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Ring transformations of β-lactam-condensed 1,3-benzothiazines to isoquinoline and thiazole derivatives by sulfur extrusion and addition sequences

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ABSTRACT

The ring transformations of dichloro-β-lactam-fused 2-aryl-1,3-benzothiazines with sodium methoxide were investigated. With 2 equiv of base, the dichloro-β-lactam derivatives underwent rearrangement and dihydro-1,4-benzothiazepines, 3,4-substituted isoquinolines and substituted thiazole disulfides were isolated. A possible reaction mechanism is proposed for the simultaneous formation of the novel products. The formation of isoquinoline and thiazole derivatives can be explained by sulfur extrusion and addition sequences.

1. Introduction

Derivatives of four-membered nitrogen heterocyclic ring systems are probably among the most widely studied families of heterocyclic compounds.[1] Within these ring systems, particular attention has been paid to azetidin-2-one counterparts.[2] The continuously increasing research interest in β-lactam chemistry originated primarily from the unquestionable usefulness of many such compounds in everyday medical practice (e.g., penicillins, cephalosporins, carbapenems, taxol derivatives, the cholesterol-lowering ezetimibe).[3] Besides these drugs, a huge number of four-membered ring compounds also exhibit valuable pharmacological effects[4] (antidiabetic,[5] anti-HIV,[6] anti-inflammatory and analgesic,[7] and inhibitors of human cytomegalovirus,[8] human leukocyte elastase,[9] tryptase[10] and thrombin[11]). From a chemical aspect, various modifications of these ring systems have been achieved and, due to their strained nature, β-lactams display relatively high reactivity. This makes them versatile intermediates for a wide range of nitrogen-containing target compounds, such as functionalized β-amino acids, β-peptides, amino alcohols, and chiral catalysts.[12] Moreover, they can be utilized as building blocks for natural products and different heterocycles.[13] Such features serve as the driving force for the invention of many synthetic pathways for the preparation of β-lactams, and consequently their reactions have been widely studied.[1–13]

Increasing attention has also been paid to halo-substituted β-lactams.[14–17] In view of their reactivity, besides the ring strain in four-membered lactams, the introduction of a halo substituent markedly extends the range of utilizability of these compounds, allowing the development of novel reactions on the ring atoms, leading to new functionalized derivatives[14] or exceptionally interesting rearragements or ring transformations.[15–17] By means of these latter methods, chloro-β-lactams have been transformed, for example, to aziridines,[15] pyrrolidin-2-ones,[16] bicyclic γ-lactams[17] or macrocyclic β-amino amides,[18] which are valuable intermediates in the synthesis of homalium alkaloids.

We recently reported a convenient and general synthetic pathway for rare 2-aryl-3-alkoxycarbonyl-substituted 4,5-dihydro-1,4-benzothiazepines, utilizing monochloro-β-lactam derivatives, *trans*-2-chloro-2*a*-aryl-2,2*a*-dihydro-5,6-dimethoxy-1*H*,8*H*-azeto[2,1-*b*][1,3]benzothiazin-1-ones, as starting materials.[19] The ring expansion of monochloro-β-lactams with sodium methoxide afforded 1,4-benzothiazepines as single products in good yields. As a further aim, in the present paper we set out to investigate the transformations of the corresponding dichloro-β-lactams, 2,2-

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dichloro-2,2*a*-dihydro-5,6-dimethoxy-1*H*,8*H*-2*a*-arylazeto[2,1-*b*][1,3]benzothiazin-1-ones in response to basic treatment.

2. Results and discussion

The Staudinger reaction was applied for the synthesis of the starting dichloro-β-lactams **2a**–**g**. The reactions of 1,3-benzothiazines **1a**–**g** with dichloroacetyl chloride in refluxing toluene furnished azeto[2,1-*b*][1,3]benzothiazin-1-ones **2a**–**g** in good yields (Table 1). The treatment of dichloro-β-lactam **2a** with excess sodium methoxide led to the formation of three compounds, which were separated by column chromatography. Surprisingly, structure investigations demonstrated that the major product was a known benzothiazepine, 7,8-dimethoxy-2-methoxycarbonyl-3-(4-methylphenyl)-4,5-dihydro-1,4-benzothiazepine **6a**. It was identical with the compound obtained earlier in the rearrangement of monochloro-β-lactam derivative **3a**[19] with sodium methoxide in dry methanol under reflux (Table 1). Similar substituted 4,5-dihydro-1,4-benzothiazepines have been prepared by the ring expansion of benzoisothiazoles on treatment with alkynes.[20]

6,7-Dimethoxy-4-methoxycarbonyl-3-(4-methylphenyl)isoquinoline **4a** was identified as the second product. It is noteworthy that the preparation of 3,4-disubstituted isoquinolines with the tools of conventional synthetic organic chemistry is relatively complicated, and novel reactions have therefore recently been developed for the synthesis of these alkaloid-type compounds.[21] The remaining compound was identified as isothiazole disulfide **5a**. To extend the possibility of this novel ring expansion, compounds **2b**–**g** were reacted under the same conditions, which led to the analogous isoquinolines (**3b**–**g**), thiazole disulfides (**4b**–**g**) and benzothiazepines (**6b**–**g**).

