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Highly regioselective halogenation of 1-phenyl-3-(3,5-dimethoxyphenyl)-propane-1,3-dione

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ABSTRACT

Halogenation of 1-phenyl-3-(3,5-dimethoxyphenyl)-propane-1,3-dione (**1**) with N–X reagents take place regioselectively at the α position (except for fluorination), while halogenation of its BF_2 derivative **3** take place regioselectively at position 2 in the activated phenyl ring. When the molar ratio of substrate to reagent is changed from 1:1.1 to 1:2.1 or 1:2.8, halogenation takes place at positions 2 and 6 of the aromatic ring. Crystallization of a BF_2 derivative from protic solvent led to hydrolysis of the BF_2 group.

1. Introduction

Halo substituted organic compounds are important intermediates in organic synthesis and are also of biological interest, since in several cases the halogen atom can change the biological activity. Halogen atoms can be introduced into organic molecules by different methods, which include electrophilic, nucleophilic or radical pathways.

Aldehydes and ketones can be halogenated at the α position with bromine, chlorine, and iodine,[1] but the reaction is not successful with fluorine.[2] Compounds containing an active methylene, such as β-keto esters and β-diketones, have been fluorinated with N–F reagents,[3] with F_2/N_2–HCOOH[4] or acetyl hypofluorite.[5] Silyl enol ethers can be fluorinated with XeF_2[6] or 5% F_2 in N_2 at −78 °C in $FCCl_3$.[7] β-Diketones and β-keto esters can also be chlorinated, brominated or iodinated and numerous reagents and methods are described in the literature.[8]

There are also other reagents and methods to introduce a halogen atom into aromatic compounds.[9] Direct fluorination of aromatic rings with F_2[10] is not feasible at room temperature because of the extreme reactivity of F_2, but this can be accomplished at low temperatures.[11] Fluorination has also been reported with acetyl hypofluorite,[12] XeF_2,[13] N–F reagents, such as F–TEDA[14] or $(CF_3SO_2)_2NF$,[15] and by the Schiemann reaction as the most common method for introducing fluorine into aromatic rings. Aromatic compounds can be chlorinated or brominated by treatment with bromine or chlorine in the presence of a catalyst.

For electron-rich substrates like phenols and anisole, reactions are so rapid that they can be carried out with a dilute solution of Br_2 or Cl_2 in water at room temperature, or with aqueous HBr in DMSO.[16] There are also other reagents, such as *N*-chloro and *N*-bromo imides[17] (especially NBS and NCS), HOCl,[18] HOBr etc., for this purpose. Iodine is the least reactive of the halogens in aromatic substitution.[19] Except for electron-rich substrates, an oxidizing agent must be present to oxidize I_2 to a better electrophile.[20–23] On the other hand ICl is a better iodinating agent than iodine itself.[24] *N*-Iodo amides reagents can also be used.[25]

2. Results and discussion

Although it is not very difficult to introduce a halogen atom at the α position in compounds with active methylenes, such as β-diketones or into activated aromatic rings, the problem appears when two such or several reactive centers are present within the same molecule. In these cases it is not so easy to introduce the halogen atom at the desired position only. For this reason, 1-phenyl-3-(3,5-dimethoxyphenyl)-propane-1,3-dione **1**[26] was used as a model compound for our studies. It contains a 1,3-dicarbonyl moiety and a highly activated aromatic ring with two methoxy groups. In acetonitrile solution the keto–enol equilibrium of **1** is shifted toward the enol form predominately (we have determined by ^1H NMR spectroscopy that less than 5% of the diketone form is present).

As halogenation agents we chose: 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis tetrafluoroborate (F–TEDA) and 1-hydroxy-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis tetrafluoroborate (NFTh) for fluorination; *N*-halo succinimide and

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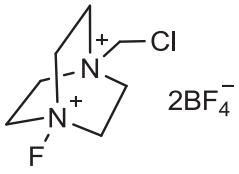
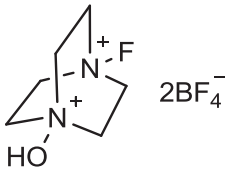
N-halo saccharin for chlorination,[27] bromination,[28] and iodination.[25a] All experiments were carried out at room temperature. Conversions were determined by ^{1}H NMR spectra and products were purified by crystallization from hexane/CH_2Cl_2.



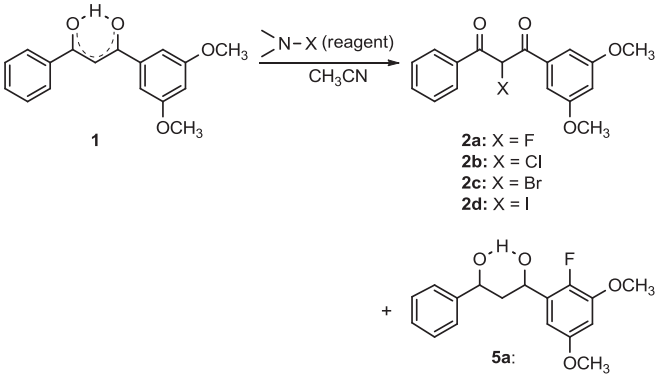
F–TEDA



NFTh

Fluorination of compound **1** was carried out in acetonitrile solution using F–TEDA as the most promising reagent for electrophilic fluorination. The crude reaction mixture was analyzed by ^{1}H and ^{19}F NMR spectroscopy. In the ^{1}H NMR spectrum besides signals corresponding to **1**, two other sets of signals appeared. There was a doublet with coupling constant 49.2 Hz at δ=6.45 ppm corresponding to the product **2a** (Table 1), as well as two dd signals at 6.82 ppm (J=7.1, 3.0 Hz) and 7.16 ppm (J=4.7, 3.0 Hz) belonging to product **5a** (see also Table 2) in which fluorination took place at position 2 in the activated phenyl ring. In the ^{19}F NMR spectrum two signals also appeared: dd at δ=−186.78 ppm with geminal H–F coupling constant=49.2 Hz and a ddd at δ=−142.51 ppm corresponding to compound **5a**. To improve the regioselectivity of fluorination, we also tested NFTh,[29] and determined that both reactive positions were again fluorinated and a mixture of **2a** and **5a** was obtained. On the other hand chlorination,[30] bromination, and iodination using NXS/$LiClO_4$ systems in CH_3CN solution were completely regioselective, and **2b**, **2c**, and **2d** were formed as the sole products (Table 1).

