Synlett R. M. Al-Zoubi et al. Letter

Mild, Efficient, and Highly Regioselective Synthesis of 2,6-Diiodobenzaldehyde Derivatives

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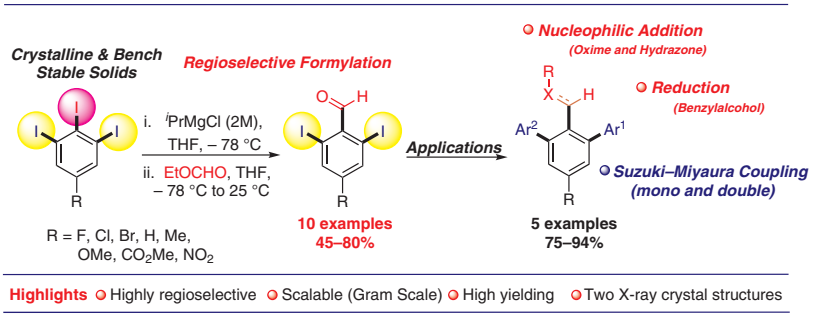

Received: 04.01.2020
Accepted after revision: 02.03.2020
Published online: 20.03.2020
DOI: 10.1055/s-0040-1708004; Art ID: st-2020-b0004-l

Abstract An efficient and versatile synthesis of 2,6-diiodobenzaldehydes via highly regioselective metal–iodine exchange (MIE) of 5-substituted 1,2,3-triiodobenzenes is reported. The nature of substituents (*R*) on the phenyl has a large influence on the reactivity of reaction but not on the regioselectivity. The regioselectivity of the MIE can be controlled by the use of ethyl formate as a formylating agent providing only the internal benzaldehyde derivatives in excellent site-selectivity. The best reactivity and the highest isolated yields were furnished with products bearing electron-rich substituents. Several chemical transformations of the target compound as a valuable precursor in synthesis were also demonstrated providing the desired derivatives in good isolated yields. This report discloses a protocol for the synthesis of 2,6-diiodobenzaldehyde derivatives that is scalable, general in scope, and indeed difficult to be made by other means.

Keywords 2,6-diiodobenzaldehydes, Grignard reactions, regioselectivity, metal–iodine exchange, substituent effect, Suzuki–Miyaura cross-coupling, nucleophilic addition

Halogenated benzaldehydes and mainly iodinated motifs are remarkable intermediates and largely utilized substrates in medicinal and pharmaceutical chemistry. Due to the unique chemical combination between two reactive functional groups, numerous applications are found in the literature. For instance, 2,6-diiodobenzaldehyde (**1**, Figure 1) is a doubly *ortho*-iodinated benzaldehyde which is used as a precursor to form (*E*)-2-(2,6-diiodobenzylidene)hydrazinecarboximidamide. Compound **1** is a therapeutic compound reported for reducing endoplasmic reticulum stress and for producing analgesia in animals.[1] Additionally, 2,3,5-triiodobenzaldehyde **2** that contains one *ortho*-iodo group at C_2 on the aryl ring is reported as useful emulsion component for improved stability and coherence. Compound **2** is useful for the treatment of tumors by embolotherapy.[2] Furthermore, 2,3,5,6-tetraiodobenzaldehyde **3** is a polyiodinated derivative that is reported as imageable radiopaque hydrogel in drug delivery.[3] Moreover, 3,5-difluoro-4′-[(4-methyl-1,4-diazocan-1-yl)methyl]-(1,1′-biphenyl)-4-carbaldehyde (**4**, Figure 1) is a doubly *ortho*-fluorinated benzaldehyde derivative which is reported to be an inhibitor of choline kinase, an enzyme that is concerned with phospholipid synthesis and key roles with the regulation of oncogenic transformation, cell proliferation, and human carcinogenesis.[4] Lastly, 3,5-dichloro-3′-fluoro-4′-hydroxy-(1,1′-biphenyl)-4-carbaldehyde (**5**, Figure 1) is a doubly *ortho*-chlorinated benzaldehyde derivative that is found to have potency and selectivity for estrogen-receptor β-ligands.[5] The status quo of these compounds and other halogenated benzaldehyde derivatives[6] as well as the excessive market price[7] for some iodinated benzaldehydes have initiated great attention and enthusiasm for developing synthetic approaches to these small molecules for their novel applications in industry and medicine. Although there are a number of published protocols for the synthesis of dihalogenated benzaldehydes,[8,9] a practical protocol to access 2,6-diiodobenzaldehyde derivatives has not been reported yet.