A possible reaction pathway for the formation of these compounds is depicted in Scheme 1. In the first step, methanol-induced dehalogenation is associated with the opening of the dichloro-β-lactam ring, affording chloroketenes **7** and methyl hypochlorite. On the addition of methanol followed by intramolecular *S*-alkylation and subsequent tautomerization, the ketene intermediates are transformed into dihydrobenzo[*f*][1,4]thiazepines (**7**→**8**→**9**→**6**). These primary products in part undergo hypochlorite-mediated *S*-chlorination, resulting in the corresponding sulfonium salt, base-catalysed deprotonation, of which and subsequent sulfur extrusion leads to isolable isoquinolines (**6**→**10**→**11**→**12**→**13**→**4**). Besides sulfur elimination, the presumed benzo[*f*][1,4]thiazepine-2-carboxylates **12** react with the elemental sulfur present in the reaction mixture in a [4+1] cycloaddition step to generate the corresponding sulfur-bridged intermediate **14**, which undergoes ring opening associated with the formation of a thiazole ring. In the final step, spontaneous oxidation of the resulting thiazolyl thiophenols gives disulfides **5** as isolable products.

The structures of the compounds investigated follow unambiguously from the data (Tables 2 and 3).

The high νC=O frequencies of **2a**–**g** (1794±4 cm^{-1}) are characteristic of β-lactams.[22] The frequencies are enhanced by the $-I$ effect of the two vicinal chlorine atoms.

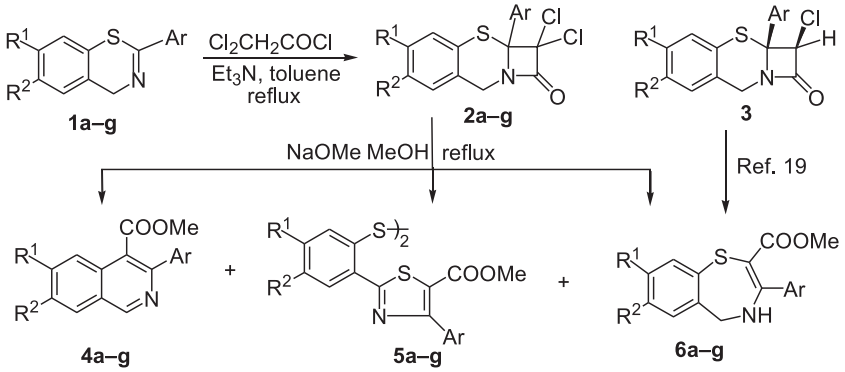
The downfield shifts of the H-5 and H-8 signals (by ~0.47 and 0.66 ppm) in **4** as compared with **2** are striking. This can be explained by the $-I$ effect of the condensed hetero ring and for H-8 by the anisotropic neighbouring effect of the ester carbonyl.[23a] The latter observation is supported by the higher downfield shift in **4b** and **4f** (0.58 and 0.81 ppm) where the *ortho*-substituted Ar group (perpendicular to the molecular skeleton in the preferred conformation because of the steric hindrance between the Ar and ester groups) forces the ester carbonyl into a coplanar arrangement with the skeleton.

This conformational preference is also revealed in the upfield shift of the methyl singlet of the ester group in **4b** and **4f** relative to the other molecules of type **4** (by 0.16 and 0.06 ppm), due to the anisotropic effect of the perpendicularly oriented Ar ring[23b] in the predominant conformation.

The downfield ^{1}H NMR signal (9.14±0.04 ppm) and ^{13}C NMR line (151±3 ppm) of H-4 and C-4, respectively, in **4** are proof of the isoquinoline moiety.[23c] Similarly, the high chemical shifts of C-2 (166.7±2 ppm) and C-4 (158.2±14 ppm) for thiazoles **5** confirm the presence of this hetero ring.[23d]

