Selective Electrochemical Fluorodesulfurization of Benzo- and Pyrido-Fused Oxazine Derivatives Using Ex-cell Halogen Mediators

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Abstract: Although the direct anodic fluorination of 3-phenyl-2*H*-1,4-benzoxazine was not very effective, the fluorodesulfurization of 3-aryl-2-(phenylsulfanyl)-2*H*-1,4-benzoxazines using various anodically generated halogen mediators in the presence of triethylamine tris(hydrogen fluoride) by an ex-cell method efficiently and selectively provided the corresponding monofluorinated products. In sharp contrast, in-cell halogen mediators did not work well. Furthermore, the selective fluorodesulfurization of pyrido[3,2-*b*][1,4]oxazine derivatives was also successfully carried out using the same ex-cell method to provide the corresponding monofluorinated products in moderate yields.

Key words: halogenation, fluorine, heterocycles, electron transfer, oxidations

Benzo- or pyrido-fused oxazine derivatives have been investigated because of their various pharmaceutical activities, e.g. as modulators of the skeletal muscle ATP-sensitive-K^+ channels (K_{ATP}),[1a–c] as central nervous system (CNS) depressants,[1d] and as 5-HT_3 receptor antagonists[1e] and for their antiproliferative[1f] and analgesic activities.[1g] In addition, much attention has been paid to organofluorine heterocycles owing to their unique and pronounced biological properties.[2] We developed the effective and selective anodic fluorination of various organic compounds which included introducing fluorine atom(s) onto the heterocyclic rings or side chains of complex heterocyclic derivatives.[3]

Previously, we reported that the anodic fluorination of N-substituted 2*H*-1,4-benzoxazin-3(4*H*)-one and 2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one derivatives in tetraethylammonium fluoride tetrakis(hydrogen fluoride)/1,2-dimethoxyethane ($Et_4NF{\cdot}4HF$/DME) at platinum plate electrodes in a divided cell provided the corresponding monofluorinated products selectively.[4] In addition, the anodic fluorination of (*E*)-3-benzylidenethiochroman-4-ones was successfully carried out in $Et_4NF{\cdot}4HF$/DME to provide the corresponding monofluorinated products, fluorinated at the α-position to the sulfur atom.[5] Under the same electrolytic conditions, the anodic fluorination of (*E*)-3-benzylidenechroman-4-one derivatives was also achieved.[6] In contrast, the direct anodic fluorination of 3-phenyl-2*H*-1,4-benzothiazine in triethylamine tris(hydrogen fluoride) ($Et_3N{\cdot}3HF$)/DME provided dimeric benzothiazine and its dehydro dimer in addition to the corresponding mono-, di-, and trifluorinated products in moderate total yield. The anodic fluorination of benzothiazine dehydro dimer derivatives afforded 2,2-difluorobenzothiazine derivatives selectively in moderate yields.[7]

In 2008, López et al. reported that the use of *N*-iodosuccinimide (NIS), *N*-bromosuccinimide (NBS), or bis(2,4,6-trimethylpyridyl)iodonium perchlorate containing an electrophilic halonium ion could transform unprotected 1-thioglycosides into glycosyl fluorides in the presence of Olah's reagent (70% HF–pyridine)[8] or $Et_3N{\cdot}3HF$ in dichloromethane at low temperature.[9] Similarly, we achieved the fluorodesulfurization of 2-(phenylsulfanyl)oxazine derivatives using various *N*-halosuccinimides in the presence of $Et_3N{\cdot}3HF$.[10]

In this paper, we report an effective electrochemical method for the fluorodesulfurization of 3-aryl-2-(phenysulfanyl)-2*H*-1,4-benzoxazines and -pyrido[3,2-*b*][1,4]oxazines using various mediators to generate active halonium ions for use in the presence of $Et_3N{\cdot}3HF$ in dichloromethane; we obtained the corresponding monofluorinated products in moderate to good yields.