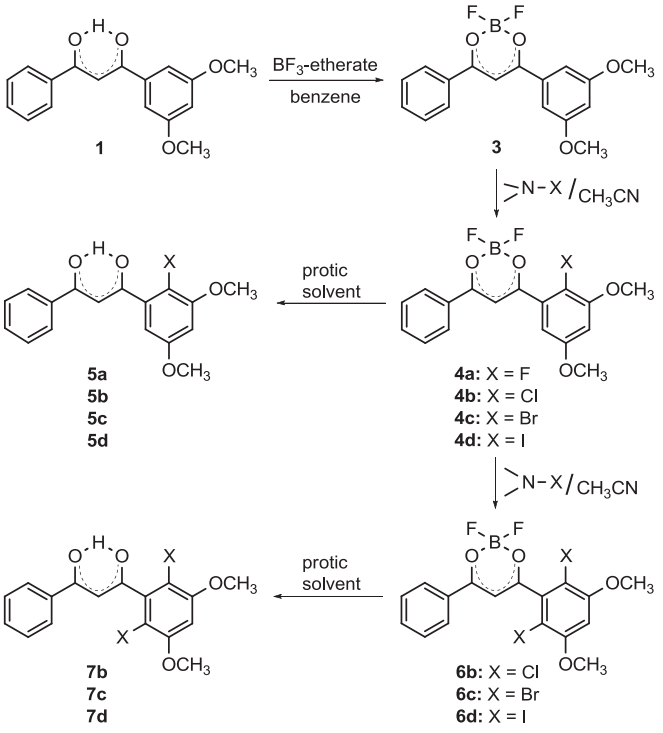
Table 1
Halogenation of compound **1**[a]



Entry	Reagent	Product	Time (h)	Conv (%)	Yield[d] (%)
1	F–TEDA	**2a**	4[c]	89	76[e]
		5a			13[e]
2	NFTh[b]	**2a**	13[c]	100	76[e]
		5a			24[e]
3	NCS	**2b**	0.5	100	90
4	NCSacc	**2b**	0.5	100	93
5	NBS	**2c**	0.5	100	87
6	NBSacc	**2c**	0.5	74	63
7	NIS	**2d**	0.5	100	90
8	NISacc	**2d**	0.5	100	92

[a] Solvent: CH_3CN; mol ratio of **1**/reagent/$LiClO_4$=1:1.1:0.6; rt.
[b] 50% NFTh/Al_2O_3; mol ratio of **1**/reagent/$LiClO_4$=1:2.2:0.6.
[c] At 0 °C.
[d] Isolated yield.
[e] Relative yield.

Table 2
Preparation and halogenations of compound **3**[a]



Entry	Reagent	mol ratio of **3**/reagent	Product	Time (h)	Yield[d] (%)
1	NFTh[b]	1:2.8	**4a**	41	78
2	NCS[c]	1:1.1	**4b**	48	81
3	NCSacc	1:1.1	**4b**	5	79
4	NCSacc	1:2.8	**6b**	24	86
5	NBS[c]	1:1.1	**4c**	1.5	83
6	NBSacc	1:1.1	**4c**	5	63
7	NBSacc	1:2.1	**6c**	20	89
8	NIS[c]	1:1.1	**4d**	48	27[e]
			6d		12[e]
9	NISacc	1:1.1	**4d**	3	27[e]
			6d		36[e]
10	NISacc	1:2.1	**6d**	20	83

[a] Solvent: CH_3CN; mol ratio of **3**/reagent=1:1.1; rt.
[b] 50% NFTh/Al_2O_3.
[c] Irradiated with λ=360 nm.
[d] Isolated yield.
[e] Relative yield.

Similar results were obtained using *N*-halo saccharin which is a better source of electrophilic halogen.[31] No halogenation of the activated phenyl ring took place. Next, using ^{1}H and ^{13}C NMR spectroscopy, we determined that α-halo substituted compounds are present as the 1,3-diketone. At this time we have no explanation for the dramatic change from predominantly enol form of **1** to the keto form upon halogenation.

These results led us to believe that for aryl ring halogenation, the diketo functionality should be deactivated. Using a known literature procedure[32] the BF_2 derivative of **1** was prepared (Table 2) in which BF_2 is a strong electron withdrawing group. The structure of **3** was determined by ^{1}H, ^{13}C, ^{19}F, and ^{11}B NMR spectroscopy. In the ^{1}H NMR spectrum besides other signals, a singlet at δ=7.20 ppm appeared, corresponding to the proton bonded at C2. In the ^{13}C NMR spectrum two signals of nearly equal intensity at δ=183.0 and 183.2 ppm were observed, corresponding to C1 and C3 atoms. The ^{11}B NMR spectrum showed one singlet at 1.46 ppm, while in the ^{19}F NMR spectrum two singlets at δ=−140.19 and −140.25 ppm with integral ratios of 0.19:1.00 were observed. We are unable to explain

that discrepancy but the same observation has been reported in the literature[32,33] for several BF_2 derivatives of symmetric and asymmetric substituted 1,3-diarylpropane-1,3-diones. The authors[33] explained that the spectra of the BF_2 derivative of β-diketones are unusual as the expected B–F coupling is not observed due to fast relaxation of quadrupolar boron nucleus. Taking all these NMR data into account we believe that the central ring in the derivative is nearly symmetric and that the fundamental state of **3** can be described as a hybrid of two resonance form **3**($\mathbf{R_1}$) and **3**($\mathbf{R_2}$) (Fig. 1).

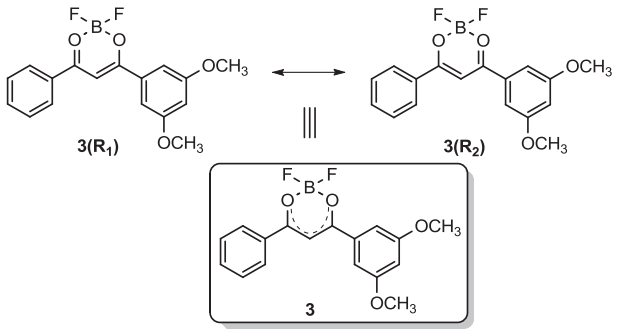


Fig. 1. Possible resonance forms for BF_2 derivative of **3**.

