r.t., 3 h	**3q:** 29, **6:** 25
2d	4-methoxyphenol	$SnCl_4$	r.t., 5 h	**3s:** 24, **3t:** 6

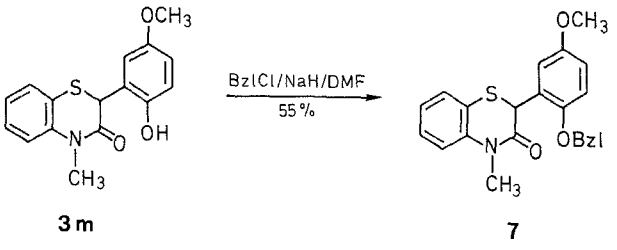
[a] Yield of isolated product.

Table 2. Reaction of 2-Chloro-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazines **2a, b, e, f** with Methoxybenzenes, Benzene, or Chlorobenzene

Substrate	ArH	Lewis acid	Reaction Temperature and Time	Product	Yield (%)[a]	mp (°C)	Molecular Formula[b]	IR (KBr) $\nu_{C=O}$ (cm^{-1})	^{1}H-NMR[c] δ, J(Hz)
2a	anisole	$AlCl_3$	reflux, 10 min	**3a**	82	186–187 (EtOAc)	$C_{15}H_{13}NO_2S$ (271.3)	1663	3.64 (s, 3H); 4.80 (s, 1H); 6.63–7.43 (m, 4H); 6.82 (d, 2H, J = 9); 7.13 (d, 2H, J = 9); 10.53–10.90 (br, 1H)
2a	veratrole	$AlCl_3$	reflux, 10 min	**3b**	90	176–177 (EtOAc)	$C_{16}H_{15}NO_3S$ (301.4)	1656	3.60 (s, 3H); 3.65 (s, 3H); 4.77 (s, 1H); 6.64–7.38 (m, 7H); 10.58–10.85 (br, 1H)
2a	1,4-dimethoxybenzene	$AlCl_3$	reflux, 10 min	**3c**	93	183–184 (EtOH/EtOAc)	$C_{16}H_{15}NO_3S$ (301.4)	1648	3.58 (s, 3H); 3.78 (s, 3H); 4.94 (s, 1H); 6.46–7.43 (m, 7H); 10.69–11.06 (br, 1H)
2b	anisole	$AlCl_3$	reflux, 10 min	**3d**	83	130–131 (EtOAc/hexane)	$C_{16}H_{15}NO_2S$ (285.4)	1661	3.46 (s, 3H); 3.68 (s, 3H); 4.57 (s, 1H); 6.57–7.41 (m, 4H); 6.74 (d, 2H, J = 8.5); 7.11 (d, 2H, J = 8.5)
2b	veratrole	$AlCl_3$	reflux, 10 min	**3e**	80	95–97 (EtOAc/hexane)	$C_{17}H_{17}NO_3S$ (315.4)	1653	3.47 (s, 3H); 3.73 (s, 3H); 3.76 (s, 3H); 4.60 (s, 1H); 6.55–7.48 (m, 7H)
2b	1,4-dimethoxybenzene	$AlCl_3$	reflux, 10 min	**3f**	83	103–105 (EtOAc/hexane)	$C_{17}H_{17}NO_3S$ (315.4)	1654	3.49 (s, 3H); 3.57 (s, 3H); 3.73 (s, 3H); 5.04 (s, 1H); 6.47–7.47 (m, 7H)
2b	benzene	$AlCl_3$	40 °C, 10 min	**3g**[22]	75	153–154 (EtOH)	$C_{15}H_{13}NOS$ (255.3)	1664	3.51 (s, 3H); 4.67 (s, 1H); 6.80–7.53 (m, 9H)
2b	chlorobenzene	$AlCl_3$	reflux, 1 h	**3h**[d]	57	132–134 (benzene/hexane)	$C_{15}H_{12}ClNOS$ (289.8)	1653	3.50 (s, 3H); 4.61 (s, 1H); 6.80–7.60 (m, 8H)
2e	anisole	$AlCl_3$	reflux, 10 min	**3i**	79	oil	$C_{20}H_{24}N_2O_2S$[e] (356.5)	1650	1.66–2.48 (m, 4H); 2.17 (s, 6H); 3.70 (s, 3H); 3.93–4.25 (m, 2H); 4.55 (s, 1H); 6.73 (d, 2H, J = 8.5); 6.82–7.37 (m, 4H); 7.13 (d, 2H, J = 8.5)
2f	anisole	$AlCl_3$	reflux, 10 min	**3j**	86	155–157 (EtOAc/i-Pr_2O)	$C_{17}H_{15}NO_4S$ (329.4)	1654	3.67 (s, 3H); 4.59 (d, 1H, J = 18); 4.70 (s, 1H); 4.86 (d, 1H, J = 18); 6.58–7.44 (m, 4H); 6.73 (d, 2H, J = 8.5); 7.23 (d, 2H, J = 8.5); 9.83–10.18 (br, 1H)