The model compound 3-phenyl-2*H*-1,4-benzoxazine (**1a**) was synthesized according to a procedure in the literature.[11] The corresponding 2-(phenylsulfanyl)-substituted oxazine derivatives **2** and **3** were prepared from α-bromo-α-(phenylsulfanyl)-substituted acetophenone derivatives in a similar manner (Scheme 1).[10,12]

First, the anodic fluorination of 3-phenyl-2*H*-1,4-benzoxazine (**1a**) (E_p^{ox} = 1.58 V vs SCE), as a model compound, was examined in detail under various electrolytic conditions. 1,2-Dimethoxyethane was found to be a more effective solvent than acetonitrile when $Et_3N{\cdot}3HF$ was used as the fluorine source. This can be explained by the nucleophilicity of the fluoride ions being significantly enhanced in 1,2-dimethoxyethane.[13] As shown in Scheme 2, the corresponding monofluorinated product **4a** was obtained in low yield along with a trace amount of difluorinated product **5a** {^{19}F NMR: δ = –32.57 (m, 1 F), –35.74 (d, 1 F, *J* = 53.6 Hz); MS: *m*/*z* = 245 [M^+], 227}. In contrast, much lower total yield was obtained when stronger fluorinating reagents (e.g., $Et_4NF{\cdot}4HF$ and $Et_3N{\cdot}5HF$) were used.

In our previous work, we found that the anodic fluorodesulfurization of dithioacetals of ketones in the presence of $Et_3N{\cdot}3HF$ provided the corresponding *gem*-difluoro com-

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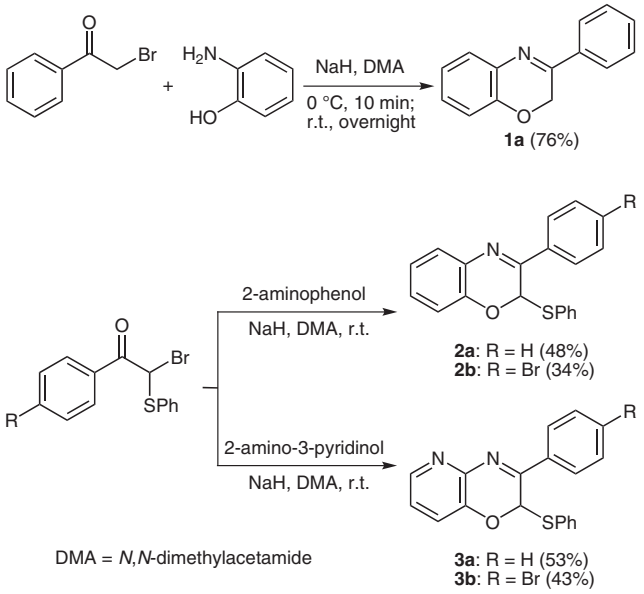
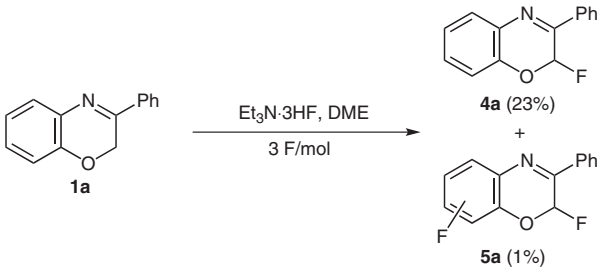


Scheme 1



Scheme 2

pounds in relatively good yields.[14] In addition, oxidative fluorodesulfurization of dithioacetals using organic oxidizing reagents, such as NBS and 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione, has been achieved in the presence of fluorinating agents, such as Olah's reagent,[8] tetrabutylammonium dihydrogen trifluoride, and 4-(difluoroiodo)toluene, to provide *gem*-difluorinated products.[15] Considering these results, we assumed that partial fluorodesulfurization could be carried out for benzoxazines in which a phenylsulfanyl group is introduced as an electroauxiliary.[9,16]

The oxidation potential of 3-phenyl-2-(phenylsulfanyl)-2*H*-1,4-benzoxazine (**2a**) was measured by cyclic voltammetry. Unexpectedly, it was found that the E_p^{ox} value of **2a** was appreciably higher than that of 2-unsubstituted compound **1a**. The calculated highest occupied molecular orbital (HOMO) energy value[17] also indicated that the oxidation of compound **2a** would be more difficult compared with that of **1a** (Figure 1).