Fluorination of BF_2 derivative **3** was carried out at room temperature with 10% excess of NFTh/Al_2O_3 in acetonitrile (Table 2). After 21 h, we determined that 70% conversion had taken place. Thus, an additional 0.6 mmol of reagent was added and the reaction was continued for 20 h. On the basis of ^1H, ^{13}C, and ^{19}F NMR spectra we concluded that fluorination had occurred only at position 2 in the electron-rich aryl ring. In the ^1H NMR spectrum besides two dd signals at δ=6.82 ppm (J=7.1, 3.0 Hz) and δ=7.14 ppm (J=4.4, 3.0 Hz) corresponding to H4 and H6 of the activated phenyl ring, two singlets at 3.92 and 3.86 ppm for two methoxy group appeared. Besides other signals, the ^{13}C NMR spectrum showed two doublets at 156.0 ppm (J=2.3 Hz) and 149.1 ppm (J=12.9 Hz) corresponding to the carbons bonded to the methoxy groups. Clearly, the dimethoxy-substituted aromatic ring is no longer symmetrical.

Chlorination, bromination, and iodination were carried out with NXS (10% excess) in acetonitrile solution that was irradiated. We determined that the BF_2 derivative **3** was stable to irradiation (λ=360 nm) in acetonitrile (Fig. 2). Whereas chlorination and bromination led to regioselective halogenation at C2 of the electron-rich aromatic ring, iodination resulted in the mixture of starting compound, 2-iodo derivative **4d** and 2,6-diiodo derivative **6d** (Table 2), which was inseparable without hydrolysis of the BF_2 group. We also wanted to study the chemoselectivity of halogenation and NXSacc was used instead of NXS. The regioselectivity of reactions were nearly the same as in previous cases: **4b**, **4c** and the mixture of **4d** and **6d** was formed (Table 2).

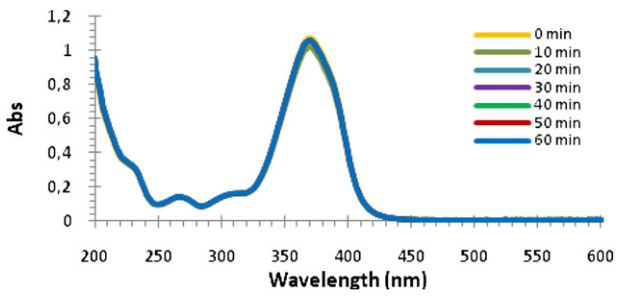


Fig. 2. UV spectra of 2×10^{-5} M CH_3CN solution of derivative **3** after different irradiation times with λ=360 nm.

Table 3
Hydrolysis of compounds **4** and **6**

Entry	Substrate	Product	X	Isolated yield
1	**4a**	**5a**	F	90
2	**4b**	**5b**	Cl	92
3	**4c**	**5c**	Br	97
4	**6b**	**7b**	Cl	96
5	**6c**	**7c**	Br	93
6	**6d**	**7d**	I	95

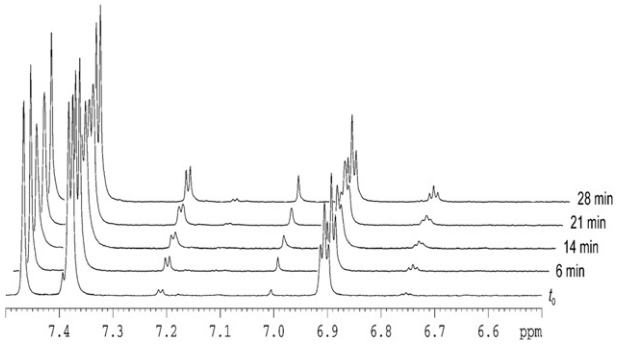
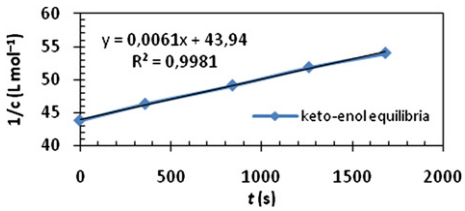


Fig. 3. Hydrolysis of **3**. Changes in ^1H NMR spectra with time.

Table 4
Kinetics of hydrolysis of derivative **3**



t (s)	c (mol L^{-1})	c^{-1} (L mol^{-1})
0	0.0228	43.77
360	0.0216	46.27
840	0.0204	49.08
1260	0.0193	51.82
1680	0.0185	53.89

When we changed molar ratio of substrate to reagent from 1:1.1 to 1:2.1, or 1:2.8 in the case of chlorination, halogenation took place at positions C2 and C6 in the electron-rich phenyl ring. The structures of products were determined on the basis of ^1H, ^{13}C, and ^{19}F NMR spectra. In the ^1H NMR spectrum only one signal was observed for the methoxy protons and in the ^{13}C NMR spectrum only one signal for the carbons bearing the methoxy groups is seen. Thus, the substituted dimethoxyphenyl ring must be symmetrical.

All halogenated BF_2 derivatives were crystallized from the mixture of aprotic solvents like CH_2Cl_2, hexane etc. When crystallization was carried out with a protic solvent, such as methanol or ethanol hydrolysis of the BF_2 group took place (Table 2). This reaction can be followed by a change of color of the suspension from yellow to nearly white. Compounds **5a**–**c** and **7b**–**d** were isolated practically in quantitative yields (Table 3). On the basis of ^1H and ^{13}C NMR spectroscopic data, we concluded that the 1,3-diketo fragment is predominantly in the enol form where a strong intramolecular hydrogen bond occurs and less than 5% of diketo form is seen in equilibrium.

The kinetics of hydrolysis of BF_2 derivative **3** were determined using ^1H NMR spectroscopy at 338 K in an NMR tube. For this purpose 6 mg of derivative **3** was dissolved in 0.75 mL CD_3CN and 10 μL of D_2O was added. To determine the change of concentration

of **3** with time, the ratio of integrals for the protons of both enol forms were used (Fig. 3). After 28 min, the signal for diketone form **1** appeared, so the integral for the methylene group of this compound was also used in the calculation of decreasing concentration of compound **3**. From the results obtained we determined that the reciprocal of concentration per unit time intervals is in a linear correlation. We can conclude that the hydrolysis is a second order reaction, as shown in Table 4.

3. Conclusion

Halogenation of 1-phenyl-3-(3,5-dimethoxyphenyl)-propane-1,3-dione **1** with N–X reagents takes place regioselectively in the α position of the 1,3-dione moiety. Deactivation of the diketo portion of the molecule via complexation with BF_2, leads to regioselective halogenation at C2 in electron-rich phenyl ring. When the molar ratio of substrate to reagent 1:2.1 or 1:2.8 is used, 2,6-disubstituted halo products are obtained. Crystallization of the BF_2 derivatives from protic solvents, such as methanol or ethanol leads to hydrolysis of BF_2 group. The results described in the present paper can be very important for regioselective halogenation of 1,3-diarylpropane-1,3-diones and similar compounds.