Herein, we report the first synthetic method for 2,6-diiodobenzaldehyde derivatives via highly regioselective metalation of 5-substituted 1,2,3-triiodonbenzene that is of wide scope, is readily scalable, and provides good isolated yields. A number of 5-substituted 1,2,3-triiodonbenzenes bearing electron-rich, electron-poor, and neutral groups were subjected to the optimized conditions affording the desired diiodinated benzaldehyde products with excellent site-selectivity and indeed are difficult to be made by other means.

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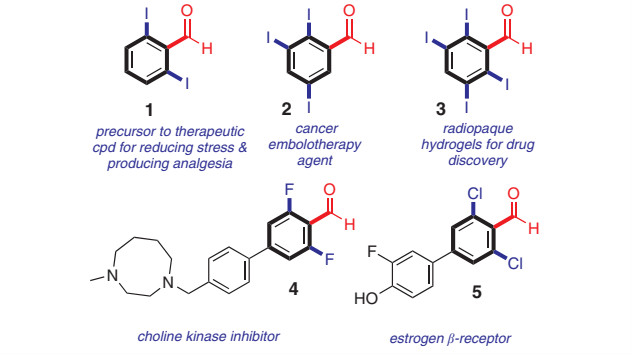
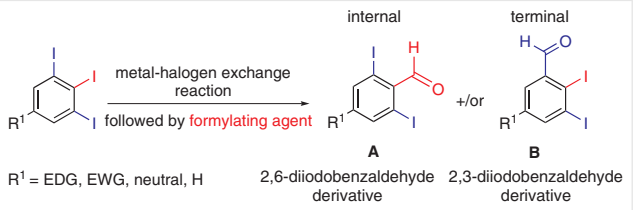


Figure 1 Some biologically active halogenated benzaldehyde compounds in medicine

Owing to the known biological and chemical activities of dihalogenated benzaldehyde derivatives in literature, we felt excited to examine metal–iodine exchange on 5-substituted 1,2,3-triiodobenzenes with the goal of making 2,6-diiodinated benzaldehyde derivatives.

A handful of examples on regioselective functionalization of 1,2-diiodo- and 1,2,3-triiodoarenes are reported in the literature. Togni and co-workers reported the synthesis of *o*-iodobenzyl alcohol derivatives with isopropylmagnesium chloride by metal–iodine exchange reaction of 1,2-diiodobenzene via addition of *o*-iodophenyl Grignard reagent to aldehydes and ketones.[10] We also reported three regioselective metal–iodine exchange reactions of 1,2,3-triiodobenzene derivatives with isopropylmagnesium chloride for the synthesis of diiodobenzyl alcohols, diiodophenylboronic acids, and iodinated benzoboroxoles.[11] The desired products were isolated in good yields where the regioselectivity and reactivity of the reactions *per se* are controlled by both the nature of the substituent at C-5 on the aryl group and the type of electrophile favoring the displacement to occur either at the terminal or internal position. Other works on regioselective metal–bromine/iodine exchange reaction for the synthesis of benzoic acid,[12a–c] benzyl alcohol,[12d] arylboronic acids,[12e] *m*-terphenyls,[12f] arylthiols,[12g] and arylamines[12h] are also reported.

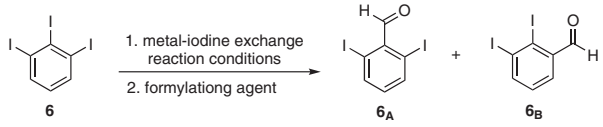
The metal–iodine exchange/functionalization sequence on 5-substituted 1,2,3-triiodobenzenes with two regiochemically different C–I positions provide no more than two possible diiodinated benzaldehydes, the internal and the terminal products (Scheme 1). Therefore, the use of only 1.0 equivalent of an adequate base is theoretically sufficient to exchange one of the iodo groups, making the arylmetal intermediate that is quenched with the formylating reagent to yield the desired diiodinated benzaldehyde product.



