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N-Iodosuccinimide (NIS) in Direct Aromatic Iodination

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*Supporting Information

ABSTRACT: NIS in pure TFA is a time-efficient and general method for the iodination of a wide range of mono- and disubstituted benzenes at room temperature as demonstrated in this paper. The starting materials were generally converted into mono-iodinated products in less than 16 hours at room temperature, without by-products. A few deactivated substrates needed addition of sulphuric acid to increase reaction rate. Another exception was methoxybenzenes that preferentially were iodinated by NIS in acetonitrile with only catalytic amounts of TFA.

INTRODUCTION

Aromatic iodo compounds are important intermediates in several reactions that have found a wide application, such as the Ullman, Heck and Suzuki reactions. Efficient methods for regioselective iodination of aromatic compounds are therefore of high interest. Several methods performing direct iodination of aromatics have consequently been published, using different conditions and sources of iodine.[1,2] Iodine is a rather poor electrophile and has to be activated with an oxidant to perform well in aromatic iodination. Another option is to use an iodination agent where iodine has a more electrophilic character, such as N-iodoamides or N-iodoimides. These have been reported to be efficient iodination agents in combination with strong protic acids/acidic ionic liquids.[1,2] The iodination agent in the reaction is believed to be the electrophilic iodine complex of the acid, formed in situ, which is a more reactive electrophile compared to the N-iodoamide/imide.[2,3] The efficiency of NIS in electrophilic iodination is therefore closely related to the acid that is used as activator.

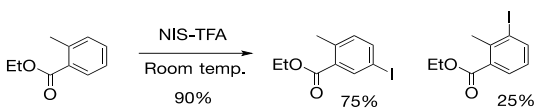
N-iodosuccinimide (NIS), in combination with different acidic catalysts, has been demonstrated to perform well in in the iodination of a variety of aromatic compounds.[3-7] Electron-rich (activated) aromatics can even be iodinated by NIS in pure acetonitrile, without adding an acidic catalyst.[8,9] Acidic conditions do, however, improve regioselectivity as well as reaction rate.[4,5,10] Catalytic amounts of *p*-toluenesulfonic acid, sulfuric acid or trifluoroacetic acid (TFA) have been used in iodination of activated aromatic compounds.[3-5] Methods for iodination of electron deficient, deactivated aromatics are less abundant, but interestingly enough, NIS has shown to work also in these reactions by choosing stronger and more concentrated acids as catalysts. A very reactive system was created by combining NIS and pure trifluoromethanesulfonic acid (triflic acid) that was demonstrated to iodinate strongly deactivated compounds, such as nitrobenzene.[6] The very aggressive triflic acid can be replaced by NIS/BF_3-H_2O[7] or concentrated sulfuric acid,[3] but reaction time has to be increased from 2 h to about 20 h. However, neither triflic acid, nor NIS/BF_3-H_2O or concentrated sulfuric acid are very benign/versatile solvents. Furthermore, solubilities of aromatic substrates are low in these systems and they are not compatible with all substrates because of side reactions due to the harsh reaction conditions.

We have concluded that NIS has a wide applicability in electrophilic iodination of benzenes, as exemplified above, but the reported reaction conditions vary so substantially that guidelines for each substitution pattern are needed. In this report the effect of substituents on the aromatic ring is evaluated and guidelines of new mild reaction conditions for iodination of mono- and disubstituted benzenes are presented. Furthermore, new observations regarding the reaction mechanism in direct aromatic iodination by NIS have been recorded.

RESULTS AND DISCUSSION

The evaluation of suitable reaction conditions for iodination by NIS was initiated because we wanted to iodinate ethyl *o*-toluate to produce a cheap and non-chiral substance related to ceralure B (ethyl 5-iodo-2-methylcyclohexane-1-carboxylate), which is a strong attractant to the Mediterranean fruitfly (*Ceratitis capitata*),[11] an insect pest. Several methods for mild and regioselective iodination were tried without success, including NIS in acetonitrile with catalytic amount of TFA.[5] Methods aiming at iodination of activated aromatics were apparently not potent enough, as the substrate (ethyl 2-methylcyclohexane-1-carboxylate or ethyl *o*-toluate) comprises a weakly activating methyl group in combination with an electron withdrawing (deactivating) carbonyl group. Eventually, pure TFA in combination with 1.1 molar eq. NIS was tried and found to perform well (Scheme 1). Iodination by NIS in pure TFA has, to our knowledge, not been reported before.

Scheme 1.