4. Experimental section

4.1. General procedure

Photochemical reactions were performed in Photochemical Reactors LTD MLU18, equipped with a black-light blue lamp (FL15BLB, Sankyo Denki, Japan) emitting at 352 nm. UV spectra were obtained using a UV–vis spectrophotometer (Varian Cary 50 Conc.). Chromatographic separations were performed using PLC plates Silica gel 60 (Merck).

NMR Spectra were recorded at 302 K on a Bruker Avance DPX 300 spectrometer operating at 300 MHz, 75 MHz, and 282 MHz for ^1H, ^{13}C, and ^{19}F, and at 298 K on a Varian Unity Inova 300 MHz spectrometer, operating at 282 MHz for ^{19}F and at 97 MHz for ^{11}B. Proton and carbon spectra were referenced to TMS as the internal standard. Some ^1H and ^{13}C chemical shifts were determined relative to the ^1H or ^{13}C signal of the solvent: $CDCl_3$ (^1H: δ 7.259 ppm, ^{13}C: δ 77.00 ppm); CD_2Cl_2 (^1H: δ 5.320 ppm, ^{13}C: δ 54.00 ppm); acetone-d_6 (^1H: δ 2.063 ppm, ^{13}C: δ 29.92 ppm). ^{19}F NMR spectra were referenced to CCl_3F as an external standard, ^{11}B NMR spectra was calibrated to external $BF_3\cdot OEt_2$. Chemical shifts are given on the δ scale (ppm). Coupling constants (J) are given in hertz. Mass spectra and high-resolution mass spectra were obtained with a Q-TOP Premier instrument. Data are reported as m/z (relative intensity). Infrared spectra were recorded on a BIO-RAD Excalibur Series spectrophotometer using samples in potassium bromide disks. Elemental analyses were performed with a Perkin–Elmer 2400 Series II CHNS/O Analyzer. All spectral data obtained for new compounds are reported here. Melting points were measured on Büchi 535.

4.2. Detailed synthetic protocols

*4.2.1. 2-Fluoro-1-phenyl-3-(3,5-dimethoxyphenyl)-propane-1,3-dione (**2a**).* (a) With F–TEDA reagent: substrate **1** (284 mg, 1 mmol) and $LiClO_4$ (64 mg, 0.6 mmol) were dissolved in CH_3CN (15 mL). The reaction mixture was stirred at 0 °C for 10 min and then F–TEDA (390 mg, 1.1 mmol) was added and stirring was continued for an additional 4 h. The solvent was evaporated under reduced pressure and CH_2Cl_2 (30 mL) was added, undissolved solid were filtered off. After removal of CH_2Cl_2, the crude reaction mixture (relative ratio of compounds **2a**/**5a**=6:1) was subjected to preparative TLC (SiO_2, hexane/CH_3COOEt=3:1). On the basis of ^1H NMR spectra and element analysis, we established that the product **2a** (a light-brown oil) was decomposed partially on silica gel. We were unable to obtain satisfactory EA. (b) With 50% NFTh/Al_2O_3 reagent: substrate **1** (284 mg, 1 mmol) and $LiClO_4$ (64 mg, 0.6 mmol) were dissolved in CH_3CN (30 mL). The reaction mixture was stirred at 0 °C for 10 min, then N–FTh was added (1.408 g of 50% NFTh/Al_2O_3 was suspended in 70 mL of CH_3CN, undissolved Al_2O_3 was filtered off, 1.1 mmol) and stirring was continued for an additional 13 h. The solvent was evaporated under reduced pressure, CH_2Cl_2 (30 mL) was added, and undissolved solids were filtered off. After removal of CH_2Cl_2, separation of compounds **2a** and **5a** (relative ratio of **2a**/**5a**=3:1) was done by repeated crystallization of **5a** with EtOH, while oily product **2a** was remained in solution and had never been purified wholly according to all spectral data. ^1H NMR ($CDCl_3$, 300 MHz, 29 °C) δ ppm 8.08 (m, 2H, *o*-Ph), 7.60 (m, 1H, *p*-Ph), 7.48 (m, 2H, *m*-Ph), 7.23 (dd, 2H, J=2.3 , 0.8 Hz), 6.67 (t, 1H, J=2.3 Hz), 6.45 (d, 1H, J=49.2 Hz), 3.83 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz, 29 °C) δ ppm 191.1 (d, J=20.4 Hz), 190.7 (d, J=19.7 Hz), 160.9 (s), 135.1 (d, J=1.9 Hz), 134.5 (s), 133.6 (d, J=2.1 Hz), 129.8 (d, J=3.5 Hz), 128.8 (s), 107.4 (s), 107.3 (d, J=3.4 Hz), 96.5 (d, J=198.8 Hz), 55.6 (s). ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C) δ=−186.78 ppm (dd, 1F, J=49.2 , 0.9 Hz). IR (NaCl) ν=1680, 1594, 1456, 1206, 1158 cm^{-1}. CIMS (m/z) 325.1 (MNa^+). CI-HRMS for $C_{17}H_{15}FO_4Na^+$: calcd 325.0852, found 325.0845.

4.3. Procedures for preparations of 2b[30]–d

(a) With NXS reagents: substrate **1** (142 mg, 0.5 mmol) and $LiClO_4$ (32 mg, 0.3 mmol) were dissolved in CH_3CN (10 mL). The reaction mixture was stirred at room temperature for 15 min. NXS (0.55 mmol) was added and stirring was continued for an additional 30 min. After removal of the solvent, the rest was dissolved in CH_3COOEt (15 mL), washed with water (3×10 mL), dried over Na_2SO_4, filtered and the solvent was evaporated. The crude reaction product was crystallized with methanol and the following quantities of pure products were obtained: **2b** (143 mg, 90%), **2c** (158 mg, 87%), **2d** (184 mg, 90%), as a white solid. (b) With NXSacc reagents: the reactions were carried out also with NXSacc under the same reaction conditions as previously mentioned. After evaporation, the residue was dissolved in CH_2Cl_2 (10 mL), washed with satd aq $NaHCO_3$ (3×10 mL), dried over Na_2SO_4, filtered and the solvent was evaporated in vacuum. The solid was suspended in MeOH (4 mL) and, to remove the unwanted saccharin, undissolved pure products were filtered to obtain **2b** (148 mg, 93%), **2c** (114 mg, 63%), **2d** (188 mg, 92%).