Scheme 1 Possible diiodinated benzaldehyde regioisomers from metal–iodine exchange (MIE) of 5-substituted 1,2,3-triiodobenzene

Therefore, to examine this hypothesis, 1,2,3-triiodobenzene (**6**) was used as a model substrate as shown in Table 1. The reaction of 1,2,3-triiodobenzene (**6**) and isopropylmagnesium chloride (2 M) in THF with different formylating reagents were examined. The use of triethyl orthoformate and ethyl formate reagents provided the internal regioisomer as a sole product in 23% and 52%, respectively (entries 1 and 2). Piperidine-1-carbaldehyde was found to be less effective providing a mixture of products in 24% (entry 3). Another formylating agent, DMF, was previously examined and found to have some reproducibility issues. The use of other bases like *t*-BuLi, *s*-BuLi, or *n*-BuLi at –78 °C in THF

Table 1 Conditions for the Regioselective Metal–Iodine Exchange Reaction of 1,2,3-Triiodobenzene (**6**) Followed by Formylating Agent[a]

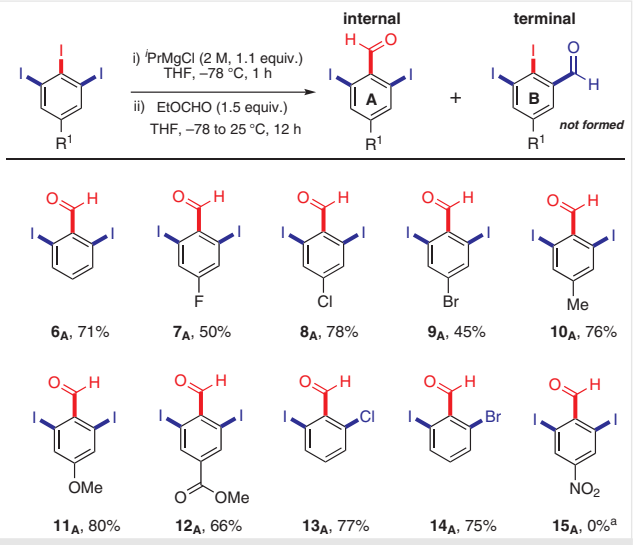


Entry	Conditions (equiv.)	Formylating agent (equiv.)	Yield of **6**$_A$ (%)[b]	Yield of **6**$_B$ (%)[b]
1	*i*-PrMgCl (1.0), THF	triethyl orthoformate (1.0)	23	0
2	*i*-PrMgCl (1.0), THF	ethyl formate (1.0)	52	0
3	*i*-PrMgCl (1.0), THF	piperidine-1-carbaldehyde (1.0)	6	18
4	*t*-BuLi (2.0), THF	ethyl formate (1.0)	0	0[c]
5	*s*-BuLi (1.0), THF	ethyl formate (1.0)	0	0[c]
6	*n*-BuLi (1.0), THF	ethyl formate (1.0)	0	9[d]
7	*i*-PrMgCl (1.0), diethyl ether	ethyl formate (1.0)	45	0
8	*i*-PrMgCl (1.0), toluene	ethyl formate (1.0)	38	0
9	*i*-PrMgCl (1.1), THF	ethyl formate (1.2)	63	0
10	*i*-PrMgCl (1.2), THF	ethyl formate (1.2)	56	0
11	*i*-PrMgCl (1.1), THF	ethyl formate (1.5)	71	0
12[e]	*i*-PrMgCl (1.1), THF	ethyl formate (1.2)	65	0

[a] Conditions: All reactions were carried out using 1.0 mmol (1.0 equiv., 0.1 M) of 1,2,3-triiodobenzene (**6**) in 10 mL solvent at –78 °C.
[b] Isolated yield.
[c] Unknown mixture of products.
[d] Impure isolated product.
[e] 1.0 gram scale (2.19 mmol).

provided nonclean reactions (entries 4–6). Changing the reaction conditions by using other solvents was found to be unsuccessful providing lower isolated yields (entries 7 and 8). Raising the amount of isopropylmagnesium chloride to 1.1 equivalents provided a higher isolated yield of the desired aldehyde **6**$_A$ (entry 9). The highest isolated yield for this transformation was achieved by using 1.1 equivalents of isopropylmagnesium chloride and 1.5 equivalents of ethyl formate at –78 °C in THF (entry 11). The reaction also worked well on gram scale (entry 12).