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NIS-TFA: Reaction time for the iodination of ethyl *o*-tolute (Figure 1 and entry 1, Table 1) was about 3 h in room temperature using the NIS-TFA method (*i.e.* 13% of starting material left according to GC-MS analysis). Only mono-iodinated products were formed and the isolated yield was 86% (83% *para*-, 17% *ortho*- according to GC-MS and NMR).

Lowering the TFA concentration by performing the reaction in acetonitrile + TFA (1:1) decreased the reaction rate substantially; only 50% ethyl *o*-toluate was iodinated in 16 h under these conditions (data not shown).

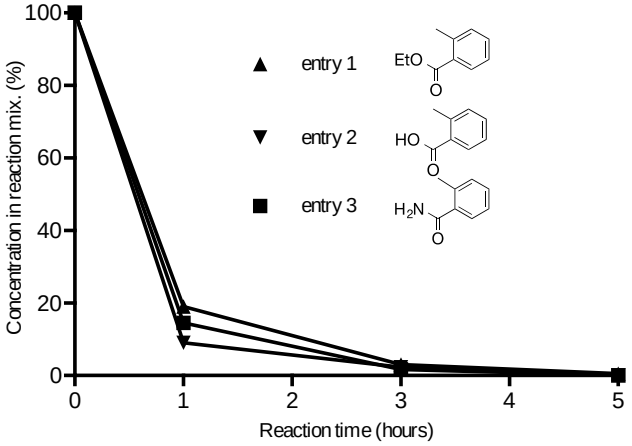

Figure 1. Reaction of benzoic acid derivatives using 1.0 mmol substrate and 1.1 mmol NIS dissolved in 3 mL TFA at room temperature. Conversion into iodinated products is shown as the decrease of substrate concentration in reaction mixtures after 1, 3 and 5 hours (determined by GC-MS).

Structurally related substrates such as *o*-toluic acid and *o*-toluamide (Figure 1 and entries 2-3, Table 1) reacted in close similarity to ethyl *o*-tolute. The reaction rates of alkylated benzaldehydes (entries 4, 5 and 6, Table 1) were however considerably slower than *o*-toluic acid and *o*-toluamide; after 3 h 20 - 30% of the aromatic aldehydes were still unreacted (Figure 2). The methyl ketone tested (entry 7, Table 1) showed similar reactivity as the aldehydes (Figure 2) although some iodination apparently occurred at the methyl group (in analogy with an earlier report on iodinations of acetophenones).[12] Even if the efficiency of these reactions were lower the isolated yields of the iodinated products (entries 4-7) were still acceptable (64% - 78%). Benzenes containing a carbonyl group in combination with an activating hydroxyl group reacted very similar to ethyl *o*-tolute, and were completed in 3 hours; see entries 19–21, Table 1.

Iodination of benzenes without any deactivating group were also studied. As expected, iodination of these substrates by NIS in pure TFA occurred almost instantly; see entries 11-14 and 18 (Table 1). Arenes, such as *o*-xylene and *o*-chlorotoluene (entries 8 and 9, Table 1), were also efficiently iodinated by the NIS-TFA method.

The only compounds that did not perform well with the NIS-TFA method were completely deactivated compounds such as *o*-nitrotoluene, benzoic acid derivatives and very activated componds such as dimethoxybenzenes. Alternative methods for these exceptional compounds are described below.

Table 1. Iodination of arenes

Entry	Substrate	Main product	Recommended procedure	Reaction time	Percent conversion[a]	Yield **	Ratio regioisomers	Diiodo byproduct
1			NIS-TFA	3h	87	86	83:17	None
2			NIS-TFA	3h	90	89	62:38	None
3			NIS-TFA	3h	100	99	88:12	None
4			NIS-TFA	16h	88	64	67:33	None
5			NIS-TFA	16h	92	70	None	None
6			NIS-TFA	16h	82	78	None	None
7			NIS-TFA	16h	83	76	None	None
8			NIS-TFA	1h	100	84	86:14	None
9			NIS-TFA	1h	>95	77	82:18	None
10			NIS-TFA + 0.3M H_2SO_4	7h	100	94	85:15	None
11			NIS-TFA	<1h	92	88	None	None
12			NIS-TFA	<1h	100	82	None	10%
13			NIS-TFA	1h	100	78	80:20	7%
14			NIS-TFA	1h	100	70	None	10%
15			NIS-TFA	3h	100	81	82:18	None
16			NIS-TFA + 0.3M H_2SO_4	1h	100	90	None	None
17			NIS-TFA + 0.1M H_2SO_4	16h	95	68	None	None
18			NIS-TFA	<1h	100	99	None	None
19			NIS-TFA	3h	95	94	None	None
20			NIS-TFA	3h	100	62	None	12%
21			NIS-TFA	3h	100	90	93:7	9%
22			NIS in ACN + 0.3 eq. TFA	36h	84	65	None	15%
23			NIS in ACN + 0.3 eq. TFA	36 h	100	83	None	15%

* Percentage of conversion in the reaction mixture was determined by GC-MS.