Next, the anodic fluorination of 2-(phenylsulfanyl)-substituted compound **2a** was conducted in the presence of $Et_3N{\cdot}3HF$ using various solvents. Unfortunately, the electrolysis of **2a** in 1,2-dimethoxyethane, acetonitrile, and dichloromethane provided the corresponding mono- and difluorinated products in very low yields (3–9 and <2%,

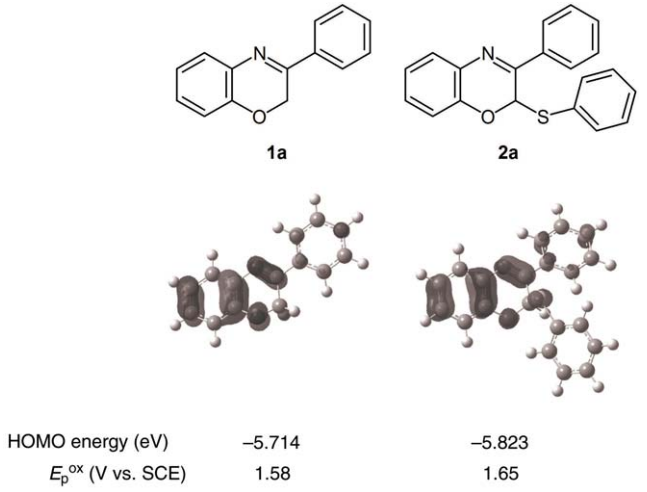
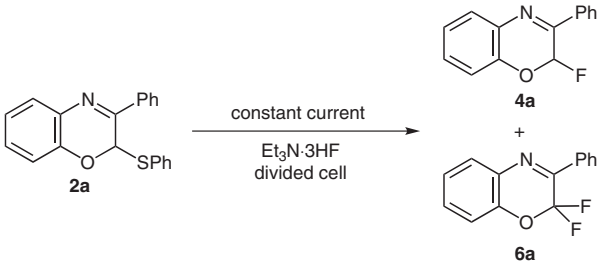


Figure 1 Highest occupied molecular orbital energies and oxidation potentials of benzoxazines **1a** and **2a**

respectively) when a theoretical quantity of electric charge was passed (2 F/mol). The yield of the difluorinated product gradually increased to 5% when further electrolysis was applied in these solvents (6 F/mol).

In a previous paper, we reported the indirect anodic fluorination of dithioacetals using a bromine (Br^+/Br^-) redox mediator in $Et_3N{\cdot}3HF/CH_2Cl_2$ which provided the corresponding monofluorinated products selectively.[18] Based on this result, the indirect anodic fluorination of **2a** was investigated using various mediators, and the results are summarized in Table 1. Using tetrabutylammonium iodide (n-Bu_4NI) as a mediator, no fluorinated product was obtained at all and the substrate was mostly recovered (entry 1). Tetraethylammonium bromide (Et_4NBr) was not a

Table 1 Anodic Fluorodesulfurization of 2-(Phenylsulfanyl)-Substituted Benzoxazine **2a** Using Various Mediators

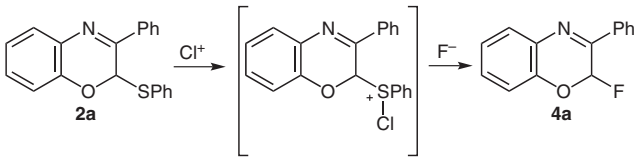


Entry	Solvent	Mediator (5 mol%)	Charge passed (F/mol)	Yield[a] (%) 4a	6a[b]
1	CH_2Cl_2	n-Bu_4NI	8	–	–
2	CH_2Cl_2	Et_4NBr	2	4	1
3	CH_2Cl_2	Et_4NCl	6	17	2
4[c]	CH_2Cl_2	Et_4NCl	2	3	0
5	MeCN	$(4\text{-}BrC_6H_4)_3N$	6	9	1

[a] Determined by ^{19}F NMR spectroscopy.
[b] ^{19}F NMR: δ = –22.28 (s, 2 F); MS: m/z = 245 [M^+].
[c] $Et_4NF{\cdot}3HF$ was used as a supporting electrolyte.

suitable mediator because only small amounts of the corresponding mono- and difluorinated products were detected (entry 2). It was found that tetraethylammonium chloride (Et_4NCl) was the most efficient mediator among the halide salts used for the anodic fluorodesulfurization of compound **2a** in the presence of $Et_3N{\cdot}3HF$; however, the yields of the products were still low (entries 3 and 4). The use of tris(4-bromophenyl)amine (E_p^{ox} = 1.06 V vs SCE)[19] as a mediator also resulted in low yields (entry 5).