*4.3.1. 2-Bromo-1-phenyl-3-(3,5-dimethoxyphenyl)-propane-1,3-dione (**2c**).* White solid, mp 128.0–129.0 °C. ^1H NMR ($CDCl_3$, 300 MHz, 29 °C) δ ppm 7.98 (m, 2H, *o*-Ph), 7.60 (m, 1H, *p*-Ph), 7.47 (m, 2H, *m*-Ph), 7.11 (d, 2H, J=2.3 Hz), 6.67 (t, 1H, J=2.3 Hz), 6.51 (s, 1H), 3.79 (s, 6H). ^{13}C NMR (CD_2Cl_2, 75 MHz, 29 °C) δ ppm 189.5, 189.2, 161.8, 136.2, 134.9, 134.4, 129.7, 129.6, 107.4, 106.9, 56.2, 52.9. IR (KBr) ν=1704, 1678, 1593, 1450, 1358, 1305, 1286, 1206, 1154, 1067, 1028, 858, 681, 628 cm^{-1}. CIMS (m/z) 387.0 (MNa^++2), 385.0 (MNa^+). CI-HRMS for $C_{17}H_{15}BrO_4Na^+$: calcd 385.0051, found 385.0061. EA for $C_{17}H_{15}BrO_4$: calcd 56.22%C, 4.16%H; found 55.75% C, 4.07%H.

*4.3.2. 2-Iodo-1-phenyl-3-(3,5-dimethoxyphenyl)-propane-1,3-dione (**2d**).* White solid, mp 151.0–152.0 °C. ^1H NMR ($CDCl_3$, 300 MHz, 29 °C) δ ppm 7.98 (m, 2H, *o*-Ph), 7.59 (m, 1H, *p*-Ph), 7.46 (m, 2H, *m*-Ph), 7.11 (d, 2H, J=2.3 Hz), 6.89 (s, 1H), 6.66 (t, 1H, J=2.3 Hz), 3.79 (s, 6H). ^{13}C NMR (CD_2Cl_2, 75 MHz, 29 °C) δ ppm 190.6, 190.3, 161.8, 135.6, 134.7, 133.8, 129.7, 129.6, 107.4, 106.7, 56.2, 34.4. IR (KBr) ν=1697, 1670, 1592, 1450, 1423, 1358, 1302, 1285, 1205, 1155, 1068, 1026, 857, 680 cm^{-1}. CIMS (m/z) 433.0 (MNa^+). CI-HRMS for

$C_{17}H_{15}IO_4Na^+$: calcd 432.9913, found 432.9923. EA for $C_{17}H_{15}IO_4$: calcd 49.78%C, 3.69%H; found 49.69%C, 3.62%H.

*4.3.3. 2,2-Difluoro-4-(-3,5-dimethoxyphenyl)-6-phenyl-2H-1,3,2-dioxaborinin (**3**).* Diketone **1** (1.42 g, 5 mmol) was dissolved in benzene (25 mL) and BF_3–etherate (700 μL, 5.5 mmol) was added in 100 mL flask, equipped with a reflux condenser. The solution was refluxed for 1 h. The reaction mixture was refrigerated over the night, the precipitate was filtered to obtain **3** as a fluorescent-yellow solid (1.46 g, 88%), which was further crystallized with the mixture of CH_2Cl_2/hexane. Mp 174.5–175.2 °C. ^{1}H NMR (CD_2Cl_2, 300 MHz, 29 °C) δ ppm 8.16 (m, 2H, *o*-Ph), 7.74 (m, 1H, *p*-Ph), 7.60 (m, 2H, *m*-Ph), 7.26 (d, 2H, *J*=2.3 Hz), 7.20 (s, 1H), 6.80 (t, 1H, *J*=2.3 Hz), 3.89 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz, 29 °C) δ ppm 183.2, 183.0, 161.1, 135.3, 133.8, 131.9, 129.2, 128.9, 107.6, 106.5, 93.7, 55.7. ^{19}F NMR (acetone-d_6, 282 MHz, 29 °C) δ ppm −140.19 (s), −140.25 (s); ratio of integrals 0.19:1.00. ^{11}B NMR ($CDCl_3$, 97 MHz, 25 °C) δ ppm 1.46 (s). IR (KBr) ν=1542, 1370, 1288, 1210, 1169, 1050,810, 775, 597 cm^{-1}. CIMS (*m*/*z*) 355.1 (MNa^+), 333.1 (MH^+). CI-HRMS for $C_{17}H_{16}BF_2O_4^+$: calcd 333.1110, found 333.1110. EA for $C_{17}H_{15}BF_2O_4$: calcd 61.48%C, 4.55%H; found 61.57%C, 4.39%H.

*4.3.4. 2,2-Difluoro-4-(2-fluoro-3,5-dimethoxyphenyl)-6-phenyl-2H-1,3,2-dioxaborinin (**4a**).* BF_2 derivative **3** (332 mg, 1 mmol) had been dissolved in CH_3CN (20 mL) before NFTh was added (1.408 g of 50% NFTh/Al_2O_3 was suspended in 50 mL of CH_3CN, undissolved Al_2O_3 was filtered off, 1.1 mmol). After stirring for 21 h at room temperature, a 70% conversion was determined by ^{1}H NMR spectra. Thus, an additional NFTh (0.3 mmol) was added and the reaction mixture was stirred for an additional 20 h. The solvent was evaporated under reduced pressure, CH_2Cl_2 (25 mL) was added and undissolved solid was filtered off. After removal of CH_2Cl_2, the residue was crystallized with MeOH to obtain **4a** (273 mg, 78%) as a yellow solid. Mp 188.9–190.0 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 29 °C) δ ppm 8.15 (m, 2H, *o*-Ph), 7.72 (m, 1H, *p*-Ph), 7.57 (m, 2H, *m*-Ph), 7.44 (s, 1H), 7.14 (dd, 1H, *J*=4.4 , 3.0 Hz), 6.82 (dd,1H, *J*=7.1 , 3.0 Hz), 3.92 (s, 3H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 29 °C) δ ppm 184.5 (d, *J*=1.3 Hz), 178.7 (d, *J*=3.7 Hz), 156.0 (d, *J*=2.3 Hz), 149.9 (s), 149.1 (d, *J*=12.9 Hz), 148.2 (d, *J*=254.1 Hz), 135.6 (s), 131.9 (s), 129.2 (s), 120.8 (d, *J*=6.8 Hz), 108.2 (d, *J*=2.4 Hz), 102.3 (s), 98.3 (d, *J*=18.9 Hz), 56.6 (s), 56.1 (s). ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C) δ ppm −183.13 (dd, 1F, *J*=7.1 , 4.4 Hz), −139.36 (s) and −139.43 (s); (2F); ratio of integrals 1.00:3.71. IR (KBr) ν=1541, 1491, 1367, 1337, 1287, 1208, 1168, 1077, 1039, 779, 689, 618 cm^{-1}. CIMS (*m*/*z*) 373.1 (MNa^+). CI-HRMS for $C_{17}H_{14}BF_3O_4Na^+$: calcd 373.0835, found 373.0832. EA for $C_{17}H_{14}BF_3O_4$: calcd 58.32%C, 4.03%H; found 58.36%C, 3.78%H.