** The isolated yield is calculated from the weight of the mono-iodinated fraction.

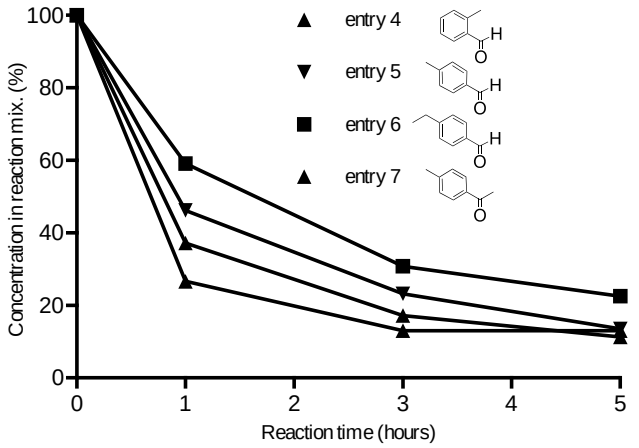

Figure 2. Reaction of benzaldehydes using 1.0 mmol substrate and 1.1 mmol NIS dissolved in 3 mL TFA at room temperature. Conversion into iodinated products is shown as the decrease of substrate concentration in reaction mixtures after 1, 3 and 5 hours (determined by GC-MS).

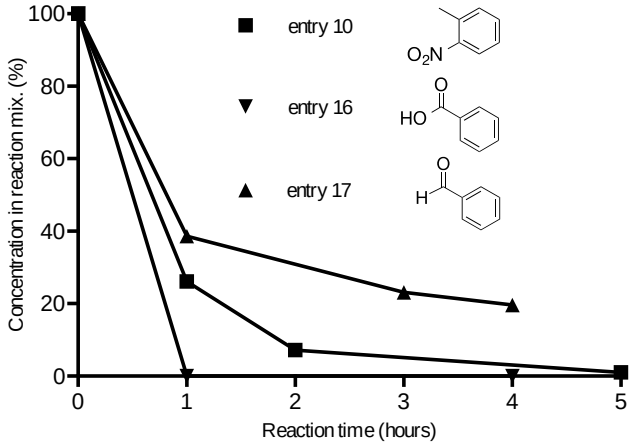

Figure 3. Reaction of "difficult substrates" using 1.0 mmol substrate and 1.1 mmol NIS dissolved in 3 mL TFA with catalytic amounts of sulfuric acid (1 mmol for *o*-nitrotoluene (entry 10) and benzoic acid (entry 16), and 0.3 mmol for benzaldehyde (entry 17)). Conversion into iodinated products is shown as the decrease of substrate concentration in reaction mixtures by time (determined by GC-MS).

NIS-TFA + H_2SO_4: Unsubstituted (deactivated) benzoic derivatives were very resistant to iodination by the NIS-TFA method; less than 3% iodinated product was achieved in 16 h with substrates such as benzaldehyde, benzoic acid and benzamide (data not shown). These compounds have previously been reported to be iodinated by NIS in concentrated sulfuric acid.[3] We found that a milder alternative to the published method is to add a small amount of sulfuric acid to the NIS-TFA reaction mixture to speed up the reaction; see entries 10, 16 and 17 (Table 1). For example, benzoic acid and *o*-nitrotoluene was iodinated by adding 1 molar eq. sulfuric acid into the NIS-TFA reaction mixture (Figure 3). Using the same amount of sulfuric acid for the analogous *m*-iodination of benzaldehyde did, however, induce oxidation to *m*-iodobenzoic acid. By decreasing the concentration of sulfuric acid to 0.3 molar eq. the oxidation could be kept on an acceptable level (< 5%) (Table 1, entry 17).