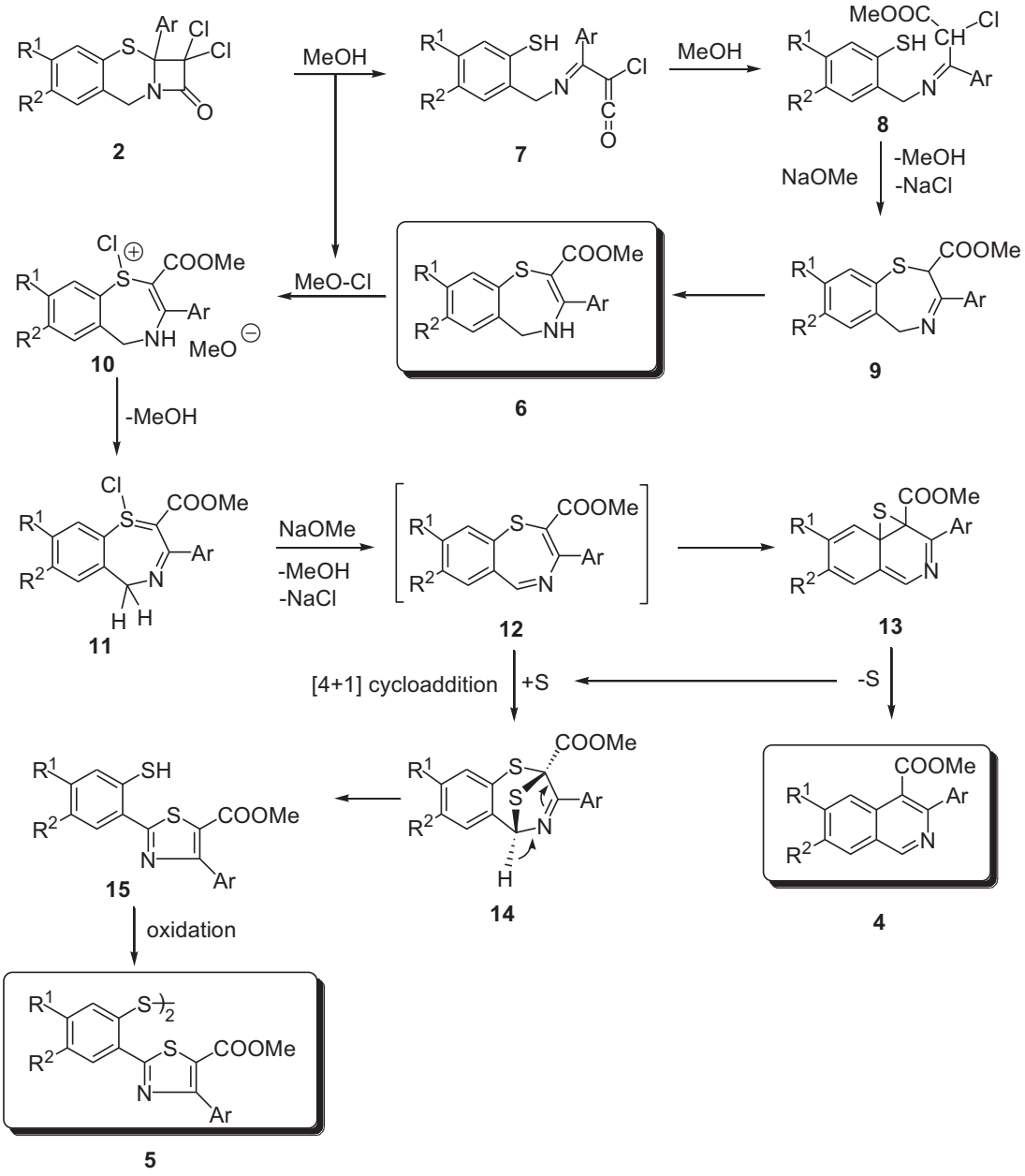
The downfield shift of the H-5 signal is due to the anisotropy of the near-lying lone pair on the N atom[23e] in the preferred rotamer. For more extended electron delocalization including the three aromatic and heteroaromatic rings, a coplanar arrangement predominates in both halves of **5**. To avoid steric interaction between H-5 and the ester group, the *S-cis* arrangement of the two S atoms and consequently the closeness of the H-5 and the nitrogen atoms are plausible.

Table 1
Synthesis of isoquinolines, thiazole derivatives and 1,4-benzothiazines from 1,3-benzothiazines via the ring transformation of β-lactam-condensed 1,3-thiazine derivatives



Ar	R^1	R^2	β-Lactam	Yield (%)	Isoquinoline	Yield (%)	Thiazole	Yield (%)	Thiazepine	Yield (%)
4-Me–C_6H_4	MeO	MeO	**2a**	92	**4a**	16	**5a**	24	**6a**	26
2-Me–C_6H_4	MeO	MeO	**2b**	90	**4b**	17	**5b**	21	**6b**	25
4-MeO–C_6H_4	MeO	MeO	**2c**	94	**4c**	-[a]	**5c**	21	**6c**	32
3,4-diMeO–C_6H_3	MeO	MeO	**2d**	95	**4d**	-[a]	**5d**	19	**6d**	28
4-Cl–C_6H_4	MeO	MeO	**2e**	89	**4e**	15	**5e**	-[a]	**6e**	22
2-Cl–C_6H_4	MeO	MeO	**2f**	90	**4f**	16	**5f**	21	**6f**	24
Ph	EtO	EtO	**2g**	88	**4g**	9	**5g**	-[a]	**6g**	28

[a] Not isolated.