4.4. Procedure for preparations of 4b–d

(a) With NXS and irradiation: BF_2 derivative **3** (166 mg, 0.5 mmol) and NXS reagent (0.55 mmol) was dissolved in CH_3CN (10 mL) before being irradiated in quartz tube with λ=360 nm (for the reaction times, see Table 2). After irradiation, the solvent was evaporated, the corresponding residue was suspended in MeOH (5 mL), to remove the unwanted succinimide, the undissolved organic was filtered, crystallized with CH_2Cl_2/hexane, and filtered to obtain **4b** (148 mg, 81%); **4c** (171 mg, 83%), as a yellow solid. We were unable to separate the mixture of compounds **4d**/**6d** (with relative ratio 2:1). (b) With NXSacc reagents: BF_2 derivative **3** (166 mg, 0.5 mmol) and NXSacc (0.55 mmol) was dissolved in CH_3CN (10 mL). The reaction mixture was stirred at room temperature (for the reaction times, see Table 2). After evaporation of the solvent MeOH (5 mL) was added, the precipitate was filtered and crystallized with hexane/CH_2Cl_2 to obtain **4b** (145 mg, 79%), **4c** (129 mg, 63%) and the mixture of **4d**/**6d** (relative ratio of compounds **4d**/**6d**=1:1). Product **4d** was not isolated in pure form.

*4.4.1. 2,2-Difluoro-4-(2-chloro-3,5-dimethoxyphenyl)-6-phenyl-2H-1,3,2-dioxaborinin (**4b**).* Yellow solid, mp 132.0–134.0 °C. ^{1}H NMR (acetone-d_6, 300 MHz, 29 °C) δ ppm 8.33 (m, 2H, *o*-Ph), 7.86 (m, 1H, *p*-Ph), 7.70 (m, 2H, *m*-Ph), 7.49 (s, 1H), 7.02 (d, 1H, *J*=2.8 Hz), 6.98 (d, 1H, *J*=2.8 Hz), 4.00 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (acetone-d_6, 75 MHz, 29 °C) δ ppm 185.7, 185.4, 160.6, 158.0, 137.1, 135.2, 132.6, 130.5, 130.4, 113.7, 107.5, 104.8, 100.4, 57.3, 56.6. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C) δ ppm −138.98 (s), −139.04 (s); ratio of integrals 1.00:3.80. IR (KBr) ν=1707, 1538, 1492, 1366, 1317, 1303, 1283, 1207, 1163, 104, 782, 687, 612 cm^{-1}. CIMS (*m*/*z*) 391.1 (MNa^++2), 389.1 (MNa^+). CI-HRMS for $C_{17}H_{14}BClF_2O_4Na^+$: calcd 389.0539, found 389.0533. EA for $C_{17}H_{14}BClF_2O_4$: calcd 55.70%C, 3.85%H; found 55.75%C, 4.07%H.

*4.4.2. 2,2-Difluoro-4-(2-bromo-3,5-dimethoxyphenyl)-6-phenyl-2H-1,3,2-dioxaborinin (**4c**).* Yellow solid, mp 135.0–137.0 °C. ^{1}H NMR (acetone-d_6, 300 MHz, 29 °C) δ ppm 8.34 (m, 2H, *o*-Ph), 7.88 (m, 1H, *p*-Ph), 7.71 (m, 2H, *m*-Ph), 7.44 (s, 1H), 7.00 (d, 1H, *J*=2.8 Hz), 6.95 (d, 1H, *J*=2.8 Hz), 4.00 (s, 3H), 3.94 (s, 3H). ^{13}C NMR (CD_2Cl_2, 75 MHz, 29 °C) δ ppm 185.6, 184.7, 160.8, 158.3, 136.8, 136.5, 132.2, 130.0, 129.9, 107.3, 104.2, 102.8, 100.3, 57.4, 56.6. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C) δ ppm −138.95 (s), −139.01 (s); ratio of integrals 1.00:3.92. IR (KBr) ν=1706, 1541, 1492, 1366, 1317, 1301, 1210, 1165, 1080, 1043, 972, 782 cm^{-1}. CIMS (*m*/*z*) 435.0 (MNa^++2), 433.0 (MNa^+). CI-HRMS for $C_{17}H_{14}BBrF_2O_4Na^+$: calcd 433.0034, found 433.0049. EA for $C_{17}H_{14}BBrF_2O_4$: calcd 49.68%C, 3.43%H; found 49.69%C, 3.62%H.

4.5. Procedure for preparations of 6b–d with NXSacc reagents

BF_2 derivative **3** (332 mg, 1 mmol) and NCSacc (609 mg, 2.8 mmol), or NBSacc (550 mg, 2.1 mmol), or NISacc (649 mg, 2.1 mmol) were dissolved in CH_3CN (36 mL/chlorination; 20 mL/bromination, iodination). The reaction mixture was stirred at room temperature for 24 h in the case of chlorination and 20 h for bromination and iodination. The solvent was evaporated and the rest was suspended in MeOH (2×3 mL), to remove the unwanted saccharine. The precipitate was filtered, crystallized with hexane/CH_2Cl_2 to obtain as the yellow solids: **6b** (345 mg, 86%), **6c** (436 mg, 89%), **6d** (484 mg, 83%).