NIS-acetonitrile + H_2SO_4: As discussed previously, it was not possible to iodinate ethyl toluate with NIS in acetonitrile + TFA, and this was the reason why pure TFA was tried. As sulfuric acid apparently is a more potent activator than TFA, and also less costly, we wanted to evaluate if it was possible to perform iodination with NIS in acetonitrile, using a low concentration of sulfuric acid as activator instead of TFA. Reactions were performed with 1 mmol ethyl *o*-toluate, 1.1 mmol NIS dissolved in 4 mL acetonitrile and different amounts of sulfuric acid. It was found that applying 10 molar equivalents of sulfuric acid as catalyst (0.55 mL sulfuric acid in 4 mL acetonitrile) were almost as efficient as performing the reaction in pure TFA (Figure 4). Reaction rate was proportional to the concentration of sulfuric acid. A drawback using NIS-sulfuric acid in acetonitrile is a lower solubility, in comparison to TFA, and also potential side reactions. For example, it was not possible to iodinate benzaldehyde by NIS-sulfuric acid (10 eq. sulfuric acid) in acetonitrile, since the substrate reacted with acetonitrile under these conditions. The amount of sulfuric acid has to be optimized in for each substrate, and the reaction in 100% TFA is therefore more straight-forward. Sulfuric acid in combination with NIS is however cost-efficient and may, in some cases, be an alternative to the NIS-TFA method presented in this paper (*e.g.* in large-scale synthesis).

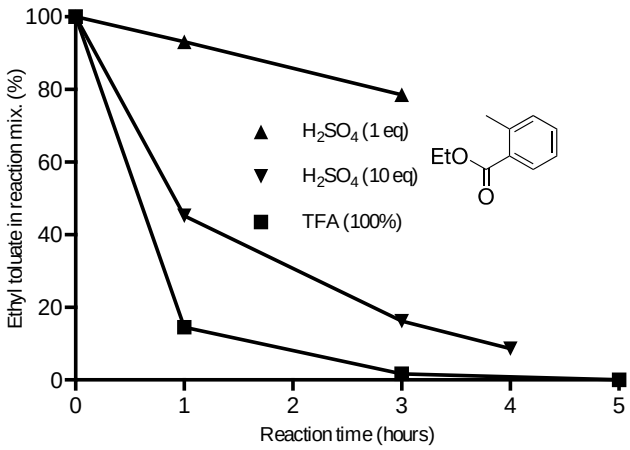

Figure 4. Reaction of ethyl toluate (entry 1) using 1.0 mmol substrate and 1.1 mmol NIS dissolved in 4 mL acetonitrile with different amounts of sulfuric acid (1 or 10 mmol). Reaction in 100% TFA from Fig. 1 is shown for comparison. Conversion into iodinated products is shown as the decrease of substrate concentration in reaction mixtures by time (determined by GC-MS).

NIS-acetonitrile + TFA: It has been reported by Castanet et al. that catalytic amount of TFA in acetonitrile (0.3 molar equivalents) is the optimal condition for iodination of activated compounds by NIS.[5] We found that this method worked well only with methoxybenzenes that was iodinated in 36-48 h at room temperature, while less than 30% of toluene and *o*-xylene were iodinated with this method during the same time (data not shown). When TFA concentration in acetonitrile was changed from 0.3 to 1.0 molar eq. the reaction rate of all substrates containing a methoxy group *decreased* while the reaction rate of toluene and *o*-xylene *increased*. In order to understand this effect of the

TFA concentration on the NIS iodination reaction rate, the amount of TFA in acetonitrile was varied between 0.1 to 10 molar equivalents in the iodination of anisole and *o*-xylene (Figure 5). We found that the iodination rate of *o*-xylene was directly related to the amount of TFA, which seems reasonable if the active agent is the iodine complex of TFA. Anisole (methoxybenzene), on the other hand, had a relatively high reaction rate at 0.1 molar equivalent TFA, but a lower reaction rate at 0.3 and 1.0 molar equivalents of TFA. Using 10 molar eq. of TFA was, however, more efficient for both substrates (Figure 5), and the iodination reactions were completed in ca 20 h with this method.

The explanation of the phenomenon with anisole is possibly the protonation of the methoxy group and the formation of TFA complexes under acidic conditions. These complexes dominate when 0.3-1 molar equivalent of TFA is used and TFA-iodine is not available as reactant. The iodination reaction is therefore faster when TFA is present in low concentrations (0.1 molar eq.), due to a negligible protonation of the methoxy group at lower acid concentration, keeping inductive and resonance effects at large. Finally, when a surplus of TFA is added (10 molar eq.), the reaction will proceed rather efficiently due to the high TFA content, even though most substrate molecules hypothetically are protonated and the ring thereby deactivated. Here we must note the NIS-TFA method is much more efficient for *o*-xylene and anisole as the reaction was completed in less than an hour (entries 8 and 12, Table 1) compared to about 20 h with 10 molar eq TFA in NIS-aceotonitrile (Figure 5).

