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Synthesis of Arylglyoxylic Acids and Their Collision-Induced Dissociation

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Abstract: A variety of substituted arylglyoxylic acids (**2a**–**g**) were synthesized via oxidation of the corresponding aryl-methylketones (**1a–e**) using selenium dioxide or Friedel–Crafts acylation of phenol (**3**) with ethyl chlorooxoacetate and further transformations. It was found that the arylglyoxylic acids (**2**) undergo facile unimolecular dissociation with loss of carbon monoxide to give the corresponding arylcarboxylic acids (**7**) under collisionally induced mass spectrometric conditions.

Keywords: Arylcarboxylic acids, arylglyoxylic acids, dissociation, synthesis

INTRODUCTION

Arylglyoxylic acids (**2**) are important structural units for a variety of applications (e.g., the preparation of oxygenated heterocycles,[1] key intermediates for generation of combinatorial libraries,[2] and substrates for asymmetric synthesis of biologically active natural products.[3,4] In addition, several natural products containing the glyoxylic acid group have been identified with potential medical applications.[5] As a result of the unique structural features of this functional unit, which is also commonly known as α-keto acid or 2-oxoacetic acid, numerous studies

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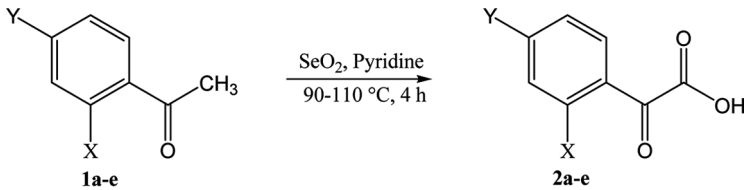
have been carried out to understand its physico-chemical properties.[6] Generally, the glyoxylic acids exhibit a tendency to decarboxylate and/or or polymerize, and therefore it is recommended that they are to be stored as metal salts or neutral solution at low temperature.[4a] Therefore, it is critical to understand the dissociation behavior of arylglyoxylic acids (**2**) to utilize this class of compounds more effectively for medical and pharmaceutical applications. In this context, sekiguch; and coworkers have recently described the dissociation of protonated glyoxylic acid ($HCO\text{-}CO_2H$) and reported that the only observed ionic product was H_3O^+, thus indicating the loss of two carbon monoxide molecules.[7] In addition, they have postulated the pattern and dynamics of glyoxylic acid dissociation process. We became interested in studying the unimolecular dissociation of arylglyoxylic acids (**2**) as well as understanding the effect of various substituents on the phenyl ring during the dissociation process. In this article, we describe the synthesis of a variety of substituted arylglyoxylic acids (**2a–g**) and evaluation of their collision-induced dissociation.

RESULTS AND DISCUSSION

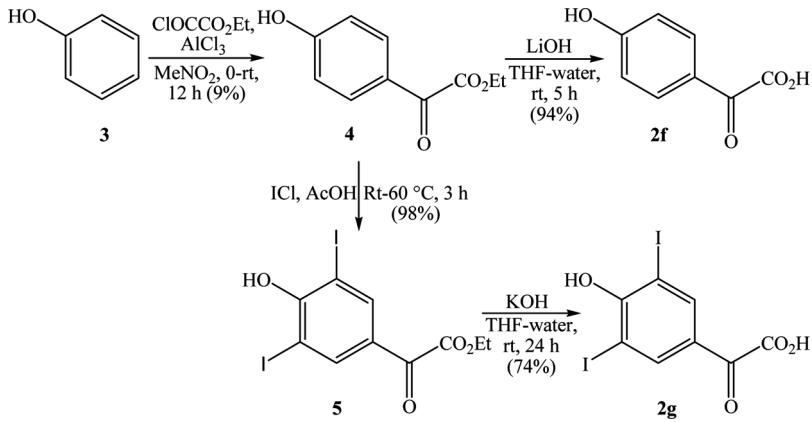
The substituted arylglyoxylic acids (**2a–e**) were synthesized based on oxidation of the corresponding aryl-methylketones (**1a–e**) using a selenium dioxide (Scheme 1) reagent.[8] The oxidation reaction was carried out in pyridine at an elevated temperature, and the desired products (**2a–e**) were isolated by silica-gel column chromatography in excellent yield (78–99%). Purity was also excellent as determined by analytical reverse-phase high performance liquid chromatography (HPLC). We have devised a different approach (Scheme 2) for the synthesis of 2-(4-hydroxy-3,5-diiodophenyl)-2-oxoacetic acid (**2g**) because the selenium dioxide oxidation method gave a complex mixture of products during the preparation of a similar acid-containing chlorines at the 3- and 5-positions of the aryl ring.