*4.5.1. 2,2-Difluoro-4-(2,6-dichloro-3,5-dimethoxyphenyl)-6-phenyl-2H-1,3,2-dioxaborinin (**6b**).* Yellow solid, mp 236.7–237.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 29 °C) δ ppm 8.13 (m, 2H, *o*-Ph), 7.74 (m, 1H, *p*-Ph), 7.56 (m, 2H, *m*-Ph), 6.76 (s, 1H), 6.68 (s, 1H), 3.96 (s, 6H). ^{13}C NMR (CD_2Cl_2, 75 MHz, 29 °C) δ ppm 186.2, 184.0, 155.8, 137.0, 134.6, 131.8, 130.1, 130.0, 112.6, 100.9, 99.7, 57.5. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C) δ ppm −138.05 (s), −138.12 (s); ratio of integrals 1.00:3.36. IR (KBr) ν=1583, 1550, 1469, 1432, 1384, 1318, 1299, 1221, 1065, 1043, 972, 820, 740 cm^{-1}. CIMS (*m*/*z*) 427.0 (MNa^++4), 425.0 (MNa^++2), 423.0 (MNa^+). CI-HRMS for $C_{17}H_{13}BCl_2F_2O_4Na^+$: calcd 423.0150, found 423.0154. EA for $C_{17}H_{13}BCl_2F_2O_4$: calcd 50.92%C, 3.27%H; found 50.93%C, 3.15%H.

*4.5.2. 2,2-Difluoro-4-(2,6-dibromo-3,5-dimethoxyphenyl)-6-phenyl-2H-1,3,2-dioxaborinin (**6c**).* Yellow solid, mp 254.0–256.0 °C. ^{1}H NMR (CD_2Cl_2, 300 MHz, 29 °C) δ ppm 8.14 (m, 2H, *o*-Ph), 7.77 (m, 1H, *p*-Ph), 7.60 (m, 2H, *m*-Ph), 6.78 (s, 1H), 6.67 (s, 1H), 3.97 (s, 6H). ^{13}C NMR (CD_2Cl_2, 75 MHz, 29 °C) δ ppm 186.3, 186.1, 157.4, 138.2, 136.9, 131.8, 130.1, 130.0, 101.2, 100.5, 99.2, 57.5. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C) δ ppm −137.85 (s), −137.92 (s); ratio of integrals 1.00:3.48. ^{11}B NMR ($CDCl_3$, 97 MHz, 25 °C) δ ppm 1.45 (s). IR (KBr) ν=1589, 1546, 1468, 1378, 1296, 1219, 1063, 1043, 971, 818, 706 cm^{-1}. CIMS (*m*/*z*) 514.9 (MNa^++4), 512.9 (MNa^++2), 510.9 (MNa^+). CI-HRMS for $C_{17}H_{13}BBr_2F_2O_4Na^+$: calcd 510.9139, found

510.9157. EA for $C_{17}H_{13}BBr_2F_2O_4$: calcd 41.68%C, 2.67%H; found 41.74%C, 2.39%H.

*4.5.3. 2,2-Difluoro-4-(2,6-diiodo-3,5-dimethoxyphenyl)-6-phenyl-2H-1,3,2-dioxaborinin (**6d**).* Yellow solid, mp 249.0–250.5 °C. ^{1}H NMR (CD_2Cl_2, 300 MHz, 29 °C) δ ppm 8.15 (m, 2H, *o*-Ph), 7.78 (m, 1H, *p*-Ph), 7.60 (m, 2H, *m*-Ph), 6.82 (s, 1H), 6.72 (s, 1H), 3.97 (s, 6H). ^{13}C NMR (CD_2Cl_2, 75 MHz, 29 °C) δ ppm 186.3, 184.0, 155.8, 137.0, 134.7, 131.8, 130.1, 130.0, 112.6, 101.0, 99.8, 57.5. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C) δ ppm −137.25 (s), −137.32 (s); ratio of integrals 1.00:3.37. ^{11}B NMR ($CDCl_3$, 97 MHz, 25 °C) δ ppm 1.41 (s). IR (KBr) ν=1566, 1538, 1466, 1374, 1294, 1220, 1061, 1042, 970, 818 cm^{-1}. CIMS (*m*/*z*) 606.9 (MNa^+). CI-HRMS for $C_{17}H_{13}BF_2I_2O_4Na^+$: calcd 606.8862, found 606.8852. EA for $C_{17}H_{13}BF_2I_2O_4$: calcd 34.97%C, 2.24%H; found 35.01%C, 1.93%H.

4.6. Procedure for preparations of 5a–c and 7b–d

Compound **4a–c** or **6b–d** (1 mmol) was suspended in MeOH (5 mL) and heated to the reflux. During heating, the reaction can be followed by the change of color of the suspensions from yellow to nearly white. After cooling in refrigerator, the pure products were filtered to obtain: **5a** (272 mg, 90%) and **5b** (293 mg, 92%) as a light yellow solid, **5c** (352 mg, 97%) and **7b** (339 mg, 96%), and **7c** (411 mg, 93%) and **7d** (509 mg, 95%) as white solids.

*4.6.1. 1-Phenyl-3-(2-fluoro-3,5-dimethoxyphenyl)-propane-1,3-dione (**5a**).* Light yellow solid, mp 114.1 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 29 °C) δ ppm 8.15 (m, 2H, *o*-Ph), 7.72 (m, 1H, *p*-Ph), 7.57 (m, 2H, *m*-Ph), 7.45 (s, 1H), 7.16 (dd, 1H, *J*=4.7 , 3.0 Hz), 6.82 (dd, 1H, *J*=7.1 , 3.0 Hz), 3.93 (s, 3H), 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 29 °C) δ ppm 185.7 (d, *J*=1.1 Hz), 182.0 (d, *J*=3.4 Hz), 155.7 (d, *J*=2.4 Hz), 148.9 (d, *J*=13.1 Hz), 146.4 (d, *J*=248.9 Hz), 135.6 (s), 135.2 (s), 132.6 (s), 129.3 (d, *J*=0.5 Hz), 128.7 (s), 127.3 (s), 124.3 (d, *J*=9.3 Hz), 105.1 (d, *J*=1.8 Hz), 102.2 (d, *J*=3.0 Hz), 98.2 (d, *J*=14.2 Hz), 56.6 (s), 55.8 (s). ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C) δ ppm −142.52 (ddd, 1F, *J*=7.1 , 4.7 , 1.0 Hz). IR (KBr) ν=1598, 1541, 1360, 1231, 1202, 1164, 1061, 843, 772, 686, 623 cm^{-1}. CIMS (*m*/*z*) 325.1 (MNa^+). CI-HRMS for $C_{17}H_{15}FO_4Na^+$: calcd 325.0852, found 325.0848. EA for $C_{17}H_{15}FO_4$: calcd 67.54%C, 5.00%H; found 67.39%C, 4.92%H.