As stated above, the highly activated dimethoxybenzenes were not compatible with the NIS-TFA method, as they over-reacted and turned to black tars when iodinated by NIS in 100% TFA, and NIS in acetonitrile with catalytic amounts of TFA is to prefer (entries 22 and 23, Table 1).

Regioselectivity and di-iodination: Initially, the regioselectivity of the reactions were confirmed by NMR e.g. for ethyl *o*-toluate, *o*-xylene and bromobenzene. As expected from theory, methyl and bromo substituents were found to direct the iodine substitution mainly to the *para*-position. The ratio of iodination *ortho/para* to the methyl group was about 15% for ethyl *o*-toluate, *o*-xylene, and bromobenzene. As the *para*- and *ortho*-substituted products show a consistent elution order from the GC column it was possible to determine the product ratios by GC-MS. Small amounts of di-iodinated products were present in some cases, especially when activated substrates were iodinated (see Table 1).

CONCLUSION

In conclusion NIS in pure TFA is an improved and time-efficient iodination method for a wide range of aromatic substrates, see Table 1. The method works well without optimization for most aromatic substrates with only few exceptions. For completely deactivated substrates we suggest that a small amount (1 molar equivalent or less) of sulfuric acid is used in combination with NIS-TFA to increase the reaction rate. Highly activated substances such as dimethoxybenzenes can be iodinated by NIS with catalytic amounts of TFA in acetonitrile.

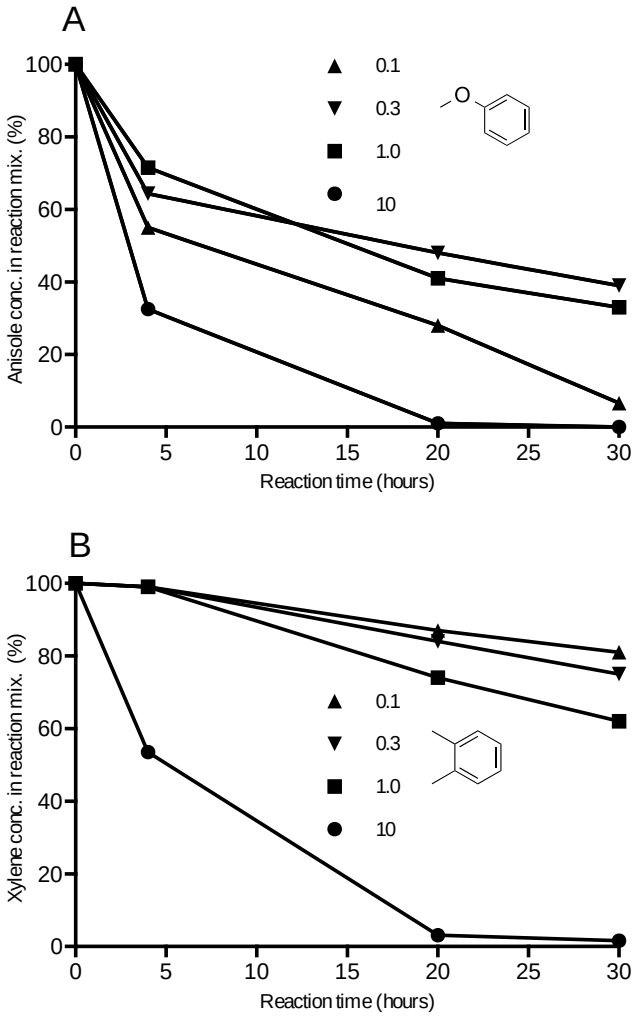

Figure 5. Reaction of two activated compounds; anisole (A) and *o*-xylene (B) using 1.0 mmol substrate and 1.1 mmol NIS dissolved in 4 mL acetonitrile with different amounts of TFA (0.1, 0.3, 1.0 or 10 mmol). Conversion into iodinated products is shown as the decrease of substrate concentration in reaction mixtures by time (determined by GC-MS).