Scheme 1.

In summary, we have investigated the ring transformation reactions of 2,2-dichloro-2,2*a*-dihydro-5,6-dimethoxy-1*H*,8*H*-2*a*-arylazeto[2,1-*b*][1,3]benzothiazin-1-one derivatives in the presence of sodium methoxide. The structures of the ring transformation products formed simultaneously (7,8-dimethoxy-2-methoxycarbonyl-3-aryl-4,5-dihydro-1,4-benzothiazepines, 6,7-dimethoxy-4-methoxycarb onyl-3-arylisoquinolines and isothiazole disulfide derivatives) were proved by means of IR and NMR spectroscopy. A possible mechanistic pathway is proposed for the formation of novel compounds.

3. Experimental

3.1. General

Melting points were determined on a Kofler micro melting apparatus. Elemental analyses were performed with a Perkin–Elmer 2400 CHNS elemental analyser in the Institute of Pharmaceutical Chemistry. Merck Kieselgel 60F_{254} plates were used for TLC, and Merck Silica gel 60 (0.063–0.100) for column chromatography. Dichloroacetyl chloride was purchased from Fluka. 1,3-Benzothiazines **1a**–**g** were prepared by literature methods.[19,24]

IR spectra were recorded in KBr pellets with a Bruker IFS 55 FT-spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at RT, on a Bruker DRX 500 spectrometer at 500 (^{1}H) or 125 (^{13}C) MHz, with TMS (δ_{TMS}=0 ppm) as internal reference, and the deuterium signal of the solvent as the lock. Assignments were supported by DEPT, HMQC and HMBC measurements. DEPT spectra were run in a standard manner, using only the Θ=135° pulse to separate CH/CH_3 and CH_2 lines phased 'up' and 'down', respectively. 2D-HMQC and 2D-HMBC spectra were obtained by using the standard Bruker pulse programs.

Table 2
Characteristic IR frequencies[a] and ^{1}H NMR data[b] of **2a**–**g**, **4a**, **b**, **e**–**g** and **5a**–**d**, **f**[c]

Compound	νC=O band	νC–O ester bands	$\gamma C_{Ar}H$ Band[d]	$\gamma C_{Ar}H$ Band[d]	XCH_3 s (3H)[e]	OCH_3 ester	OCH_3 (Pos. 6,7)	NCH_2 s,d or dd[f]	H-5[j] *s* (1H)	H-8[j] *s* (1H)	H-2′	H-6′	H-3′	H–5′	H-4′
											Ar group attached to the heteroring[g]				
2a	1794	—	809	843	2.38	—	3.87, 3.84	4.20,4.89	6.76	6.77	7.32		7.23		—
2b	1794	—	740	831	2.60	—	3.89, 3.84	4.27,4.92	6.83	6.79	—	7.29		~7.25	
2c	1795	—	801	853	3.81	—	3.85, 3.83	4.22,4.88	6.74	6.75	7.36		6.92		—
2d	1794	—	809	868	3.89, 3.93	—	3.86, 3.84	4.19,4.87	6.74	6.76	6.91	6.97	—	6.86	—
2e	1797	—	810	845	—	—	3.86, 3.83	4.20,4.88	6.74		7.37				—
2f	1790	—	744	832	—	—	3.86, 3.80	4.26,4.92	6.78	6.76	—	7.47	~7.25[i]	~7.3[i]	~7.25[i]
2g	1792	—	748	827	1.42, 1.45	—	4.06[h]	4.20,4.87	6.78	6.79	7.42				7.39
4a	1723	1204,1151	820	846	2.41	3.73	4.03, 4.04	9.13	7.24	7.31	7.57		7.26		—
4b	1717	1210,1154	749	841	2.23	3.55	4.06, 4.05	9.16	7.29	7.37	—	7.20		7.28	
4e	1705	1214,1161	823	835	—	3.71	4.02[i]	9.10	7.22	7.29	7.60		7.41		—
4f	1722	1239,1155	780	839	—	3.61	4.07, 4.05	9.17	7.28	7.57	—	7.48	7.33	7.34	7.40
4g	1731	1249,1164	705	853	1.55[i]	3.69	4.25[h]	9.12	7.24	7.31	7.67		7.46		7.39
5a	1711	1263,1019	822	875	2.42	3.82	3.84, 3.79	—	7.68	7.09	7.77		7.26		—
5b	1714	1256,1017	755	869	2.25	3.77	3.88, 3.78	—	7.77	7.06	—	7.37	7.30	7.26	7.35
5c	1721	1253,1021	832	870	3.88	3.84	3.85, 3.80	—	7.66	7.12	7.89		6.99		—
5d	1688	1241,1029	759	877	3.95[i]	3.84	3.86, 3.79	—	7.65	7.12	7.61	7.58	—	6.96	—
5f	1718	1260,1019	760	875	—	3.78	3.87, 3.80	—	7.76	7.05	—	7.54	7.49	7.33	7.38

