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Synthesis and properties of liquid phenyliodine dicarboxylates

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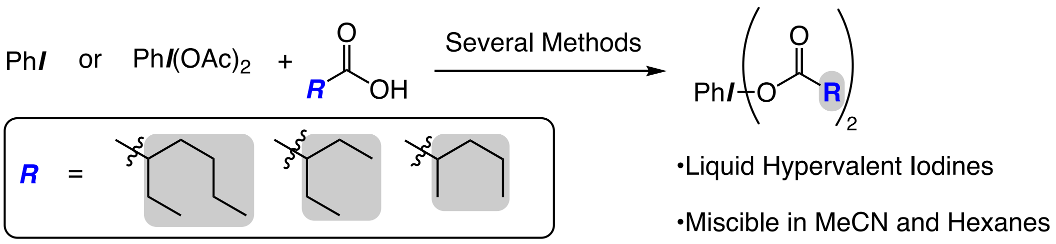
Abstract

Hypervalent iodine (HVI) reagents are versatile reagents that have a wide variety of uses in organic synthesis. However, these reagents are quite polar and are often limited to be used in polar solvents. Disclosed here are four new reagents, three of which are liquids that are miscible in both hexanes and acetonitrile. The partition coefficients of these liquid reagents are measured between hexanes and acetonitrile. Liquid reagents have advantages in applications using flow reactors and solventless transformations. Synthesis of these new reagents by adapting previously disclosed syntheses as well as developing new methods, are disclosed below. During this study, we developed a method to remove an overlooked impurity in commercially available phenyliodine diacetate.



Keywords: Hypervalent iodine, solubility, PIDA, ligand- exchange, liquid reagents, miscibility, partition coefficient

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Introduction

Hypervalent iodine (HVI) compounds are useful in both inorganic and organic transformations ranging from oxidation to C-C bond formation.[1–4] Many of these transformations use the commercially available hypervalent iodine(III) reagent, phenyliodine diacetate (**1a,** Figure 1). While popular, **1a** does not have high solubility in less polar solvents (e.g., it is insoluble in hexanes, Figure 1) and is generally only used in CH_2Cl_2 and acetonitrile.[5] Poor solubility results in a limited number of solvents that can be screened to accomplish a desired transformation. Reagents with better solubility profiles allow for more thorough optimization as well as greener transformations due to less solvent required to dissolve the reagents and therefore perform the reaction.[6] A related class of HVI reagents, i.e. iodoniums, iodonium ylides, are insoluble in all but the most polar of solvents (e.g. DMSO). Development of more soluble iodonium ylides resulted in increased utility of these reagents.[7–10] A class of hypervalent iodine reagents used as benzyne precursors were made soluble in non-polar solvents by the addition of dodecyl or tetradecyl groups to one of the aromatic rings of the reagents.[11,12] Previously reported reagents **1b** and **1c**, derived from *n*-butanoic and *n*-hexanoic acid respectively, were synthesized to make a reagent that was soluble in hexanes.[5] While the longer carbon chains in **1c** led to increased solubility in hexanes vs. commonly used **1a**, a solubility of 1.94 x 10^{-2} mmol/mL leaves room for improvement.