Thus, arylglyoxylic acids (**2f–g**) were synthesized from phenol (**3**) based on Friedel–Crafts acylation using ethyl chlorooxoacetate[9] and



1a-e **2a-e**

Scheme 1. Synthesis of arylglyoxylic acids (**2a–e**). **a**) X = H, Y: Cl; **b**) X = H, $Y = NO_2$; **c**) X=Y=OMe; **d**) X = H, Y = OPh; and **e**) X = H, Y = OPh-*p*-OMe.



Scheme 2. Synthesis of arylglyoxylic acids (**2f–g**).

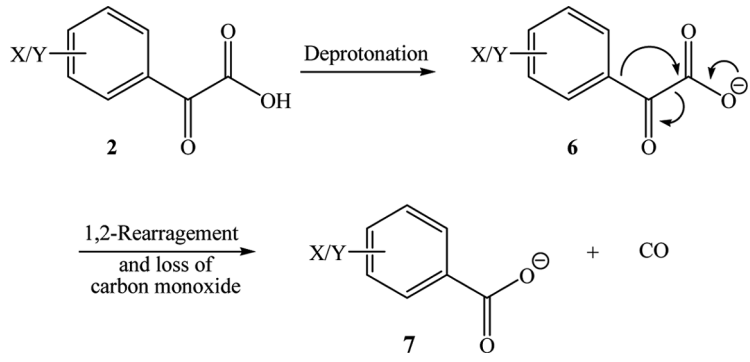
subsequent transformations (Scheme 2). Accordingly, the phenol (**3**) was treated with anhydrous aluminum chloride and ethyl chlorooxoacetatein nitromethane to afford the key intermediate, ethyl (4-hydroxyphenyl)-2-oxoacetate (**4**), in low yields. In this acylation reaction, the corresponding *O*-substituted regioisomer was also formed, as determined by HPLC and liquid chromatography-mass spectrometry (LC-MS), which was separated easily during the silica-gel column chromatography purification process. The ester **4** was then hydrolyzed using lithium hydroxide in THF–water mixture at room temperature followed by crystallization to afford 2-(4-hydroxyphenyl)-2-oxoacetic acid (**2f**) in 94% yield.[10] Reaction of ethyl 2-(4-hydroxyphenyl)-2-oxoacetate (**4**) with 3.7 equivalents of iodine monochloride in a mixture of acetic acid and water afforded the corresponding 3,4-diiodo ester (**5**) in an excellent yield (>98%). Finally, hydrolysis of the ethyl ester (**5**) was achieved using potassium hydroxide in THF–water to give 2-(4-hydroxy-3,5-diiodophenyl)-2-oxoacetic acid (**2g**) in 74% yield.

The arylglyoxylic acids (**2a–g**) were analyzed on a ThermoFinnigan LCQ DECA XP system using negative-ion atmospheric pressure chemical ionization [APCI(-)]. The MS/MS (tandem mass spectrometry) analysis of the parent ion was carried out at 35% collision energy levels. The resulting MS/MS spectra from the collision-induced dissociation of the deprotonated molecular ion of arylglyoxylic acids (**2a** and **2c–g**) showed the loss of carbon monoxide $(M–H–CO)^-$ (Table 1) and resulted in formation of corresponding arylcarboxylic acids (**7**). Although, the oxidative decarboxylation of arylglyoxylic acids (**2**) using singlet oxygen has been reported,[11] the

Table 1. Collision-induced dissociation of arylglyoxylic acids (**2a–g**)