[a] In KBr discs (cm^{-1}). Further IR bands, $\gamma C_{Ar}C_{Ar}$ (*ortho*-disubstituted Ar group): 692 (**2g**), 679 **4g**; νC–Cl: 1 or 2 bands between 662 and 698 cm^{-1} (**2a**–**g**).
[b] In $CDCl_3$ solution at 500 MHz. Chemical shifts in ppm (δ_{TMS}=0 ppm), coupling constants in Hz.
[c] Assignments were supported by 2D-HMQC and 2D-HMBC measurements.
[d] Ar/condensed (**2**, **4**) or *S*-substituted (**5**) benzene ring.
[e] 2×s (2×3H) for **2d**, **5d**, 2×t (2×3H) for **2g**, t (6H) for **4g**, X: Ar (**a**, **b**), O (**c**, **d**), CH_2 (**g**), *J*: 7.0 (**2g**), 7.0 (**4g**).
[f] 2×d, *J*: 16.1 (**2a**), 15.6 (**2b**), 16.0 (**2c**), 15.8 (**2d**,**e**), 15.7 (**2g**), CH=N, s (1H) for **4**.
[g] AA′BB′-type spectrum, ~d (2H), *J*: 8.1 (**2a**, **4a**, **5a**), 8.8 (**2c**, **4c**, **5c**), 8.3 (**4e**).
[h] CH_2(OEt), m (4H, **2g**), qa (4H, **4g**).
[i] Two overlapping signals.
[j] The IUPAC numbering of the benzothiazines (**2**) is used here and in the spectroscopic part of the text for the condensed (**4**) and *S*-substituted benzene ring (**5**).

3.2. General procedure for the preparation of dichloroazeto [2,1-*b*][1,3]benzothiazines (2a–g)

To a stirred solution of the 4*H*-1,3-benzothiazine (**1a**–**g**) (2.0 mmol) in anhydrous toluene (10 mL), dichloroacetyl chloride (3.0 mmol) was added. The solution was refluxed, and triethylamine (0.4 mL, 3.0 mmol) in anhydrous toluene (20 mL) was added dropwise over 1 h under reflux. The reaction mixture was then cooled and filtered, and the remaining triethylammonium chloride was washed with toluene. The organic layer was extracted with brine (20 mL) and dried with Na_2SO_4. After evaporation, the oily residue crystallized on trituration with ethanol.

*3.2.1. 2,2-Dichloro-2,2a-dihydro-5,6-dimethoxy-1H,8H-2a-(4-methylphenyl)azeto[2,1-b][1,3]benzothiazin-1-one (**2a**).* A white crystalline powder; mp 118–120 °C; 0.75 g, yield 92%; R_f (55%, chloroform:methanol 99:1). Anal. Calcd for $C_{19}H_{17}Cl_2NO_3S$

Table 3
^{13}C NMR chemical shifts[a] of **2a**–**g**, **4a**, **b**, **e**–**g** and **5a**–**d**, **f**[b]