*4.6.2. 1-Phenyl-3-(2-chloro-3,5-dimethoxyphenyl)-propane-1,3-dione (**5b**).* Light yellow solid, mp 96.0–97.5 °C. ^{1}H NMR (acetone-d_6, 300 MHz, 29 °C) δ ppm 8.07 (m, 2H, *o*-Ph), 7.65 (m, 1H, *p*-Ph), 7.56 (m, 2H, *m*-Ph), 6.84 (d, 1H, *J*=2.8 Hz), 6.82 (d, 1H, *J*=2.8 Hz), 6.81 (s, 1H), 3.96 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (acetone-d_6, 75 MHz, 29 °C) δ ppm 189.3, 185.1, 160.4, 157.5, 139.0, 135.6, 133.9, 129.9, 128.2, 112.3, 106.5, 102.7, 99.2, 57.0, 56.3. IR (KBr) ν=1594, 1573, 1456, 1346, 1290, 1206, 1169, 1091, 1042, 816, 780, 692 cm^{-1}. CIMS (*m*/*z*) 343.1 (MNa^++2), 341.1 (MNa^+), 319.1 (MH^+). CI-HRMS for $C_{17}H_{16}ClO_4^+$: calcd 319.0737, found 319.0741. EA for $C_{17}H_{15}ClO_4$: calcd 64.06%C, 4.74%H; found 63.68%C, 4.38%H.

*4.6.3. 1-Phenyl-3-(2-bromo-3,5-dimethoxyphenyl)-propane-1,3-dione (**5c**).* White solid, mp 93.5–94.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 29 °C) δ ppm 16.10 (br s, −OH), 7.94 (m, 2H, *o*-Ph), 7.55 (m, 1H, *p*-Ph), 7.47 (m, 2H, *m*-Ph), 6.70 (d, 1H, *J*=2.8 Hz), 6.61 (s, 1H), 6.58 (d, 1H, *J*=2.8 Hz), 3.91 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (CD_2Cl_2, 75 MHz, 29 °C) δ ppm 190.3, 184.0, 160.7, 157.9, 141.1, 135.2, 133.3, 129.3, 127.7, 106.1, 102.0, 101.1, 99.0, 57.2, 56.4. IR (KBr) ν=1588, 1572, 1455, 1343, 1207, 1167, 1081, 1040, 815, 777, 690 cm^{-1}. CIMS (*m*/*z*) 387.0 (MNa^++2), 385.0 (MNa^+), 365.0 (MH^++2), 363.0 (MH^+). CI-HRMS for $C_{17}H_{16}BrO_4^+$: calcd 363.0232, found 363.0220. EA for $C_{17}H_{15}BrO_4$: calcd 56.22%C, 4.16%H; found 56.24%C, 4.29%H.

*4.6.4. 1-Phenyl-3-(2,6-dichloro-3,5-dimethoxyphenyl)-propane-1,3-dione (**7b**).* White solid, mp 161.2–161.3 °C. ^{1}H NMR (CD_2Cl_2, 300 MHz, 29 °C) δ ppm 15.73 (br s, OH), 7.92 (m, 2H, *o*-Ph), 7.58 (m, 1H, *p*-Ph), 7.48 (m, 2H, *m*-Ph), 6.65 (s, 1H), 6.35 (s, 1H), 3.95 (s, 6H). ^{13}C NMR ($CDCl_3$/CD_2Cl_2, 75 MHz, 29 °C) δ ppm 188.6, 181.9, 154.7, 137.9, 133.7, 132.6, 128.5, 126.9, 111.2, 98.5, 97.7, 56.5. IR (KBr) ν=1581, 1455, 1432, 1345, 1215, 1042, 812, 776, 735, 696 cm^{-1}. CIMS (*m*/*z*) 379.0 (MNa^++4), 377.0 (MNa^++2), 375.0 (MNa^+). CI-HRMS for $C_{17}H_{14}Cl_2O_4Na^+$: calcd 375.0167, found 375.0150. EA for $C_{17}H_{14}Cl_2O_4$: calcd 57.81%C, 4.00%H; found 57.61%C, 3.67%H.

*4.6.5. 1-Phenyl-3-(2,6-dibromo-3,5-dimethoxyphenyl)-propane-1,3-dione (**7c**).* White solid, mp 195.0–196.5 °C. ^{1}H NMR (CD_2Cl_2, 300 MHz, 29 °C) δ ppm 15.64 (br s, −OH), 7.92 (m, 2H, *o*-Ph), 7.57 (m, 1H, *p*-Ph), 7.48 (m, 2H, *m*-Ph), 6.60 (s, 1H), 6.31 (s, 1H), 3.95 (s, 6H). ^{13}C NMR (CD_2Cl_2, 75 MHz, 29 °C) δ ppm 192.1, 182.1, 157.2, 142.4, 134.4, 133.4, 129.3, 127.6, 100.6, 98.9, 98.1, 57.4. IR (KBr) ν=1605, 1576, 1462, 1425, 1340, 1213, 1040, 810, 782, 688 cm^{-1}. CIMS (*m*/*z*) 466.9 (MNa^++4), 464.9 (MNa^++2), 462.9 (MNa^+), 444.9 (MH^++4), 442.9 (MH^++2), 440.9 (MH^+). CI-HRMS for $C_{17}H_{15}Br_2O_4^+$: calcd 440.9337, found 440.9348. EA for $C_{17}H_{14}Br_2O_4$: calcd 46.18%C, 3.19%H; found 46.10%C, 3.08%H.

*4.6.6. 1-Phenyl-3-(2,6-diiodo-3,5-dimethoxyphenyl)-propane-1,3-dione (**7d**).* White solid, mp 207.5–208.0 °C. ^{1}H NMR (CD_2Cl_2, 300 MHz, 29 °C) δ ppm 15.62 (br s, −OH), 7.93 (m, 2H, *o*-Ph), 7.57 (m, 1H, *o*-Ph), 7.49 (m, 2H, *m*-Ph), 6.47 (s, 1H), 6.27 (s, 1H), 3.94 (s, 6H). ^{13}C NMR (CD_2Cl_2, 75 MHz, 29 °C) δ ppm 196.1, 182.1, 160.5, 149.4, 134.5, 133.3, 129.3, 127.6, 98.2, 96.0, 74.1, 57.5. IR (KBr) ν=1603, 1564, 1459, 1415, 1333, 1212, 1040, 810, 778, 693 cm^{-1}. CIMS (*m*/*z*) 558.9 (MNa^+), 536.9 (MH^+). CI-HRMS for $C_{17}H_{15}I_2O_4^+$: calcd 536.9060, found 536.9074. EA for $C_{17}H_{14}I_2O_4$: calcd 38.09%C, 2.63%H; found 38.05%C, 2.72%H.

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Supplementary data

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