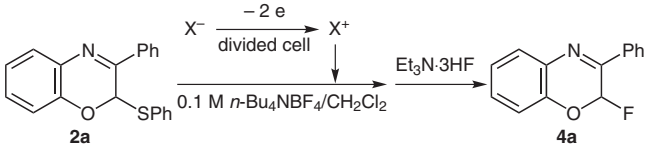
In the case of the anodic fluorodesulfurization of **2a** using Et_4NCl as a mediator, we supposed that anodically generated chloronium (Cl^+) might attack the sulfur atom of the phenylsulfanyl group of **2a** to form an active leaving group. Then, the resulting intermediate would react with a fluoride ion to afford monofluorinated product **4a** (Scheme 3). However, the desired fluorinated product **4a** was not formed in good yield. Thus, the in-cell mediator was not effective. We anticipated that the fluorodesulfurization would be achieved in the presence of stoichiometric amounts of electrophilic halonium ions.



Scheme 3

With this in mind, we performed the anodic fluorodesulfurization using mediators by an ex-cell method, i.e. the substrate was mixed with anodically generated active halonium ions, followed by the addition of the fluorine source. The results are summarized in Table 2. Initially, we used stoichiometric amounts of Et_4NCl (1 equiv) (E_p^{ox} = 1.12 V vs SCE) as the mediator, and the fluorodesulfurization of compound **2a** was carried out in $Et_3N{\cdot}3HF/CH_2Cl_2$ using the ex-cell method. The corresponding monofluorinated product **4a** was formed selectively in 9% yield (entry 1), and a large amount of the recovered substrate was also detected by ^1H NMR spectroscopy. When two equivalents of Et_4NCl were used, the substrate was consumed completely; however, the yield was moderate (entry 2). We then used the bromonium ion (Br^+) as an oxidant, generated from Et_4NBr (E_p^{ox} = 0.84 V vs SCE). The use of one equivalent of Et_4NBr resulted in the formation of the corresponding monofluorinated product **4a** in higher yield compared with that achieved with Et_4NCl (cf. entries 3 and 1). Notably, the desired product **4a** was obtained in good yield when two equivalents of Et_4NBr were used (entry 4). Using the in-cell method under the same conditions, a small amount of monofluorinated product **4a** was obtained (entry 5). Tetraethylammonium iodide (Et_4NI) (E_p^{ox} = 0.42 V vs SCE) was also a good choice as the halonium ion source, and a relatively good result was obtained when 3 F/mol of charge was passed (entries 6 and 7). Because Cl^+ is a much stronger oxidant than either Br^+ or iodonium (I^+), overoxidation of the substrate occurs to result in lower fluorination yields. Previously, we showed that the fluorodesulfurization reaction of **2a** with *N*-chlorosuccinimide gave a much lower yield compared with that achieved using NBS or NIS.[10]

Table 2 Anodic Fluorodesulfurization of 2-(Phenylsulfanyl)-Substituted Benzoxazine **2a** Using Ex-cell Mediators

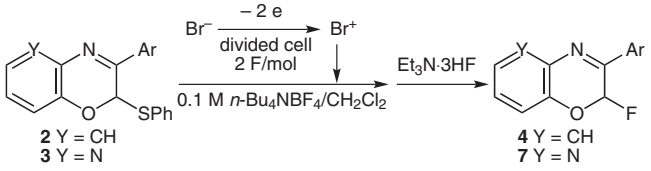


Entry	Halogen source (equiv)	Charge passed (F/mol)	Yield[a] (%)
1	Et_4NCl (1)	2	9
2	Et_4NCl (2)	2	40
3	Et_4NBr (1)	2	45
4	Et_4NBr (2)	2	81 (72)
5[b]	Et_4NBr (2)	2	2
6	Et_4NI (2)	2	55
7	Et_4NI (2)	3	76

[a] Determined by ^{19}F NMR spectroscopy; isolated yield is shown in parentheses.
[b] In-cell method.