Compound	C=O	OCH_3	NC[c]	C-4a	C-5	C-6	C-7	C-8	C-8a	N–C quat.[e]	$C_q(sp^3)$;	C-1′	C-2′	C-6′	C-3′	C-5′	C-4′
		Benzothiazine (**2**), isoquinoline (**4**) or subst.-benzene and thiazole (**5**)[d]									$C_q(sp^2)$[f]	Ar attached to the skeleton (**2**,**4**) or thiazole (**5**)					
2a	163.6	56.48, 56.52	44.4	125.3	111.7	148.6	149.5	113.1	122.0	82.6	90.3	135.0	126.0		129.8		139.7
2b	163.6	56.5[g]	45.2	126.7	111.7	148.7	149.6	113.1	122.1	83.7	89.7	137.2	135.7	129.5	132.4	126.4[h]	125.4[h]
2c	163.5	56.48, 56.51	44.3	124.9	111.7	148.6	149.5	113.1	122.0	82.3	90.5	129.9	127.7		114.4		160.6
2d	163.6	56.3,[h] 56.6[h]	44.4	125.2	111.7	148.7	149.5	113.1	122.0	82.6	90.5	136.9	130.2	118.9	149.6	111.2	150.2
2e	163.4	56.50, 56.53	44.5	124.9	111.8	148.8	149.6	113.2	121.4	82.1	89.9	136.6[h]	129.3		127.7		135.7[h]
2f	163.3	56.5[g]	44.8	124.9	111.5	148.6	149.7	113.0	121.9	82.3	89.6	137.2	132.6	131.4	127.1[h]	130.7	127.3[h]
2g	163.6	62.22,[i] 62.26[i]	44.6	125.4	113.8	148.4	149.3	115.1	121.8	82.6	90.2		129.1[h]		129.6[h]		120.0
4a	170.3	56.5, 56.6	151.3	123.5	105.9	150.9[g]	154.5	102.9	130.8	150.9[g]	121.7	138.2	128.8		129.5		138.6
4b	169.2	56.57, 56.64	150.8	123.7	106.1	151.1	154.7	103.1	130.8	151.9	123.1	136.8	140.3	129.3	125.7	128.6	130.5
4e	169.9	56.5, 56.6	151.3	123.7	105.9	151.1	154.7	102.9	130.8	149.4	122.0	139.5	130.3		129.0		134.9
4f	168.7	56.56, 56.63	151.5	124.2	106.0	151.3	154.7	103.5	130.8	150.2	121.9	140.4	133.4	129.8	126.9[h]	131.1	129.7[h]
4g	170.2	65.0,[i] 65.1[i]	151.2	123.6	107.0	150.5[h]	154.3	103.7	130.7	150.6[h]	122.7	141.1	128.9		128.8		128.6
5a	162.6	56.54, 56.45	166.6	129.1	112.7	150.3	150.9	117.8	126.5	159.8	122.6	131.7	130.3		128.9		139.6
5b	162.2	56.5, 56.6	166.7	129.2[g]	112.9	150.4	150.8	118.2	126.7	160.1	124.8	135.0	137.2	130.3	130.4	125.6	129.2[g]
5c	162.7	56.4, 56.5	166.5	129.0	112.7	150.2	150.9	117.7	126.6	159.3	121.8	126.9	132.0		113.6		160.8
5d	162.7	56.43,[h] 56.5[h]	166.5	128.7	112.7	150.2[h]	151.0	117.3	126.8	159.3	121.9	127.0	114.0	123.7	148.5	123.7	150.4[h]
5f	162.0	56.5, 56.6	166.9	129.5	112.9	150.6	150.8	118.6	126.4	156.6	126.1	134.7	134.1	131.7	129.5	126.8	130.4

[a] In ppm (δ_{TMS} 0 ppm) at 125.7 MHz. Solvent: $CDCl_3$. Further signals, CH_3(Et): 15.1, 15.2 (**2g**), 14.8, 14.9 (**4g**); $ArCH_3$: 21.6 (**2a**,**b**), 21.7 (**4a**), 20.2 (**4b**), 21.9 (**5a**), 20.4 (**5b**); OCH_3 (Ar): 55.7 (**2c**), 56.50, 56.52 (**2d**)[h] 55.7 (**5c**), 56.32[h] 56.39[h] (**5d**); OCH_3 (ester): 52.8 (**4a**,**g**), 52.5 (**4b**), 52.9 (**4e**), 52.6 (**4f**, **5a**–**c**), 52.7 (**5d**,**f**).
[b] Assignments were supported by DEPT, HMQC and HMBC measurements.
[c] NCH_2 (**2**), N=CH (**4**), N–C(sp^2) –Ar (**5**).
[d] The IUPAC numbering of the benzothiazines (**2**) is used here and in the spectroscopic part of the text for the condensed (**4**) and *S*-substituted benzene ring (**5**).
[e] S–C–N (**2**), C-3 (isoquinoline, **4**), C-4 (thiazole, **5**).
[f] CCl_2 (**2**), C-4 (isoquinoline, **4**), C-5 (thiazole, **5**).
[g] Two overlapping lines.
[h] Reversed assignments is also possible.
[i] OCH_2 (Et).

(410.31): C, 55.62; H, 4.18; N, 3.41; S, 7.82. Found: C, 55.93; H, 4.45; N, 3.22; S, 8.05.

*3.2.2. 2,2-Dichloro-2,2a-dihydro-5,6-dimethoxy-1H,8H-2a-(2-methylphenyl)azeto[2,1-b][1,3]benzothiazin-1-one (**2b**).* A white crystalline powder; mp 173–176 °C; 0.74 g, yield 90%; R_f (56%, chloroform:methanol 99:1). Anal. Calcd for $C_{19}H_{17}Cl_2NO_3S$ (410.31): C, 55.62; H, 4.18; N, 3.41; S, 7.82. Found: C, 55.88; H, 4.42; N, 3.70; S, 7.61.