EXPERIMENTAL SECTION

Starting materials and reactants were obtained from commercial sources and used without further purification. Reaction mixtures and products were analyzed by separation on a GC-MS (6890 GC and 5973 mass detector, Hewlett Packard, Palo Alto, CA, USA). Helium was used as carrier gas and a nonpolar capillary column (HP5, 30 m x 0.25 mm, ID 0.25 µm, J&W Scientific, USA). The temperature programme was 50 °C (2 min hold) then 10 °C/min to 200 °C (15 min hold). Mass fragments are given in decreasing order of intensity. NMR spectra were recorded at 400 MHz (^{1}H) and at 100 MHz (^{13}C). Chemical shifts (δ) are reported in ppm, using the residual solvent peak in $CDCl_3$ (H = 7.26 and C = 77.0 ppm), Acetone-d_6 (H = 2.05 and C = 29.84

ppm) or DMSO-d_6 (H = 2.50 and C = 39.52 ppm) as internal standard, and coupling constants (J) are given in Hz.

Iodination procedure NIS-TFA: Iodinations were performed with 1 mmol of the aromatic starting material, which was dissolved in 3 mL pure TFA (Sigma-Aldrich, St Louis, MO, USA). Then 1.1 mmol of NIS (Alfa Aesar, Karlsruhe, Germany) was added in small portions. The reaction mixture was stirred at ambient temperature while sampled at time intervals by mixing two drops of the reaction mixture into 3 mL of cold water, followed by extraction with 0.5 mL of dichloromethane (DCM). The extract was analyzed by GC-MS. Sampling was repeated until all starting material was iodinated, or when the reaction had stopped according to GC-MS. The iodinated products were isolated by pouring the reaction mixture into cold water and then extracting it with DCM (3 x 2.5 ml). The combined organic extracts were washed with 10% $Na_2S_2O_4$ in water, and dried over Na_2SO_4. The crude residue obtained was subjected to silicagel column chromatography using cyclohexane / ethyl acetate. The distribution of isomers and di-iodinated products were determined by GC-MS / NMR.

Iodination procedure NIS-TFA + H_2SO_4: Iodination of *o*-nitrotoluene and benzoic acid (1 mmol) was performed by dissolving the starting in 3 mL pure TFA. Thereafter 1.1 mmol of NIS was added in small portions. When NIS was dissolved, 55 µL concentrated H_2SO_4 (1.0 molar equivalent) was added. All subsequent steps were identical to procedure NIS-TFA. Iodination of benzaldehyde was performed with 18 µL H_2SO_4 (0.3 molar equivalents).

Iodination procedure NIS-acetonitrile + TFA: Iodinations were performed with 1 mmol of the aromatic starting material, which was dissolved in 4 ml of acetonitrile. Then 1.1 mmol of NIS was added in small portions. When NIS was dissolved, 25 µL TFA (0.3 molar equivalent) was added. All subsequent steps were in analogy to procedure NIS-TFA. In one set of experiments different amounts of TFA (8 µL, 25 µL, 76 µL and 760 µL) was tried in the iodination of anisole and *o*-xylene, while keeping the total volume at 4 mL.

Ethyl 5-iodo-2-methylbenzoate (1): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (t, J = 7.2 Hz, 3H), 2.53 (s, 3H), 4.35 (q, J = 7.2 Hz, 2H), 6.98 (d, J = 8.0 Hz, 1H), 7.68 (dd, J = 8.0, 2.0 Hz, 1H), 8.20 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 14.2, 21.2, 61.3, 89.9, 133.4, 139.0, 139.6, 140.5, 142.3, 166.1; GC-MS: *m/z* 244 (100%), 290 (M^+), 245, 261, 89, 90, 216, 217, 134, 63. Spectroscopy data accords with the literature.[13]

5-iodo-2-methylbenzoic acid (2): White solid; ^{1}H NMR (400 MHz, Acetone-d_6): δ 2.67 (s, 3H), 7.09 (d, J = 8.0 Hz, 1H), 7.75 (dd, J = 8.0, 1.8 Hz, 1H), 8.21 (d, J = 1.8 Hz, 1H), 10.27 (s, 1H); ^{13}C NMR (100 MHz, Acetone-d_6): δ 21.3, 90.2, 133.6, 134.5, 139.9, 140.5, 141.2, 179.8; GC-MS: *m/z* 264 (M^+, 100%), 109, 244, 216, 83, 89, 137. Spectroscopy data accords with the literature.[14]

Iodo-2-methylbenzamide (3): White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.29 (s, 3H), 7.04 (d, J = 8.0 Hz, 1H), 7.43 (s, 1H), 7.64 (s, 2H), 7.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 90.6, 132.7, 135.0, 135.2, 137.7, 139.2, 169.3; GC-MS *m/z* 261 (M^+, 100%), 244, 245, 89, 217, 90, 216, 63, 122.