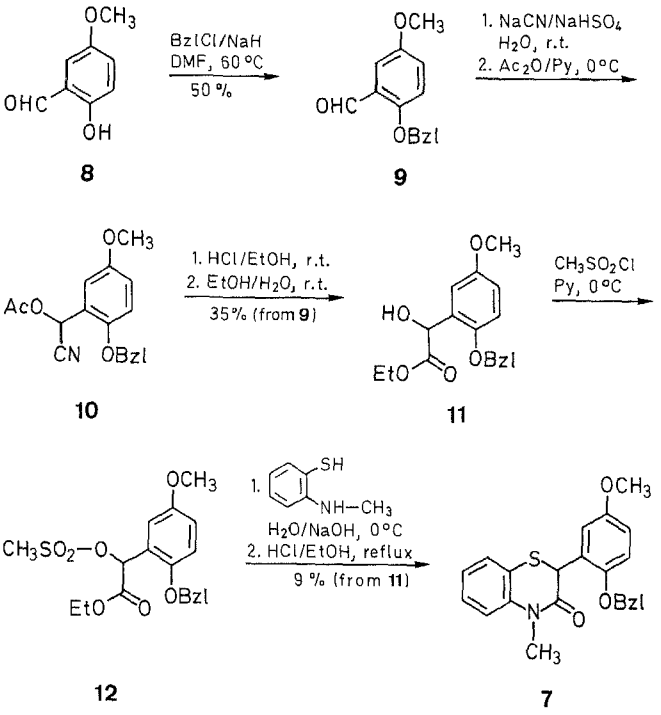
[a] Yield of isolated product.
[b] Satisfactory microanalyses obtained: C ±0.28, H ±0.15, N ±0.09.
[c] Compounds **3a**, **3b**, and **3c** were dissolved in DMSO-d_6, the others in $CDCl_3$.
[d] Product **4** was obtained in 9% yield.
[e] Exact Mass: ($C_{20}H_{24}N_2O_2S$) calc. 356.1557, found 356.1560.

Compounds **2b, c, d** reacted with 4-methoxyphenol to give two isomeric products in each case: **3m** + **3n**, **3q** + **r**, and **3s** + **3t**, respectively. The structures of these products were confirmed by an independent synthesis of the *O*-benzyl derivative **7** (Scheme **C**) which is easily prepared from the hydroxy compound **3m**.



3m **7**

Thus, compound **7** was synthesized from 2-hydroxy-5-methoxybenzaldehyde (**8**) by *O*-benzylation to **9**, cyanohydrin formation[9-11] from aldehyde **9** followed by *O*-acetylation to give α-acetoxynitrile **10**, which is not purified by column chromatography or distillation because of its instability but immediately subjected to a two-step solvolysis to give the mandelic acid derivative **11** (35% yield from **9**). Treatment of **11** with methanesulfonyl chloride/pyridine at 0°C gave the unstable α-mesyloxyester **12** (which decomposes at room temperature within one day) which was condensed with 2-methylaminobenzenethiol[23] in two steps to give **7** in 9% yield from **11**. This result showed that the new C–C bond of **3m** was formed at the position *ortho* to the phenolic hydroxy group.