The superb site-selectivity and promising isolated yield (entry 11) encouraged us to examine our previously synthesized 5-substituted 1,2,3-triiodobenzenes under the optimized conditions aiming to expand the scope of 2,6-diiodinated benzaldehydes for their application in industry and medicine. Consequently, a variety of 5-substituted 1,2,3-triiodobenzenes were subjected to the optimized reaction conditions and formed the desired aldehyde products with superior regioselectivity after flash chromatography (Scheme 2).



Scheme 2 Internal diiodinated benzylaldehyde derivatives via regioselective metal–iodine exchange of 5-substituted 1,2,3-triiodobenzenes and ethyl formate. Yields are given for isolated compounds (reaction scale: 1.00 mmol). [a] Unidentified mixture of products.

We found that the nature of substituents on the 1,2,3-triiodobenzene (R^1, Scheme 2) has a large influence on the reactivity but not on the regioselectivity. The formation of the terminal regioisomer (**B**, Scheme 2) was not observed with ethyl formate in all examples. The scope is summarized in Scheme 2. It is found that bearing neutral and electron-rich groups afforded the desired products in good to high isolated yields (Scheme 2: **6**$_A$,**8**$_A$,**10**$_A$,**11**$_A$,**13**$_A$, and **14**$_A$). In contrast, electron-withdrawing groups gave low to moderate isolated yields (**7**$_A$, **9**$_A$, and **12**$_A$, Scheme 2). Furthermore, products bearing electron-rich groups had the best reactivity and gave the highest isolated yields (**11**$_A$, Scheme 2). No exchange reaction with bromo or chloro groups was observed (**8**$_A$, **9**$_A$, **13**$_A$, and **14**$_A$, Scheme 2). Unfortunately, a derivative bearing a nitro group at the C-5 was found to be unsuccessful providing a mixture of unidentified products (**15**$_A$, Scheme 2).

The geometry of 2,6-diiodobenzaldehyde derivatives is confirmed by X-ray crystallography of product, 2,6-diiodo-4-methylbenzaldehyde (**10**$_A$, Figure 2). It shows clearly the position of both the iodo and the formyl groups.[13]

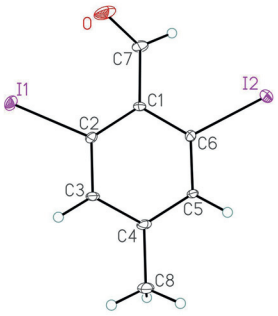
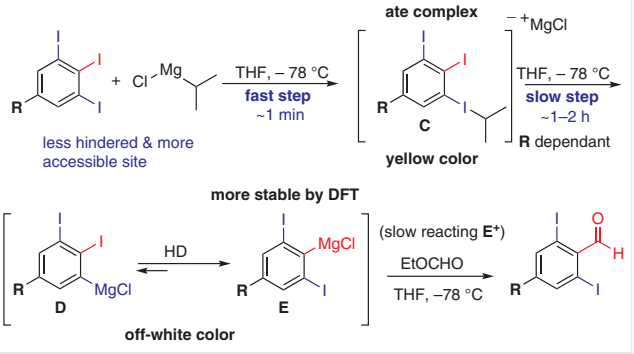


Figure 2 ORTEP view of 2,6-diiodo-4-methylbenzaldehyde **10**$_A$. Thermal Gaussian ellipsoids at 30% probability level.