5-Iodo-2-methylbenzaldehyde (4): Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (s, 3H), 7.01 (d, J = 8.0 Hz, 1H), 7.76 (dd, J = 8.0, 2.0 Hz, 1H), 8.07 (d, J = 2.0 Hz, 1H), 10.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 90.7, 133.6, 135.6, 139.9, 140.2, 142.2, 191.0; GC-MS: *m/z* 246 (M^+, 100%), 245, 217, 90, 91, 89, 63, 65, 127.

3-Iodo-4-methylbenzaldehyde (5): Yellow flakes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 3H), 7.38 (d, J = 7.8 Hz, 1H), 7.74 (dd, J = 7.8, 1.5 Hz, 1H), 8.28 (d, J = 1.5 Hz, 1H), 9.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.6, 101.2, 129.2, 130.2, 135.7, 140.2, 148.6, 190.2; GC-MS: *m/z* 246 (M^+, 100%), 245, 91, 90, 89, 217, 127. Spectroscopy data accords with the literature.[15]

4-Ethyl-3-iodobenzaldehyde (6): Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, J = 7.6 Hz, 3H), 2.78 (q, J = 7.6 Hz, 2H), 7.34 (d, J = 7.8 Hz, 1H), 7.76 (dd, J = 7.8, 1.5 Hz, 1H), 8.27 (d, J = 1.6 Hz, 1H), 9.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 34.4, 100.5, 128.4, 128.8, 135.7, 140.6, 153.4, 190.2; GC-MS: *m/z* 260 (M^+, 100%), 259, 245, 217, 77, 103, 105, 104, 131, 231.

1-(3-Iodo-4-methylphenyl)ethan-1-one (7): **B**rown liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.54 (s, 3H), 7.30 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz), 8.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.5, 28.3, 101.2, 128.3, 129.6, 136.3, 138.8, 146.9, 196.2; GC-MS: *m/z* 245 (100%), 260 (M^+), 90, 217, 89, 63. Spectroscopy data accords with the literature.[16]

4-Iodo-1,2-dimethylbenzene (8): Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.210 (s, 3H), 2.22 (s, 3H), 6.88 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 19.4, 90.6, 131.4, 134.7, 136.1, 138.1, 139.0; GC-MS: *m/z* 232 (M^+, 100%), 105, 103, 79, 77, 127, 217. Spectroscopy data accords with the literature.[17,18]

2-Chloro-4-iodo-1-methylbenzene (9): Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 7.05 (d, J = 8.3 Hz, 1H), 7.43 (dd, J = 8.3, 2.2 Hz, 1H), 7.56 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 91.2, 130.7, 132.3, 136.0, 138.4, 139.5; GC-MS: *m/z* 252 (M^+, 100%), 254, 125, 89, 217, 127, 63.

4-Iodo-1-methyl-2-nitrobenzene (10): Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.54 (s, 3H), 7.07 (d, J = 8.1 Hz, 1H), 7.79 (dd, J = 8.1, 1.6 Hz, 1H), 8.26 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1, 89.7, 127.9, 133.1, 134.2, 141.8, 143.1; GC-MS: *m/z* 246 (100%), 263 (M^+), 90, 89, 119, 91, 218, 63. Spectroscopy data accords with the literature.[19-21]

4-Iodophenol (11): Brown solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 82.6, 117.8, 138.4, 155.3; GC-MS: *m/z* 220 (M^+, 100%), 93, 65, 127, 110, 191. Spectroscopy data accords with the literature.[22,23]

1-Iodo-4-methoxybenzene (12): White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H), 6.68 (dd, J = 7.2 Hz,

2H), 7.55 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 82.6, 116.3, 138.2, 159.4; GC-MS: *m/z* 234 (M^+, 100%), 219, 191, 92, 77, 63, 64, 127. Spectroscopy data accords with the literature.[22,24,25]

1-Iodo-4-methylbenzene (13): Brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 6.93 (d, J = 7.8 Hz, 2H), 7.55 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.6, 90.1, 131.2, 137.2; GC-MS: *m/z* 218 (M^+, 100%), 91, 65, 127. Spectroscopy data accords with the literature.[25]

Iodobenzene (14): White solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ δ 7.41 (s, 5H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 93.4, 129.2, 139.3, 139.5; GC-MS: *m/z* 204 (M^+, 100%), 77, 51, 127, 102. Spectroscopy data accords with literature.[25,26]

1-Bromo-4-iodobenzene (15): White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, J = 7.8 Hz, 2H), 7.54 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 92.0, 122.2, 133.4, 139.0; GC-MS: *m/z* 281/283 (M^+, 100%), 155/157, 75, 76, 74, 50, 141/143, 127.