8 **9** **10** **11** **12** **7**

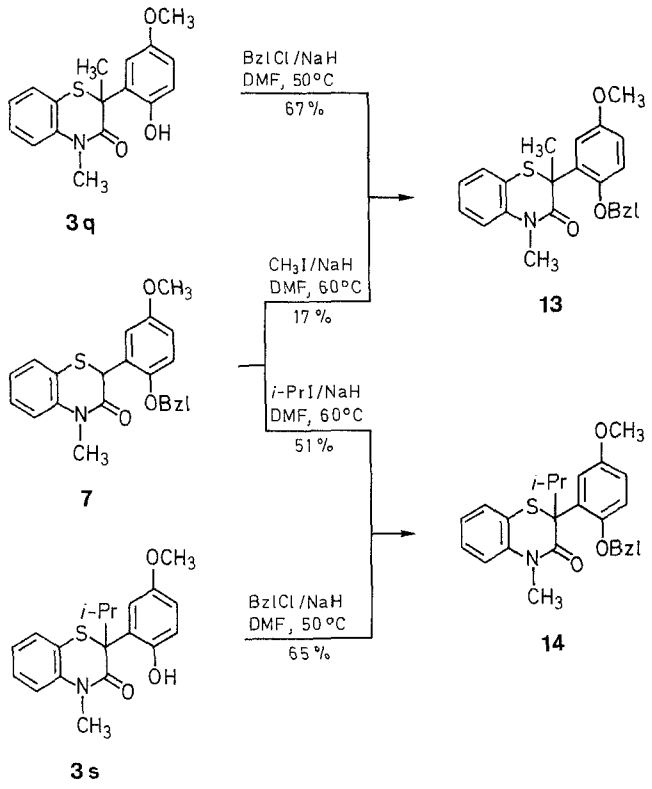
Scheme **C**

The structures of **3q, s** were confirmed by comparison of the *O*-benzyl derivatives prepared from **3q, s** with the 2-methyl and 2-isopropyl derivatives **13** and **14**, respectively, obtained from **7** according to Scheme **D**. The structures of **3n, r, t**, i.e., the regioisomers of **3m, q, s**, then followed automatically.