Next, the anodic fluorodesulfurization of 1,4-benzoxazine derivative **2b** and pyrido[3,2-*b*][1,4]oxazine derivatives **3a** and **3b** was carried out under the optimized conditions. The results are shown in Table 3. 4-Bromophenyl derivative **2b** also gave the corresponding monofluorinated product in good yield (entry 2). However, in the case of pyrido[3,2-*b*][1,4]oxazine derivative **3a**, three equivalents

Table 3 Anodic Fluorodesulfurization of 2-(Phenylsulfanyl)-Substituted Benzoxazine Derivatives **2** and Pyrido[3,2-*b*][1,4]oxazine Derivatives **3** Using Tetraethylammonium Bromide as an Ex-cell Mediator

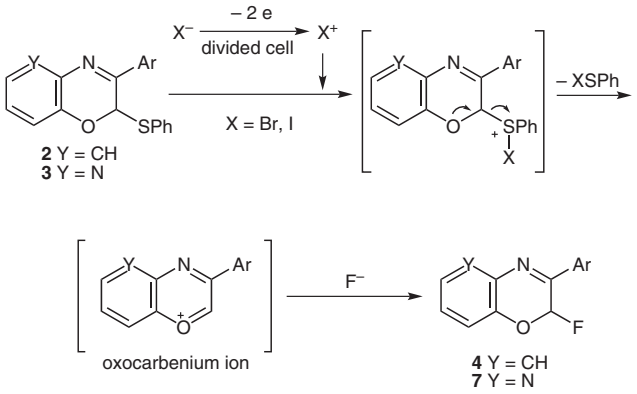


Entry	Compound	Y	Ar	Amount of Et_4NBr (equiv)	Product	Yield[a] (%)
1	**2a**	CH	Ph	2	**4a**	81 (72)
2	**2b**	CH	4-BrC_6H_4	2	**4b**	70 (60)
3	**3a**	N	Ph	2	**7a**	44
4	**3a**	N	Ph	3	**7a**	61 (51)
5	**3b**	N	4-BrC_6H_4	3	**7b**	54 (42)

[a] Determined by ^{19}F NMR spectroscopy; isolated yields are shown in parentheses.

of Et_4NBr were necessary to provide product **7a** in reasonable yield (cf. entries 3 and 4). Under the same modified conditions, the anodic fluorodesulfurization of bromo derivative **3b** was also successful (entry 5).

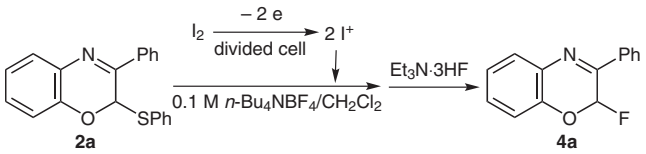
A plausible mechanism for the anodic fluorodesulfurization of **2** and **3** is shown in Scheme 4. In this mechanism, active halonium ions are generated by the anodic oxidation of halide salts, such as Et_4NBr and Et_4NI, and react with the phenylsulfanyl group of **2** and **3**. This is followed by desulfurization to form an oxocarbenium ion. The intermediate thus generated is then attacked by a nucleophilic fluoride ion to produce the corresponding monofluorinated product selectively.



Scheme 4

In addition, the fluorodesulfurization of **2a** was examined using iodine as a mediator; iodine has a higher oxidation potential (E_p^{ox} = 0.73 V vs SCE) than Et_4NI (E_p^{ox} = 0.42 V vs SCE). The results are shown in Table 4. First, model compound **2a** was treated with one equivalent of molecular iodine as the halogen source in $Et_3N{\cdot}3HF/CH_2Cl_2$ at room temperature without any passage of charge. The corresponding monofluorinated product **4a** was obtained in 43% yield (entry 1), and half the amount of substrate **2a** was recovered. When two equivalents of molecular iodine were used under the same conditions, **2a** was mostly consumed (monitored by TLC) and monofluorinated product **4a** was formed in excellent yield (entry 2). Thus, molecular iodine was also effective for the fluorodesulfurization of **2a**, although double amounts of iodine were necessary for successful fluorination. To our knowledge, the two-electron oxidation of molecular iodine affords two I^+ cations.[20] Based on the results of the fluorodesulfurization of **2** and **3** using halide salts and the ex-cell method, the fluorodesulfurization of **2a** was carried out with one equivalent of iodine as the halonium ion source using the same method.[21] When 2 F/mol of charge was passed, the corresponding monofluorinated product **4a** was obtained in moderate yield (entry 3), and unreacted substrate **2a** was also detected by ^1H NMR spectroscopy. However, after electrolysis with 3 F/mol of charge passed, **2a** was consumed completely and monofluorinated product **4a** was obtained in good yield (entry 4).