*3.2.3. 2,2-Dichloro-2,2a-dihydro-5,6-dimethoxy-1H,8H-2a-(4-methoxyphenyl)azeto[2,1-b][1,3]benzothiazin-1-one (**2c**).* A white crystalline powder; mp 143–146 °C; 0.80 g, yield 94%; R_f (56%, chloroform:methanol 99:1). Anal. Calcd for $C_{19}H_{17}Cl_2NO_4S$ (426.31): C, 53.53; H, 4.02; N, 3.29; S, 7.52. Found: C, 53.78; H, 4.28; N, 3.02; S, 7.32.

*3.2.4. 2,2-Dichloro-2,2a-dihydro-5,6-dimethoxy-1H,8H-2a-(3,4-dimethoxyphenyl)azeto[2,1-b][1,3]benzothiazin-1-one (**2d**).* A white crystalline powder; mp 202–204 °C; 0.87 g, yield 95%; R_f (57%, chloroform:methanol 99:1). Anal. Calcd for $C_{20}H_{19}Cl_2NO_5S$ (456.34): C, 52.64; H, 4.20; N, 3.07; S, 7.03. Found: C, 52.47; H, 4.48; N, 3.31; S, 7.29.

*3.2.5. 2,2-Dichloro-2,2a-dihydro-5,6-dimethoxy-1H,8H-2a-(4-chlorophenyl)azeto[2,1-b][1,3]benzothiazin-1-one (**2e**).* A white crystalline powder; mp 114–116 °C; 0.77 g, yield 89%; R_f (58%, chloroform:methanol 99:1). Anal. Calcd for $C_{18}H_{14}Cl_3NO_3S$ (430.73): C, 50.19; H, 3.28; N, 3.25; S, 7.44. Found: C, 49.98; H, 3.45; N, 3.42; S, 7.71.

*3.2.6. 2,2-Dichloro-2,2a-dihydro-5,6-dimethoxy-1H,8H-2a-(2-chlorophenyl)azeto[2,1-b][1,3]benzothiazin-1-one (**2f**).* A white crystalline powder; mp 122–124 °C; 0.78 g, yield 90%; R_f (56%, chloroform:methanol 99:1). Anal. Calcd for $C_{18}H_{14}Cl_3NO_3S$ (430.73): C, 50.19; H, 3.28; N, 3.25; S, 7.44. Found: C, 50.43; H, 3.45; N, 3.11; S, 7.52.

*3.2.7. 2,2-Dichloro-2,2a-dihydro-5,6-diethoxy-1H,8H-2a-phenyl-azeto[2,1-b][1,3]benzothiazin-1-one (**2g**).* A white crystalline powder; mp 122–123 °C; 0.75 g, yield 88%; R_f (52%, chloroform:methanol 99:1). Anal. Calcd for $C_{20}H_{19}Cl_2NO_3S$ (424.34): C, 56.61; H, 4.51; N, 3.30; S, 7.56. Found: C, 56.85; H,; N, 4.73; S, 7.81.

3.3. General procedure for the preparation 6,7-dimethoxy-4-methoxycarbonyl-3-phenylisoquinoline (4), 4,4′,5,5′-tetramethoxy-[2,2′-di-(5″-methoxycarbonyl-4″-aryl-2″-thiazolyl)]-diphenyl disulfide (5) and 7,8-dimethoxy-2-methoxycarbonyl-3-aryl-4,5-dihydro-1,4-benzotiazepines (6)

Compound **2** (5 mmol) was dissolved in methanol (20 mL), and NaOMe (0.54 g, 10 mmol) was added, and the solution was stirred under reflux. After 3 h, the reaction mixture was diluted with chloroform (150 mL) and extracted with water. The organic layer was dried (Na_2SO_4) and evaporated to dryness, the residue was dissolved in the minimum amount of chloroform, and the solution was chromatographed on a silica column. The column was developed with a 1% solution of methanol in chloroform.

*3.3.1. 6,7-Dimethoxy-4-methoxycarbonyl-3-(4-methylphenyl)isoquinoline (**4a**).* A white crystalline powder; mp 156–159 °C; 0.27 g, yield 16%; R_f (62%, chloroform:methanol 99:1). Anal. Calcd for $C_{20}H_{19}NO_4$ (337.37): C, 71.20; H, 5.68; N, 4.15. Found: C, 71.42; H, 5.81; N, 3.98.

*3.3.2. 6,7-Dimethoxy-4-methoxycarbonyl-3-(2-methylphenyl)isoquinoline (**4b**).* A white crystalline powder; mp 159–161 °C; 0.29 g, yield 17%; R_f (61%, chloroform:methanol 99:1). Anal. Calcd for $C_{20}H_{19}NO_4$ (337.37): C, 71.20; H, 5.68; N, 4.15. Found: C, 71.11; H, 5.86; N, 4.01.