Table 4. Physical and Spectral Data of Compounds **3k–t**

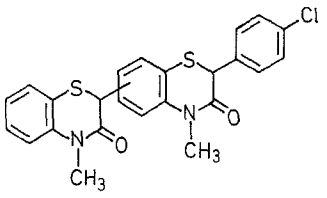
Compound	mp (°C)	Molecular Formula[a]	IR (KBr) ν(cm^{-1})	^{1}H-NMR[b] δ, J(Hz)
3k	180–181 (MeOH/EtOH)	$C_{15}H_{13}NO_2S$ (271.3)	3064, 1609	3.42 (s, 3H); 4.83 (s, 1H); 6.45–7.45 (m, 4H); 6.65 (d, 2H, J = 8.5); 6.98 (d, 2H, J = 8.5); 7.45–8.82 (br, 1H)
3l	161–162 (EtOAc/hexane)	$C_{15}H_{13}NO_2S$ (271.3)	3020, 1617	3.45 (s, 3H); 4.92 (s, 1H); 6.42–7.48 (m, 8H); 9.62 (s, 1H)
3m	204–206 (dec) (MeOH/EtOH)	$C_{16}H_{15}NO_3S$ (301.4)	3212, 1628	3.46 (s, 3H); 3.50 (s, 3H); 4.86 (s, 1H); 6.18–7.43 (m, 7H); 7.80–9.70 (br, 1H)
3n	191–192 (MeOH/EtOH)	$C_{16}H_{15}NO_3S$ (301.4)	3152, 1629	3.41 (s, 3H); 3.67 (s, 3H); 4.85 (s, 1H); 6.25–7.42 (m, 7H); 8.82 (s, 1H)
3o	238–240 (dec) (EtOAc/hexane)	$C_{15}H_{12}N_2O_4S$ (316.3)	3008, 1605	3.47 (s, 3H); 5.01 (s, 1H); 6.90–7.47 (m, 4H); 7.03 (d, 1H, J = 9); 7.76 (d, 1H, J = 2.5); 8.03 (dd, 1H, J = 9, 2.5); 11.43–11.80 (br, 1H)
3p	159–160 (EtOAc/hexane)	$C_{16}H_{15}NO_2S$ (285.4)	3244, 1624	1.64 (s, 3H); 3.42 (s, 3H); 6.38–7.42 (m, 4H); 6.54 (d, 2H, J = 8.5); 7.10 (d, 2H, J = 8.5); 9.25 (s, 1H)
3q	176–177 (EtOAc/hexane)	$C_{17}H_{17}NO_3S$ (315.4)	3192, 1628	1.76 (s, 3H); 3.42 (s, 3H); 3.54 (s, 3H); 6.46–7.43 (m, 7H); 9.03 (s, 1H)
3r	150–152 (EtOH/EtOAc)	$C_{17}H_{17}NO_3S$ (315.4)	3224, 1636	1.67 (s, 3H); 3.39 (s, 3H); 3.60 (s, 3H); 6.46 (dd, 1H, J = 9, 2); 6.65 (d, 1H, J = 9); 6.72 (d, 1H, J = 2); 6.80–7.43 (m, 4H); 8.77 (s, 1H)
3s	143–144 (EtOAc/hexane)	$C_{19}H_{21}NO_3S$ (343.5)	3128, 1624	0.83 (d, 3H, J = 7); 1.27 (d, 3H, J = 7); 2.86–3.68 (m, 1H); 3.44 (s, 3H); 3.53 (s, 3H); 6.56–7.56 (m, 7H); 7.68 (s, 1H)
3t	174–175 (EtOAc/hexane)	$C_{19}H_{21}NO_3S$ (343.5)	3292, 1634	0.94 (d, 3H, J = 7); 1.46 (d, 3H, J = 7); 2.53–3.13 (m, 1H); 3.40 (s, 3H); 3.60 (s, 3H); 6.19 (s, 1H); 6.46–7.43 (m, 7H)

[a] Satisfactory microanalyses obtained: C ±0.34, H ±0.19, N ±0.15. [b] Compounds **3s** and **3t** were dissolved in $CDCl_3$, the others in DMSO-d_6.



Scheme **D**

In conclusion, the present method is convenient in terms of simplicity, good yields, and short reaction times. It may be applied to large-scale production, and it may also be applied to complex or unstable substrates. There are some limitations as regards the reactivity of compounds **2** and of the substituted benzenes in so far as compounds **2** possessing high steric hindrance at C-2 and electron-poor substituted benzenes show low reactivity in the reaction **2** → **3**



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Melting points were determined in open glass capillaries with a Yamato MP-21 melting point apparatus and are uncorrected. Microanalyses were performed on a Yanagimoto MT-3 CHN Corder element analyzer. Mass spectra were obtained on a Hitachi M-80 B double-focusing mass spectrometer. IR spectra were recorded on a JASCO A-302 infrared spectrophotometer; only the strongest and/or structurally most important peaks are given. ^{1}H-NMR spectra were measured on a JEOL PMX-60 spectrometer (60 MHz).

The solvents THF, CH_2Cl_2, benzene, and DMF were dried by standard methods before use. All yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogeneous products.