Entry	Arylglyoxylic acid (2)	Formula	Nominal mass	Molecular ion $(M–H)^-$	$(M–H–CO)^-$
1	**2a**	$C_8H_5ClO_3$	184	183 $C_8H_4ClO_3$	155 $C_7H_4ClO_2$
2	**2b**	$C_8H_5NO_5$	195	194 $C_8H_4NO_5$	Not observed
3	**2c**	$C_{10}H_{10}O_5$	210	209 $C_{10}H_9O_5$	181 $C_9H_9O_4$
4	**2d**	$C_{14}H_{10}O_4$	242	241 $C_{14}H_9O_4$	213 $C_{13}H_9O_3$
5	**2e**	$C_{15}H_{12}O_5$	272	271 $C_{15}H_{11}O_5$	243 $C_{14}H_{11}O_4$
6	**2f**	$C_8H_6O_4$	166	165 $C_8H_5O_4$	137 $C_7H_5O_3$
7	**2g**	$C_8H_4I_2O_4$	417	416 $C_8H_3I_2O_4$	389 $C_7H_3I_2O_3$

loss of carbon monoxide under the mass spectrometric collision-induced conditions is unique for this class of compounds. The facile nature of this unimolecular dissociation process is general which is shown with a variety of substitution on the aryl ring (e.g., hydroxy, methoxy, chloride, phenoxy, and iodine groups). The arylglyoxylic acid (**2b**), which contains a nitro group ($–NO_2$), did not show the loss of carbon monoxide $(M–H–CO)^-$, presumably because of the meta-directing effect of the nitro group rather than electron-withdrawing effect, because the **2a**, which contains chlorine (–Cl) at para-position, underwent dissociation with loss of carbonmoxide. MSMS spectra analysis of **2a** and **2c–g** further indicated that decarbonylation peak $(M–H–CO)^-$ for carboxylate ion (**7**) is major. In addition, the parent ion $(M–H)^-$ and a peak corresponding to the further dissociation of **7** with loss of carbon dioxide $(M–H–CO–CO_2)^-$ were also present. We believe that the dissociation process involved (Scheme 3) an initial deprotonation of arylglyoxylic acid (**2**) followed by 1,2-rearrangement



Scheme 3. Collision-induced dissociation of arylglyoxylic acids (**2**).

with migration of aryl group from the carbonyl carbon to carboxylic acid carbon, and thus loosing carbon monoxide and leading to the formation of the corresponding arylcarboxylic acids (**7**). An analogous migration of the aryl group has been proposed with the loss of carbon monoxide from the deprotonated benzyl benzoate esters under activated mass spectrometric conditions.[12]

In summary, we have synthesized a variety of substituted arylglyoxylic acids (**2a–g**) and analyzed their unimolecular dissociation by mass spectrometry. The loss of carbon monoxide is facile under these collisionally induced mass spectrometric conditions, and the dissociation process is general with a variety of substituents. The arylglyoxylic acid (**2**) containing highly electron-withdrawing groups, such as $-NO_2$, proved to be stable under these conditions and did not undergo dissociation.

EXPERIMENTAL

General Methods and Materials

^1H and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (400 MHz), and the chemical shifts (δ) were reported. Mass spectrometry was performed on a ThermoFinnigan LCQ DECA XP quadrupole ion trap mass spectrometer utilizing negative-ion APCI(-). Sample introduction was accomplished by flow injection with a flow solvent consisting of 1:1 acetonitrile/0.1 M NH_4OH at a flow rate of 0.3 mL/min. High-resolution exact mass determinations were carried out on an Agilent LC/MSDTOF instrument using negative-ion electrospray [ESI(-)] using internal mass references. Helium is used as the collision gas for acquisition of LCQ DECA data. Sample introduction was accomplished by flow injection with a flow solvent consisting of 1:1 acetonitrile/0.1% HCOOH at a flow rate of 0.3 mL/min. Thin-layer chromatography (TLC) was performed on precoated Whatman MK6F silica gel 60-Å plates (layer thickness: 250 μm) and visualized with UV light, $KMnO_4$ reagent [$KMnO_4$ (1.0 g) and NaOH (8.0 g) in water (200 mL)], and phosphomolybdic acid reagent (20 wt% solution in ethanol). Column chromatography was performed on silica gel, Merck grade 60 (230–400 mesh). All reagents were purchased from Aldrich Chemical Co. (Milwaukee, Wisc.) and used without purification, except where noted. All of the solvents employed were of HPLC grade purchased from EM Science (Gibbstown, N.J.) and used as received. Analytical reverse-phase (RP) HPLC was performed using an Agilent Zorbax Eclipse XDB-C18 8 × 100-mm, 5-μm column (solvents ratio v/v reported) unless otherwise stated.