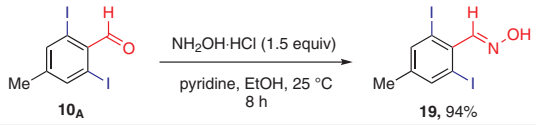
A plausible mechanism for the regioselective formation of 2,6-diiodobenzaldehydes is proposed in Scheme 3. Several approaches for metal–iodine exchange of diiodo intermediates using isopropylmagnesium chloride/bromide have been previously studied and reported,[14] The treatment of 5-substituted 1,2,3-triiodobenezne with isopropylmagnesium chloride at –78 °C in THF provided immediately the yellow-colored ate complex **C** with the less hindered and more accessible iodo group. It became an intense yellow color within ca. 1 minute and faded within 1–2 hours based on the nature of the R substituent. It is believed that the *ortho*-iodine atom conveyed much thermodynamic stability of the ate complex by stabilizing the negative charge on the *ortho* carbon. Electron-withdrawing groups (*R*) were found to further increase the thermodynamic stability by preserving the intense yellow color for longer time (ca. 2 h). The addition of ethyl formate reagent, which is known as a slow-reacting electrophile,[15] decolorized the mixture by transforming the ate complex **C** to the new Grignard **D**. Halogen-dance (HD) rearrangement provided the internal Grignard **E**, which is the more stable regioisomer (calculated by using DFT), that quenched with ethyl formate reagent to form the desired benzaldehyde derivative.



Scheme 3 Plausible mechanism for the formation of 2,6-diiodobenzaldehydes

We then turn our thoughts to examine the reactivity of the other two iodo groups under different reaction conditions aiming to expand their applications in synthesis. Therefore, mono and double Suzuki–Miyaura cross-coupling reactions of 2,6-diiodo-4-methylbenzaldehyde (**10$_A$**) with phenylboronic acid were performed and provided the coupling products **16** and **17** in good isolated yields (Scheme 4).

The process to access functionalized and active molecules from readily available starting materials is essential in synthesis and biology. A quick screening in the literature revealed that 2,6-dichloroarylcarbaldehyde oximes are biological active derivatives in medicine.[5b,c] We decided to examine them if we could use this chemistry and quickly access oxime and hydrazone derivatives from our 2,6-diiodinated benzaldehydes (vide supra). Gladly, the use of 4-chloro-2,6-diiodobenzaldehye (**8$_A$**) with hydrazine carboxamide formed the desired condensation product as a mixture of *E*/*Z* isomers in a 10:1 ratio and in 91% isolated yield (Scheme 5). Whereas the reaction of 2,6-diiodo-4-methylbenzaldehyde (**10$_A$**) with hydroxylamine gave the oxime product **19** in excellent isolated yield (Scheme 6). The structure of 1-(2,6-diiodo-4-methylphenyl)-*N*-hydroxy methanimine (**19**) is confirmed by X-ray crystallography as shown in Figure 3.[14]



Scheme 6 Synthesis of 1-(2,6-diiodo-4-methylphenyl)-*N*-hydroxy methanimine (**19**) from 2,6-diiodo-4-methylbenzaldehyde (**10$_A$**)

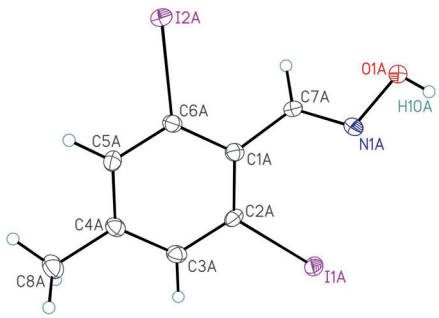
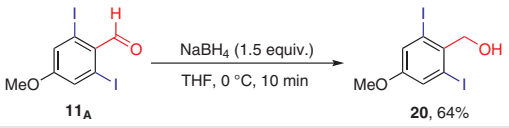
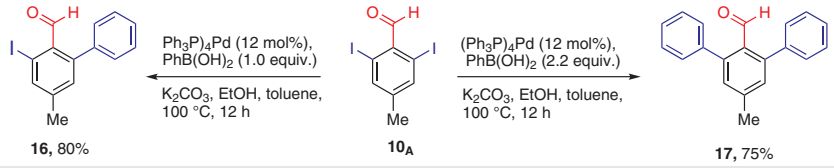


Figure 3 ORTEP view of methanimine **19**; thermal Gaussian ellipsoids at 30% probability level