4-Methyl-2-(1-methylethyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine (1d):

A solution of 4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine (**1b**; 20.0 g, 112 mmol) in THF (80 mL) is added with stirring to lithium diisopropylamide [1.05 equiv; prepared *in situ* from BuLi (1.05 equiv in hexane) in THF (20 mL) and *i*-Pr_2NH (13.6 g, 1.2 equiv) in THF (200 mL) under N_2 at −78 °C]. The mixture is stirred for 15 min at −78 °C, then *i*-PrI (20.9 g, 1.1 equiv) is added, stirring is continued for 30 min at −78 °C and for 3 h at room temperature, and saturated NH_4Cl solution (200 mL) is added. The mixture is extracted with EtOAc (2 × 200 mL), washed with brine (50 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude product is column-chromatographed on silica gel (benzene/EtOAc 50:1) to give **1d**; yield: 20.5 g (83%); mp 32–33 °C (from hexane).

$C_{12}H_{15}NOS$	calc.	C 65.12	H 6.83	N 6.33
(221.3)	found	65.07	6.85	6.40

IR (KBr): ν = 2912, 1653, 1570, 1459, 1437, 1352 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.01 (d, 6H, J = 6 Hz); 1.51–2.13 (m, 1H); 3.06 (d, 1H, J = 8 Hz); 3.42 (s, 3H); 6.73–7.48 (m, 4H).

2-Chloro-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazines (2); General Procedure:

To a stirred suspension of a compound **1** (10.0 mmol) in CH_2Cl_2 (10 mL), SO_2Cl_2 (0.80–0.96 mL, 1.0–1.2 equiv) is added dropwise at room temperature and stirring is continued for the appropriate time. The mixture is evaporated under reduced pressure to give a colorless solid which is isolated by suction to give the crude product **2** (Table 1).

2-Aryl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazines (3); General Procedure:

To a stirred suspension of the substituted benzene (1.2 equiv) and the Lewis acid (1.0 equiv) in CH_2Cl_2 (1 mL), the respective compound **2** (4.50 mmol) is added at room temperature. The resultant mixture is refluxed with stirring for the appropriate time (evolution of HCl gas). After cooling, the mixture is treated with H_2O (15 mL). If the product **3** precipitates as crystals it is isolated by suction, washed with conc. aqueous HCl (10 mL) and Et_2O (20 mL), and dried. Otherwise, the mixture is extracted with $CHCl_3$ (2 × 20 mL); the extract is washed with saturated $NaHCO_3$ solution (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The precipitated crystalline product is isolated, washed with an appropriate solvent, and freed from solvent by suction to give the major product **3**. The mother liquor is chromatographed on silica gel to yield an additional amount of the major product **3** and a minor amount of its regio isomer (Tables 2,3,4).

2-(4-Chlorophenyl)-4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine (3h) and 2-(4-Chlorophenyl)-5,6,7, or 8-(4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)-4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine (4):

To a stirred suspension of chlorobenzene (0.63 g, 1.2 equiv) and $AlCl_3$ (0.62 g, 1.0 equiv) in CH_2Cl_2 (1 mL), compound **2b** (1.00 g, 4.68 mmol) is added in small portions at room temperature and the mixture is refluxed with stirring for 10 min (evolution of HCl gas). After cooling, the mixture is treated with H_2O (15 mL) and extracted with $CHCl_3$ (2 × 20 mL). The extract is washed with saturated $NaHCO_3$ solution (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue is column-chromatographed on silica gel (benzene/EtOAc 5:1) to give products **3h** and **4**.

Compound **3h**; yield: 0.77 g (57%); mp 132–134 °C (benzene/hexane); see Table 2.

Compound **4**; yield: 0.10 g (9%); mp 173–175 °C (benzene/hexane).

$C_{24}H_{19}ClN_2O_2S_2$	calc.	C 61.73	H 4.10	N 6.00
(519.1)	found	61.75	4.13	6.02

IR (KBr): ν = 1651, 1465, 1406, 1346, 1269, 1236 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 3.38 (s, 3H); 3.46 (s, 3H); 4.55 (s, 2H); 6.87–7.45 (m, 11H).