*3.3.3. 6,7-Dimethoxy-4-methoxycarbonyl-3-(4-chlorophenyl)isoquinoline (**4e**).* A white crystalline powder; mp 184–187 °C; 0.27 g, yield 15%; R_f (60%, chloroform:methanol 99:1). Anal. Calcd for $C_{19}H_{16}ClNO_4$ (357.79): C, 63.78; H, 4.51; N, 3.92. Found: C, 64.02; H, 4.80; N, 3.76.

*3.3.4. 6,7-Dimethoxy-4-methoxycarbonyl-3-(2-chlorophenyl)isoquinoline (**4f**).* A white crystalline powder; mp 215–218 °C; 0.29 g, yield 16%; R_f (64%, chloroform:methanol 99:1). Anal. Calcd for $C_{19}H_{16}ClNO_4$ (357.79): C, 63.78; H, 4.51; N, 3.91. Found: C, 63.92; H, 4.66; N, 3.82.

*3.3.5. 6,7-Diethoxy-4-methoxycarbonyl-3-phenylisoquinoline (**4g**).* A white crystalline powder; mp 153–155 °C; 0.16 g, yield 9%; R_f (60%, chloroform:methanol 99:1). Anal. Calcd for $C_{21}H_{21}NO_4$ (351.40): C, 71.78; H, 6.02; N, 3.99. Found: C, 71.52; H, 6.20; N, 4.21.

*3.3.6. 4,4′,5,5′-tetramethoxy-}2,2′-di-[5″-methoxycarbonyl-4″-(4-methylphenyl)-2″-thiazolyl]}-diphenyl disulfide (**5a**).* A yellow crystalline powder; mp 213–216 °C; 0.96 g, yield 24%; R_f (82%, chloroform:methanol 99:1). Anal. Calcd for $C_{40}H_{36}N_2O_8S_4$ (800.99): C, 59.98; H, 4.53; N, 3.50; S, 16.01. Found: C, 60.23; H, 4.70; N, 3.65; S, 16.28.

*3.3.7. 4,4′,5,5′-tetramethoxy-}2,2′-di-[5″-methoxycarbonyl-4″-(2-methylphenyl)-2″-thiazolyl]}–diphenyl disulfide (**5b**).* A yellow crystalline powder; mp 190–193 °C; 0.84 g, yield 21%; R_f (83%, chloroform:methanol 99:1). Anal. Calcd for $C_{40}H_{36}N_2O_8S_4$ (800.99): C, 59.98; H, 4.53; N, 3.50; S, 16.01. Found: C, 60.24; H, 4.70; N, 3.68; S, 15.89.

*3.3.8. 4,4′,5,5′-tetramethoxy-}2,2′-di-[5″-methoxycarbonyl-4″-(4-methoxyphenyl)-2″-thiazolyl]}–diphenyl disulfide (**5c**).* A yellow crystalline powder; mp 182–185 °C; 0.87 g, yield 21%; R_f (82%, chloroform:methanol 99:1). Anal. Calcd for $C_{40}H_{36}N_2O_{10}S_4$ (832.99): C, 57.68; H, 4.36; N, 3.36; S, 15.40. Found: C, 57.82; H, 4.58; N, 3.11; S, 15.12.

*3.3.9. 4,4′,5,5′-tetramethoxy-}2,2′-di-[5″-methoxycarbonyl-4″-(3,4-dimethoxyphenyl)-2″-thiazolyl]}-diphenyl disulfide (**5d**).* A yellow crystalline powder; mp 192–195 °C; 0.85 g, yield 19%; R_f (86%, chloroform:methanol 99:1). Anal. Calcd for $C_{42}H_{40}N_2O_{12}S_4$ (893.04): C, 56.49; H, 4.51; N, 3.14; S, 14.36. Found: C, 56.65; H, 4.78; N, 3.35; S, 14.59.

*3.3.10. 4,4′,5,5′-tetramethoxy-}2,2′-di-[5″-methoxycarbonyl-4″-(2-chlorophenyl)-2″-thiazolyl]}-diphenyl disulfide (**5f**).* A yellow crystalline powder; mp 153–155 °C; 0.88 g, yield 21%; R_f (81%, chloroform:methanol 99:1). Anal. Calcd for $C_{38}H_{30}Cl_2N_2O_8S_4$ (841.82): C, 54.22; H, 3.59; N, 3.33; S, 15.24. Found: C, 54.48; H, 3,76; N, 3.58; S, 15.10.

*3.3.11. 7,8-Dimethoxy-2-methoxycarbonyl-3-aryl-4,5-dihydro-1,4-benzotiazepines (**6a**–**g**).* The physical and analytical data on **6a**–**g** were identical to those published earlier.[19,24]

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