General Procedure for the Preparation of Arylglyoxylic Acids (2a–e)

In a dry, single-neck, 25-mL, round-bottom flask equipped with a stir bar and flushed with nitrogen, the substituted aryl-methylketone (**1a–e**, 1.0 mmol) and selenium dioxide (SeO_2, 0.167 g, 1.5 mmol, 1.5 equiv.) were added followed by anhydrous pyridine (10 mL). The reaction mixture was heated in an oil bath to 110 °C for 1 h, and then the bath temperature was reduced to 90 °C. The mixture was stirred at this temperature (90 °C) for an additional 4 h, and progress of the reaction was monitored by TLC. After completion of the reaction, as determined by TLC, the solution containing precipitated selenium was filtered using a Buckner funnel, and the residue was washed with ethyl acetate (50 mL). The combined filtrate was treated with 1 N HCl (20 mL), the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3×50 mL). The organic layers were combined and treated with 1N NaOH (50 mL), and the aqueous layer was separated. The organic layer was extracted with water (25 mL) and the combined aqueous layers were acidified using 1N HCl to about pH 1.5. The mixture was extracted with ethyl acetate (3×50 mL), and the combined organic layers were dried (anhydrous Na_2SO_4) and concentrated on a rotary evaporator (Bath temperature: 40–45 °C). The crude arylglyoxylic acid products **2a–e** were purified by silica-gel column chromatography using ethyl acetate/hexane (ratio: 9:1) as solvent system for elution.

Data

2-(4-Chlorophenyl)-2-oxoacetic Acid (**2a**)[13]

Yield: 0.162 g in 89%. Analytical HPLC: gradient solvent system, 0.1% aqueous phosphoric acid–MeCN 80:20 to 10:90 in 7 min and then hold for 3 min, 1.5 mL/min at 230 nm, R_t: 3.84 min, 94.5%; ^{1}H NMR ($CDCl_3$): δ 8.30 (d, 2H, $J = 8.7$ Hz), 7.54 (d, 2H, $J = 8.6$ Hz), 6.60 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 182.9, 161.5, 142.1, 132.2, 131.3, 129.1; HRMS: calcd. m/z for $C_8H_5ClO_3$, 182.9854 $(M–H)^-$; observed m/z, 182.9854.

2-(4-Nitrophenyl)-2-oxoacetic Acid (**2b**)[14]

Yield: 0.172 g in 88%. Analytical HPLC: gradient solvent system, 0.1% aqueous phosphoric acid–MeCN 80:20 to 10:90 in 7 min and hold for 3 min, 1.5 mL/min at 230 nm, R_t: 2.10 min, 98.5%; ^{1}H NMR ($CDCl_3$) δ 8.55 (d, 2H, $J = 9.1$ Hz), 8.40 (d, 2H, $J = 9.1$ Hz), 5.36 (br s, 1H); ^{13}C

NMR ($CDCl_3$): δ 182.5, 159.6, 135.8, 132.1, 123.7; ESI-MS (m/z): 196.1 $(M+H)^+$, HRMS: calcd. m/z for $C_8H_5NO_5$, 194.0095 $(M–H)^-$; observed m/z, 194.0091.

2-(2,4-Dimethoxyphenyl)-2-oxoacetic Acid (**2c**)[15]

Yield: 0.173 g in 82%. Analytical HPLC: gradient solvent system, 0.1% aqueous phosphoric acid–MeCN 80:20 to 10:90 in 7 min and hold for 3 min, 1.5 mL/min at 230 nm, R_t: 3.00 min, 99.6%; ^1H NMR ($CDCl_3$): δ 8.01 (d, 1H, $J=8.8$ Hz), 6.65 (d, 1H, $J=8.7$ Hz), 6.50 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 183.0, 167.9, 166.6, 162.3, 133.1, 115.1, 106.7, 98.2, 56.1, 55.9; HRMS: calcd. m/z for $C_{10}H_{10}O_5$, 209.0455 $(M–H)^-$, observed m/z, 209.0453.