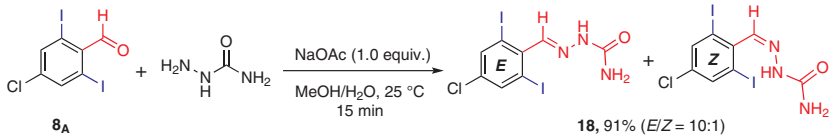
Alternatively, a reduction reaction with $NaBH_4$ was also examined with 2,6-diiodo-4-methoxybenzaldehyde (**11$_A$**). Having a symmetrical molecule with one regiochemical carbon occupied with iodine, it can be easily found if nucleophilic reduction using sodium borohydride can affect iodine by displacement reaction. Supremely, the reaction was achieved successfully with 1.5 equivalents of $NaBH_4$ in THF providing the desired benzyl alcohol **20** in 64% isolated (Scheme 7)



Scheme 7 Synthesis of (2,6-diiodo-4-methoxyphenyl)methanol (**20**) from 2,6-diiodo-4-methoxybenzaldehyde (**11$_A$**)



Scheme 4 Mono and double Suzuki–Miyaura cross-coupling reactions of 2,6-diiodo-4-methylbenzaldehyde (**10$_A$**) with phenylboronic acid



Scheme 5 Synthesis of (*E*)- and (*Z*)-2-(4-chloro-2,6-diiodobenzylidene) hydrazonecarboxamide (**18**) from 4-chloro-2,6-diiodobenzaldehyde (**8$_A$**) with hydrazinecarboxamide

In summary, we developed the first synthesis of 2,6-diiodobenzaldehyde derivatives via highly regioselective metal–iodine exchange strategy from 5-substituted 1,2,3-triiodobenzenes.[16] The regioselectivity is remarkably controlled by using ethyl formate as a formylating agent providing the internal regioisomer as a sole product in good isolated yields. The best yields were furnished with products bearing electron-rich groups on the aryl ring. The geometries of the products were further confirmed by X-ray crystallographic analysis. The target products were employed as versatile intermediates in synthesis and were also performed in different chemical transformations such as Suzuki–Miyaura cross-couplings, nucleophilic addition and reduction reactions. Having other iodo groups on these products, further elaboration could be easily explored.

Funding Information

This work was generously funded by Jordan University of Science and Technology (JUST) - Deanship of Research - Jordan (Grant No. 393/2016).

Acknowledgment

We thank the Department of Chemistry at University of Alberta for X-ray crystallographic analysis.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1708004.

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(16) **General Procedure for the MIE Reaction between 5-Substituted 1,2,3-Triiodobenzenes and Ethyl Formate**

A flame-dried round-bottom flask was charged with 5-substituted 1,2,3-triiodobenzene (1.02 mmol, 1.0 equiv.) and 10 mL of freshly dried THF. The mixture was cooled down under argon gas to –78 °C. 2 M solution of isopropylmagnesium chloride (1.15 mmol, 1.1 equiv.) was added dropewise over 1 h. The solution was stirred for 30 min at the same temperature. Ethyl formate (1.53 mmol, 1.50 equiv.) was added and the mixture left to warm up overnight. Saturated NH_4Cl (20 mL) was added, and the reaction mixture was extracted with diethyl ether (2 × 50 mL). Organic layers were combined, washed with brine, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (5% EtOAc/hexane) to yield the pure desired product.

2,6-Diiodobenzaldehyde (6$_A$)

Yellow solid (261 mg, 71% yield). Mp 58–60 °C. IR (cast film): 3026, 3008, 2913, 2887, 1715, 1613, 1598, 983, 864 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.78 (s, 1 H), 8.01 (d, 2 H, *J* = 7.8 Hz), 6.86 (t, 1 H, *J* = 7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.7, 141.6, 135.6, 134.6, 97.5. HRMS (ESI): *m/z* calcd for $C_7H_5I_2O$ [M + H]$^+$: 358.8430; found: 358.8425.

4-Fluoro-2,6-diiodobenzaldehyde (7$_A$)

Yellow solid (192 mg, 50% yield). Mp 91–93 °C. IR (cast film): 3028, 3004, 2979, 2846, 1719, 1642, 1599, 976, 817, 688, 524 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73 (s, 1 H), 7.80 (d, 2 H, *J* = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.5, 164.5, 161.8, 131.3 131.29, 129.2 129.0, 97.7, 97.6. HRMS (ESI): *m/z* calcd for $C_7H_4FI_2O$ [M + H]$^+$: 376.8336; found: 376.8331.