2-(4-Hydroxyphenyl)-2,4-dimethyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine (3p) and 4-Methyl-2-(2,4-dimethyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylmethylene)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine (6):

To a stirred solution of 2,4-dimethyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine (**1c**; 1.00 g, 5.17 mmol) in CH_2Cl_2 (5 mL), SO_2Cl_2 (0.46 mL, 1.1 equiv) is added dropwise at 0 °C and stirring is continued for 30 min to generate compound **2c**. Then, a solution of phenol (0.54 g, 1.2 equiv) in CH_2Cl_2 (4 mL) is added at 0 °C and stirring is continued for 3 h at room temperature. The mixture is then treated with H_2O (30 mL) and extracted with $CHCl_3$ (2 × 30 mL). The extract is washed with saturated $NaHCO_3$ solution (30 mL) and brine (30 mL). The organic layer is dried ($MgSO_4$) and concentrated under reduced pressure. The residue is column-chromatographed on silica gel (hexane/EtOAc 3:1) to give products **3p** and **6**.

Compound **3p**; yield: 0.74 g (50%); mp 159–160 °C (EtOAc/hexane); see Table 4.

Compound **6**; *yield: 0.26 g (26%); mp 165–166 °C (benzene/hexane).*

$C_{20}H_{18}N_2O_2S_2$ (382.5) calc. C 62.80 H 4.74 N 7.32; found 63.02 4.76 7.39

IR (KBr): ν = 1634, 1576, 1437, 1342, 1257 cm⁻¹.

^{1}H-NMR ($CDCl_3$): δ = 1.74 (s, 3H); 3.34 (s, 3H); 3.49 (s, 3H); 6.76–7.40 (m, 9H).

2-(2-Benzyloxy-5-methoxyphenyl)-4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine (7):

Method A (from **3m**): A solution of compound **3m** (2.00 g, 6.64 mmol) *in DMF (8 mL) is added to a stirred suspension of NaH (60% mineral* oil dispersion; 0.29 g, 1.1 equiv) in DMF (2 mL) at 0–10 °C and stirring is continued for 15 min. Benzyl chloride (1.01 g, 1.2 equiv) is then added and the mixture is stirred for 1 h at 50 °C. After cooling, the mixture is treated with H_2O (50 mL) and extracted with EtOAc (2 × 50 mL). The extract is washed with brine (50 mL) and dried ($MgSO_4$). The solvent is evaporated and the crystalline residue is washed with Et_2O and isolated by suction; *yield of* **7**: *1.43 g (55%); mp 133–134 °C (EtOAc/hexane).*

Method B (from **8**):

2-Benzyloxy-5-methoxybenzaldehyde (**9**): A solution of 2-hydroxy-5-*methoxybenzaldehyde* (**8**; *10.0 g, 65.7 mmol) in DMF (50 mL)* is added to a stirred suspension of NaH (60% mineral oil dispersion; 3.16 g, 1.2 equiv) in DMF (30 mL) at 0–10 °C and stirring is continued for 15 min. Benzyl chloride (10.0 g, 1.2 equiv) is then added and stirring is continued for 4 h at 70 °C. After cooling, the mixture is treated with H_2O (250 mL) and extracted with EtOAc (2 × 250 mL). The extract is washed with brine (250 mL), dried ($MgSO_4$), and evaporated. The residue is column-chromatographed on silica gel *(benzene as eluent) to give product* **9**; yield: 8.00 g (50%); mp 48–49 °C (hexane).

$C_{15}H_{14}O_3$ (242.3) calc. C 74.36 H 5.82; found 74.26 5.79

IR (KBr): ν = 1670, 1487, 1449, 1421, 1266 cm⁻¹.

^{1}H-NMR ($CDCl_3$): δ = 3.75 (s, 3H); 5.07 (s, 2H); 6.78–7.48 (m, 8H); 10.40 (s, 1H).