2-Oxo-2-(4-phenoxyphenyl)acetic Acid (**2d**)[16]

Yield: 0.186 g in 77%. Analytical HPLC: gradient solvent system, 0.1% aqueous phosphoric acid–MeCN 80:20 to 10:90 in 7 min and hold for 3 min, 1.5 mL/min at 230 nm, R_t: 4.93 min, 93.5%; ^1H NMR ($CDCl_3$): δ 8.36 (d, 2H, $J=9.1$ Hz), 7.48–7.44 (m, 2H), 7.32–7.26 (m, 1H), 7.16–8.12 (m, 2H), 7.06 (d, 2H, $J=9.1$ Hz); ^{13}C NMR ($CDCl_3$): δ 182.1, 163.9, 162.1, 154.9, 133.6, 129.9, 125.8, 125.0, 120.4, 116.9; HRMS: calcd. m/z for $C_{14}H_{10}O_4$, 241.0506 $(M–H)^-$; observed m/z, 241.0509.

2-(4-(4-Methoxyphenoxy)phenyl)-2-oxoacetic Acid (**2e**)

Yield: 0.269 g in 99%. Analytical HPLC: gradient solvent system, 0.1% aqueous phosphoric acid–MeCN 80:20 to 10:90 in 7 min and hold for 3 min, 1.5 mL/min at 230 nm, R_t: 4.97 min, 93.8%; ^1H NMR ($CDCl_3$): δ 8.40 (d, 2H, $J=8.9$ Hz), 7.07 (d, 2H, $J=9.0$ Hz), 7.01 (d, 2H, $J=8.8$ Hz), 6.98 (d, 2H, $J=9.1$ Hz), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 181.7, 164.8, 161.0, 156.6, 147.3, 133.9, 125.4, 121.6, 116.3, 114.9, 55.8; HRMS: calcd. m/z for $C_{15}H_{12}O_5$, 271.0612 $(M–H)^-$, observed m/z, 271.0611.

2-(4-Hydroxyphenyl)-2-oxoacetic Acid (2f)

In a dry, two-neck 1.0-L, round-bottom flask, equipped with a stir bar, anhydrous aluminum chloride (156.0 g, 1.17 mol, 2.0 equiv.) was suspended in nitromethane (300 mL) and cooled with an ice–salt bath

to −5 °C. Separately, in a 250-mL, round-bottom flask, phenol (**3**, 54.1 g, 0.574 mol, 1.0 equiv.) and ethyl chlorooxoacetate (87.0 g, 0.637 mol, 1.1 equiv.) was dissolved in nitromethane (75 mL), and the mixture was added slowly to aluminum chloride–nitromethane while maintaining the internal temperature colder than 0 °C temperature. After the addition was complete, the mixture was warmed to 40 °C and stirred for an additional 2 h. The reaction mixture was quenched into ice water (0.5 Kg) and acidified using 3 N HCl and diluted with isopropyl acetate (450 mL). The organic layer was separated and washed with 1.0 M aqueous K_2CO_3 solution (3 × 100 mL), dried ($MgSO_4$), and concentrated on a rotary evaporator (bath temperature 40–45 °C). The crude product was purified by silica-gel column chromatography (20% IPAc in heptane) to afford 10.1 g of ethyl 2-(4-hydroxyphenyl)-2-oxoacetate (**4**) in 9.1% yield.