4-Chloro-2,6-diiodobenzaldehyde (8$_A$)

Yellow solid (312 mg, 78% yield). Mp 65–67 °C. IR (cast film): 3012, 3004, 2941, 2876, 1709, 1621, 1587, 1008, 867, 726, 553 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.72 (s, 1 H), 8.05 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.7, 141.1, 139.7, 133.5, 97.4. HRMS (ESI): *m/z* calcd for $C_7H_4ClI_2O$ [M + H]$^+$: 392.8040; found: 392.8033.

4-Bromo-2,6-diiodobenzaldehyde (9$_A$)

Yellow solid (201 mg, 45% yield). Mp 101–103 °C. IR (cast film): 3024, 3004, 2943, 2869, 1706, 1607, 1587, 943, 634 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (s, 1 H), 8.19 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.8, 143.8, 134.0, 128.3, 97.6. HRMS (ESI): *m/z* calcd for $C_7H_4BrI_2O$ [M + H]$^+$: 436.7535; found: 436.7528.

2,6-Diiodo-4-methylbenzaldehyde (10$_A$)

Yellow solid (288 mg, 76% yield). Mp 130–132 °C. IR (cast film): 3031, 3010, 3004, 2953, 2896, 1713, 1621, 1589, 981, 736 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (s, 1 H), 7.86 (s, 2 H), 2.31 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5, 146.1, 142.5, 132.2, 98.0, 20.5. HRMS (ESI): *m/z* calcd for $C_8H_7I_2O$ [M + H]$^+$: 372.8586; found: 372.8584.

2,6-Diiodo-4-methoxybenzaldehyde (11$_A$)

Yellow solid (317 mg, 80% yield). Mp 83–85 °C. IR (cast film): 3027, 3011, 2945, 2879, 1713, 1621, 1587, 1207, 1186, 873, 736 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$): δ = 9.71 (s, 1 H), 7.59 (s, 2 H), 3.86 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.8, 162.6, 127.8, 126.7, 99.4, 56.2. HRMS (ESI): *m/z* calcd for $C_8H_7I_2O_2$ [M + H]$^+$: 388.8535; found: 388.8529.

Methyl 4-formyl-3,5-diiodobenzoate (12$_A$)

Yellow solid (280 mg, 66% yield). Mp 76–78 °C. IR (cast film): 3031, 3015, 2983, 2907, 1741, 1716, 1627, 1583, 1207, 1131, 867, 627 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.78 (s, 1 H), 8.61 (s, 2 H), 3.96 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.2, 163.5, 142.1, 139.4, 134.9, 96.1, 53.2. HRMS (ESI): *m/z* calcd for $C_9H_7I_2O_3$ [M + H]$^+$: 416.8485; found: 416.8477.

2-Chloro-6-iodobenzaldehyde (13$_A$)

Yellow solid (209 mg, 77% yield). Mp 80–82 °C. IR (cast film): 3021, 3002, 2937, 2889, 1719, 1641, 1599, 867, 764, 537 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.19 (s, 1 H), 7.94 (d, 1 H, *J* = 8.0 Hz), 7.48 (d, 1 H, *J* = 8.0 Hz), 7.13 (t, 1 H, *J* = 7.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.7, 140.1, 136.9, 134.1, 133.1, 131.2, 96.4. HRMS (ESI): *m/z* for C_7H_5ClIO [M + H]$^+$: 266.9074; found: 266.9067.

2-Bromo-6-iodobenzaldehyde (14$_A$)

Yellow solid (238 mg, 75% yield). Mp 87–89 °C. IR (cast film): 3019, 3004, 2983, 2876, 1714, 1607, 1596, 861, 584 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.05 (s, 1 H), 7.98 (d, 1 H, *J* = 8.0 Hz), 7.68 (d, 1 H, *J* = 8.0 Hz), 7.03 (t, 1 H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.1, 140.9, 134.6, 134.4, 134.4, 125.4, 96.5. HRMS (ESI): *m/z* for C_7H_5BrIO [M + H]$^+$: 310.8568; found: 310.8564.