Ethyl 2-(2-Benzyloxy-5-methoxyphenyl)-2-hydroxyacetate (**11**): To a stirred suspension of compound **9** (5.83 g, 24.1 mmol) and $NaHSO_3$ (2.88 g, 1.15 equiv) in H_2O (12 mL), a solution of NaCN (3.78 g, 3.2 equiv) in H_2O (9 mL) is added dropwise at room temperature and stirring is continued for 3 h. The mixture is extracted with Et_2O (2 × 30 mL) and the extract is washed with brine (30 mL) and dried ($MgSO_4$). The solvent *is evaporated under reduced pressure, the residue is dissolved in* Et_2O (6 mL), Ac_2O (4.55 mL, 2.0 equiv) and pyridine (2.86 g, 1.5 equiv) are added at 0 °C, and stirring is continued for 2 h at 0 °C. Then, a solution of $NaHCO_3$ (6.07 g, 3.0 equiv) in H_2O (50 mL) is added at room temperature and stirring is continued for 30 min. The mixture is extracted with Et_2O (2 × 50 mL), washed with brine (30 mL), and dried ($MgSO_4$). Evaporation of the solvent gives crude 2-acetoxy-2-(2-benzyloxy-5-methoxyphenyl)acetonitrile **10** (7.00 g) as an oil. The crude nitrile **10** is dissolved in a 3 N solution of HCl in EtOH (35 mL) and stirring is continued at room temperature for 4 h. The mixture is evaporated under reduced pressure. The residue is dissolved in H_2O (10 mL)/EtOH *(10 mL), this solution is stirred* at room temperature for 2.5 h, and then extracted with EtOAc (2 × 50 mL). The extract is washed with brine (50 mL), dried ($MgSO_4$), and evaporated. The residue is column-chromatographed on silica gel (benzene/EtOAc 10:1) to give ester **11** as an oil; yield: 2.70 g (35% from **9**).

Exact Mass: ($C_{18}H_{20}O_5$) calc. 316.1309, found 316.1313.

IR (film): ν = 3440, 1729, 1499, 1453, 1213 cm⁻¹.

^{1}H-NMR ($CDCl_3$): δ = 1.16 (t, 3H, *J* = 7 Hz); 3.50 (d, 1H, *J* = 7 Hz); 3.71 (s, 3H); 4.12 (q, 2H, *J* = 7 Hz); 5.00 (s, 2H); 5.29 (d, 1H, *J* = 7 Hz); 6.72–7.52 (m, 8H).

2-(2-Benzyloxy-5-methoxyphenyl)-4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzothiazine (**7**): Methanesulfonyl chloride (0.435 g, 1.2 equiv) is added to a stirred mixture of compound **11** (1.00 g, 3.16 mmol) and pyridine (0.50 g, 2 equiv) at 0 °C and stirring is continued for 3 h. *The mixture is* then treated with 1 N aqueous HCl (30 mL) and extracted with EtOAc (2 × 30 mL). The extract is washed with brine (30 mL), dried ($MgSO_4$), and evaporated to give crude ethyl 2-(2-benzyloxy-5-methoxyphenyl)-2-*methanesulfonyloxyacetate* (**12**; *1.20 g*) as an oil. To a stirred solution of crude **12** in THF (6 mL), a solution of 2-methylaminobenzenethiol (0,44 g, 1.0 equiv) in 1 N aqueous NaOH (3.3 mL) is added dropwise at 0 °C and stirring is continued for 1 h. The mixture is then treated with *1 N aqueous HCl (22 mL) and extracted with* Et_2O (2 × *30 mL). The* extract is evaporated under reduced pressure. The residue is dissolved in 3 N HCl in EtOH (2.2 mL) and refluxed for 2 h. After cooling, the mixture is concentrated under reduced pressure and the residue is dissolved in EtOAc (50 mL). This solution is washed with 1 N aqueous NaOH (20 mL) and with brine (30 mL). The organic layer is dried ($MgSO_4$) and evaporated under reduced pressure and the residue is column-chromatographed on silica gel(benzene/EtOAc 20:1) to give **7**; yield: 0.11 g (9% from **11**); mp 133–134 °C (EtOAc/hexane).