Table 4 Fluorodesulfurization of 2-(Phenylsulfanyl)-Substituted Benzoxazine **2a** Using Iodine as an Oxidant or Mediator



Entry	I_2 (equiv)	Charge passed (F/mol)	Yield[a] (%)
1	1	–	43
2	2	–	92 (85)
3	1	2	60
4	1	3	86 (75)

[a] Determined by ^{19}F NMR spectroscopy; isolated yields are shown in parentheses.

In conclusion, the anodic fluorodesulfurization of 3-aryl-2-(phenylsulfanyl)-2*H*-1,4-benzoxazine derivatives **2** was achieved using halonium cations generated by anodic oxidation of the corresponding halide salts as mediators by an ex-cell method, providing the corresponding monofluorinated products **4** in good yields. Furthermore, the anodic fluorodesulfurization of 3-aryl-2-(phenylsulfanyl)-2*H*-pyrido[3,2-*b*][1,4]oxazine derivatives **3** was also successfully carried out using the same procedure to give monofluorinated products **7** in moderate yields. In addition, molecular iodine was found to be highly effective for oxidative fluorodesulfurization.

The ^1H, ^{19}F, and ^{13}C NMR spectra were recorded at 270, 254, and 68 MHz, respectively, using a JEOL JNM EX-270 (270.05 MHz) spectrometer in $CDCl_3$ solution relative to TMS (δ = 0.00 ppm) as an internal standard; monofluorobenzene (δ = –36.5 ppm) was used as an internal standard for the ^{19}F NMR spectra. Purification of the fluorinated products was achieved by flash chromatography using Nacalai Tesque silica gel 60 (spherical, neutral) or by HPLC performed using a Shiseido column (SUPERIOREX ODS, 5 μm, 20 mm i.d. × 250 mm). Electron impact MS was obtained using a Shimadzu GCMS-QP5050A instrument. High-resolution MS was performed on a JEOL JMS-700 or Bruker Daltonics micrOTOF II mass spectrometer. Cyclic voltammetry was measured using ALS CH Instruments Electrochemical Analyzer Model 600 C. Electrolysis experiments were carried out using Metronix Corp. constant current power supply model 5944 monitored with Hokuto Denko coulomb/ampere hour meter HF-201.

Anodic Fluorodesulfurization of Oxazine Derivatives (Ex-cell Method); General Procedure

The anodic oxidation of the halide salt (0.2 or 0.3 mmol) was carried out with Pt plate electrodes (1 cm × 1 cm) in 0.1 M n-Bu_4NBF_4 in CH_2Cl_2 (10 mL) using a divided cell under a N_2 atmosphere at r.t. A constant current (8 mA/cm^2) was applied and a theoretical charge of 2 F/mol was passed. After electrolysis, substrate **2** or **3** (0.1 mmol) was added, followed by stirring at r.t. for 10 min, and then $Et_3N{\cdot}3HF$ (0.3 mL, 2.5 mmol) was added using a Teflon syringe. When the starting material was mostly consumed (monitored by TLC), the mixture was quenched with Et_3N (ca. 1 mL) and passed through a short column (silica gel, EtOAc) to remove fluoride salts. The eluent was evaporated under reduced pressure, and the residue

was further purified by flash chromatography (silica gel, EtOAc–hexane) to provide monofluorinated products **4** or **7**.

Spectral data of **4** and **7** were reported in our previous paper.[10]

Anodic Fluorodesulfurization of 2a Using Iodine (Ex-cell Method)

This was carried out in a similar manner to the procedure shown above, using iodine instead of the halide salt.

Chemical Fluorodesulfurization of 2a Using Iodine

To a solution of the 3-phenyl-2-(phenylsulfanyl)-2*H*-1,4-benzoxazine (**2a**; 0.1 mmol) in anhydrous CH_2Cl_2 (5 mL) under a nitrogen atmosphere at r.t. was added I_2, followed by $Et_3N{\cdot}3HF$ (0.3 mL, 2.5 mmol) using a Teflon syringe. After the starting materials had been completely consumed (ca. 30 min, monitored by TLC), the reaction mixture was quenched by the addition of Et_3N (ca. 1 mL) and then partially concentrated under reduced pressure. The residue was passed through a short pad of silica gel, then subjected to flash silica gel chromatography (EtOAc–hexane as eluent) to provide pure product **4a**.

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