In a 25-mL, single, neck, round-bottom flask equipped with a stir bar, ethyl 2-(4-hydroxyphenyl)-2-oxoacetate (**4**, 0.291 g, 1.5 mmol, 1.0 equiv.) was dissolved in THF (12 mL) and cooled to 5–10 °C using an ice-water bath. Separately, lithium hydroxide (0.72 g, 3.0 mmol, 2.0 equiv.) was dissolved in water (4 mL) and added to the reaction mixture. Progress of the reaction was monitored by HPLC, and after 1 h, an additional amount of lithium hydroxide (0.72 g, 3.0 mmol, 2.0 equiv.) was added. The mixture was stirred for 30 min and acidified using acetic acid (2.0 mL), and the mixture was washed with isopropyl acetate (40 mL). The aqueous layer was diluted with 10% aqueous NaCl solution (20 mL) and kept at room temperature for 24 h. The solid was separated by filtration, and the wet cake was dried in a vacuum oven at 50 °C for 21 h to afford 0.235 g of 2-(4-hydroxyphenyl)-2-oxoacetic acid (**2f**) in 94% yield.[9] Analytical HPLC (Synergi Max-RP column): 20:80 ratio of MeCN–organic-phosphate buffer blend (0.35% aqueous K_2HPO_4 solution and MeCN in 45:55 ratio), 0.5 mL/min at 230 nm, R_t: 4.39 min, 96.6%; ^{1}H NMR [D_2O and 3-(trimethylsilyl)propionic acid-d_4 sodium salt]: δ 7.86 (6, 2 H, $J = 8.9$ Hz), 6.99 (d, 2 H, $J = 9.1$ Hz); ^{13}C NMR [D_2 O and 3-(trimethylsilyl)propionic acid-d_4 sodium salt]: δ 197.4, 175.4, 164.3, 134.8, 126.3, 118.3; HRMS: calcd. m/z for $C_8H_6O_4$, 165.0193 $(M - H)^-$; observed m/z, 165.0195.

2-(4-Hydroxy-3,5-diiodophenyl)-2-oxoacetic Acid (2g)

To a 500-mL, single-neck, round-bottom flask equipped with a stir bar, ethyl 2-(4-hydroxyphenyl)-2-oxoacetate (**4**, 5.0 g, 25.76 mmol, 1.0 equiv.) and acetic acid (130 mL) were added. To this mixture, iodine monochloride (16.0 g, 4.94 mL, 98.5 mmol, 3.82 equiv.) was added at room temperature and then heated to 57 °C. Water (150 mL) was added in three

portions while maintaining the solution temperature between 57 and 60 °C and then stirred for 30 min. The mixture was cooled to room temperature, quenched with sodium sulfite (12 g), and then diluted with isopropyl acetate (400 mL). The organic layer was separated and washed with 4 N NaOH solution (20 mL) followed by 10% aqueous K_2CO_3 solution (3×25 mL) and dried ($MgSO_4$). Concentration of the solution on a rotary evaporator (bath temperature 40–45 °C) afforded 11.41 g of ethyl 2-(4-hydroxy-3,5-diiodophenyl)-2-oxoacetate (**5**) in >98% yield.

In a 25-mL, single-neck, round-bottom flask equipped with stir bar, ethyl 2-(4-hydroxy-3,5-diiodophenyl)-2-oxoacetate (**5**, 0.3 g, 0.673 mmol, 1.0 equiv.) was dissolved in THF (8 mL) and cooled to 5 °C. To this mixture, 25 drops of aqueous potassium hydroxide solution (0.5 g of KOH dissolved in 3.0 mL of water) was added over a 1 h period and stirred for an additional 1 h. The reaction mixture was diluted with water and lyophilized. The crude lyophilized powder was suspended in *tert*-butylmethyl ether (40 mL), and acetic acid (11 drops) was added at room temperature and stirred overnight for 18 h. The solid was separated by filtration, washed with *tert*-butylmethyl ether (20 mL), and dried in a vacuum oven at 22 °C for 24 h to afford 0.210 g of 2-(4-hydroxy-3,5-diiodophenyl)-2-oxoacetic acid (**2g**) in 74% yield.[10] Analytical HPLC (Synergi Max-RP column): 20:80 ratio of MeCN–organic-phosphate buffer blend (0.35% aqueous K_2HPO_4 solution and MeCN in 45:55 ratio), 0.5 mL/min at 230 nm, R_t: 5.23 min, 88.6%; ^{1}H NMR (D_2O and 3-(trimethylsilyl) propionic acid-d_4 sodium salt): δ 8.27 (s, 2 H); ^{13}C NMR (D_2O and 3-(trimethylsilyl)propionic acid-d_4 sodium salt): δ 194.0, 175.4, 172.9, 143.9, 122.8, 91.2; HRMS: calcd. m/z for $C_8H_4I_2O_4$, 416.8126 $(M-H)^-$; observed m/z, 416.8119.

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