$C_{23}H_{21}NO_3S$ (391.5) calc. C 70.56 H 5.41 N 3.58; found 70.84 5.31 3.80

IR (KBr): ν = 1641, 1580, 1498, 1464, 1443, 1362, 1238 cm⁻¹.

^{1}H-NMR ($CDCl_3$): δ = 3.50 (s, 3H); 3.57 (s, 3H); 5.00 (s, 2H); 5.07 (s, 1H); 6.43–7.50 (m, 12H).

2-(2-Benzyloxy-5-methoxyphenyl)-2,4-dimethyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine (13):

Method A (from **3q** by *O*-Benzylation): A solution of **3q** (0.32 g, 1.00 mmol) in DMF (1 mL) is added to a stirred suspension of NaH (60% mineral oil dispersion; 0.044 g, 1.1 equiv) in DMF (1.5 mL) at 0–10 °C and stirring is continued for 15 min. Benzyl chloride (0.152 g, 1.2 equiv) is then added dropwise. The mixture is stirred for 1 h at 50 °C, cooled, treated with H_2O (20 mL), and extracted with EtOAc (2 × 20 mL). The extract is washed with brine (20 mL), dried ($MgSO_4$), and evaporated. The residue is column-chromatographed on silica gel(hexane/benzene/EtOAc *1:5:1)* to give **13**; yield: 0.27 g (67%); mp 112–113 °C (MeOH).

Method B (from **7** by *C*-Alkylation): A solution of **7** (0.39 g, *1.00 mmol) in DMF (1 mL) is added dropwise to a stirred suspension of* NaH (60% mineral oil dispersion; 0.044 g, 1.1 equiv) in DMF (1.5 mL) at room temperature and stirring is continued for 30 min. Then, CH_3I (0.85 g, 6.0 equiv) is added, the mixture is stirred for 2 h at 60 °C, then cooled, treated with H_2O (20 mL), and extracted with EtOAc (2 × 20 mL). The extract is washed with brine (20 mL), dried ($MgSO_4$), and evaporated. The residue is column-chromatographed on silica gel(benzene/EtOAc 20:1) to give **13**; yield: 0.07 g (17%); mp 112–113 °C (MeOH).

$C_{24}H_{23}NO_3S$ (405.5) calc. C 71.09 H 5.72 N 3.45; found 70.88 5.73 3.47

IR (KBr): ν = 1669, 1584, 1478, 1341, 1212 cm⁻¹.

^{1}H-NMR ($CDCl_3$): δ = 1.84 (s, 3H); 3.24 (s, 3H); 3.61 (s, 3H); 4.94 (s, 2H); 6.51–7.57 (m, 12H).

2-(2-Benzyloxy-5-methoxyphenyl)-4-methyl-2-(1-methylethyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine (14):

Method A (from **3s** by *O*-Benzylation): Following procedure A described for **13** but using **3s** (0.34 g, 1.00 mmol) as starting material, product **14** is obtained; yield: 0.28 g (65%); mp 104–105 °C (MeOH).

Method B (from **7** by *C*-Alkylation): Following procedure B described for **13** but using **7** *(0.39 g, 1.00 mmol) and 2-iodopropane (0.51 g, 3.0* equiv) as starting materials, product **14** is obtained; yield: 0.22 g (51%); mp 104–105 °C (MeOH).

$C_{26}H_{27}NO_3S$ (433.6) calc. C 72.03 H 6.28 N 3.23; found 71.80 6.22 3.37

IR (KBr): ν = 1669, 1576, 1458, 1271, 1206 cm⁻¹.

^{1}H-NMR ($CDCl_3$): δ = 1.03 (d, 3H, *J* = 7 Hz); 1.17 (d, 3H, *J* = 7 Hz); 2.86 (hept, 1H, *J* = 7 Hz); 3.17 (s, 3H); 3.57 (s, 3H); 4.91 (s, 3H); 6.22–7.72 (m, 12H).

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