3-Iodobenzoic acid (16): White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30 (t, J = 7.8 Hz, 1H), 7.92−7.98 (m 2H), 8.22 (t, J = 1.6 Hz, 1H), 13.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 94.6, 128.6, 130.8, 132.9, 137.6, 141.3, 165.9; GC-MS: *m/z* 248 (M^+, 100%), 121, 231, 65, 203, 76, 50. Spectroscopy data accords with literature.[27]

3-Iodobenzaldehyde (17): Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (t, J = 7.6 Hz, 1H) 7.83 (dt, J = 7.6 , 1.3 Hz, 1H), 7.94 (dt, J = 7.6, 1.6 Hz, 1H), 8.19 (t, J = 1.6 Hz, 1H), 9.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 94.6, 128.8, 130.7, 137.9, 138.4, 143.1, 190.6; GC-MS: *m/z* 232 (M^+, 100%), 231, 203, 76, 77, 50, 127, 105. Spectroscopy data accords with the literature.[28,29]

3-Iodo-4-methoxytoluene (18): Brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.26 (s, 3H), 3.85 (s, 3H), 6.71 (d, J = 8.3 Hz, 1H), 7.10 (dd, J = 8.3, 2.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.9, 56.4, 85.7, 110.7, 129.9, 132.0, 139.8, 156.0; GC-MS: *m/z* 248 (M^+, 100%), 233, 106, 78, 91, 121. Spectroscopy data accords with the literature.[24]

1-(4-hydroxy-3-iodophenyl)ethan-1-one (19): White solid; ^{1}H NMR (400 MHz, Acetone-d_6): δ 2.51 (s, 3H), 7.02 (d, J = 8.5 Hz, 1H), 7.88 (dd, J = 8.5, 2.1 Hz, 1H), 8.34 (d, J = 2.1 Hz, 1H), 10.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3, 84.3, 115.3, 131.3, 132.2, 140.9, 161.5, 195.3; GC-MS: *m/z* 247 (100%), 262 (M^+), 219, 92, 120, 63. Spectroscopy data accords with the literature.[30,31]

Methyl 4-Hydroxy-3-iodobenzoate (20): White solid; ^{1}H NMR (400 MHz, Acetone-d_6): δ 3.83 (s, 3H), 7.03 (d, J = 8.5 Hz, 1H), 7.87 (dd, J = 8.5, 2.1 Hz, 1H), 8.33 (d, J = 2.1 Hz, 1H), 10.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.2, 83.8, 115.2, 124.0, 132.0, 141.5, 161.5, 165.5; GC-MS: *m/z* 247 (100%), 278 (M^+), 219, 92, 63, 136, 120. Spectroscopy data accords with the literature.[32]

Ethyl 2-hydroxy-5-iodobenzoate (21): White solid; ^{1}H NMR (400 MHz, Acetone-d_6): δ 1.41 (t, J = 7.1 Hz, 3H), 4.44 (q, J = 7.1 Hz, 2H), 6.81 (d, J = 8.8 Hz, 1H), 7.80 (dd, J = 8.8, 2.3 Hz, 1H), 8.12 (d, J = 2.3 Hz, 1H), 10.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 62.8, 80.4, 115.7, 120.9, 138.9, 144.9, 162.1, 169.6; GC-MS: *m/z* 246 (100%), 292 (M^+), 218, 63, 92, 190, 137, 119. Spectroscopy data accords with the literature.[33]

4-iodo-1,2-dimethoxybenzene (22): White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 3H), 3.82 (s, 3H), 6.84 (s, 2H), 7.34 (d, J = 2.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.9, 56.9, 85.9, 111.5, 114.6, 124.8, 152.6, 153.7; GC-MS: *m/z* 264 (M^+, 100%), 249, 94, 79, 221, 63. Spectroscopy data accords with the literature.[34-38]

2-Iodo-1,4-dimethoxybenzene (23): White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 3H), 3.85 (s, 3H), 6.61 (d, J = 8.4 Hz, 1H), 7.10 (s, 1H), 7.20−7.23 (m, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.9, 56.0, 82.3, 113.1, 120.3, 129.7, 149.1, 149.8; GC-MS: *m/z* 264 (M^+, 100%), 249, 94, 221, 79, 63. Spectroscopy data accords with the literature.[36-38]

ASSOCIATED CONTENT

*S Supporting Information

The Supporting Information is available on the Wiley Publications website.

^{1}H and ^{13}C NMR spectra of compounds not previously reported in the literature.

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Notes

The authors declare no competing financial interest.

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