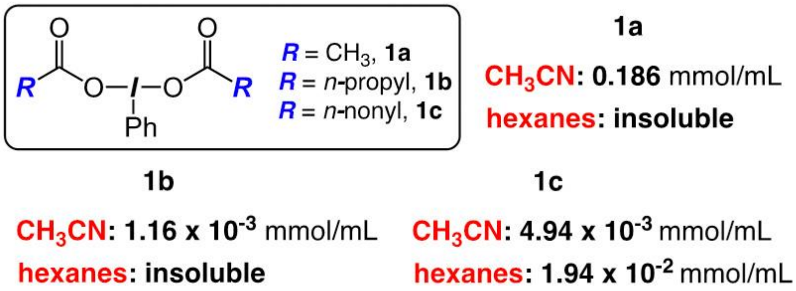


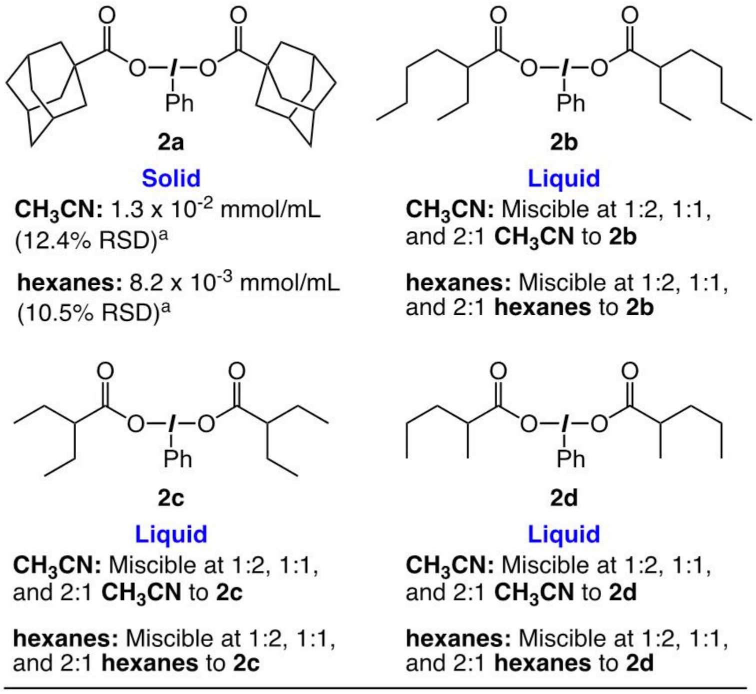
Figure 1. Previously reported solubilities of HVI reagents.

Taking inspiration from the polymerization catalyst tin (II) 2-ethylhexanoate,[13] which is a liquid salt that easily dissolves in non-polar hydrocarbons, new hypervalent iodide reagents were synthesized from carboxylic acids that contain a branched α-position. We hypothesized that due to increased sterics, hypervalent iodide reagents synthesized from α-branched carboxylic acids would have weaker intermolecular forces holding them together. The lower intermolecular force should increase the solubility of the reagents and perhaps result in liquid-state hypervalent iodide reagents. Liquid reagents have advantages over solid reagents in applications such as flow chemistry due to their ability to avoid clogging in the stream or deposit on top of supported catalysts.[14–16] Liquid reagents can also be removed from solid desired products using filtration or washing rather than chromatography. Iodine-containing ionic liquids have been disclosed that can be used as either catalysts or as stoichiometric oxidants,[17–19] though the polarity of these molecules makes it unlikely they are soluble in a wide range of solvents. Hypervalent iodine reagents that contain α-branching have been synthesized before, and examination of the supporting information reveals some of these reagents are liquids, but no comments on solubility or miscibility are made in these manuscripts.[20,21] The solubilities, miscibilities, and/or partition coefficients of new hypervalent iodide derivatives, many of which are liquids, are herein reported.

Two main methods exist for forming phenyliodine dicarboxylates: ligand exchange starting from the commercially available reagent **1a** and oxidation of phenyliodine in the presence of a carboxylic acid. Our previous report used ligand exchange methods, but removing the excess equivalents of long-chain, hydrophobic carboxylic acids from the final compound proved difficult.[5] Due to the carboxylic acids' high boiling points and poor water solubility while deprotonated, difficulty in their removal by evaporation and bicarbonate extractions resulted in the superiority of oxidation over ligand exchange methods. The following phenyliodine dicarboxylates were synthesized from phenyliodide via oxidation with mCPBA,[22] Oxone,[23,24] or a novel method using hydrogen peroxide. Methods that use sodium perborate were not performed because they use triflic acid or have long reaction times (without triflic acid at high temperature).[25]

Results and Discussion

Utilizing α-branched carboxylic acids that were readily commercially available, hypervalent iodides **2a**-**2d** (Figure 2) were synthesized. Only **2a**, which was derived from 2-adamantane carboxylic acid, was a solid – compounds **2b** to **2d** were all liquids. While **2a** was measurably soluble in hexanes (vs. PIDA **1a**, which is insoluble in hexanes), it only possesses a solubility of 8.2 x 10^{-3} mmol/mL in hexanes, which is less than that of the previously reported decanoic acid-derived **1c** (Figure 1). The solubility of **2a** (Figure 2) was only 1.3 x 10^{-2} mmol/mL in acetonitrile compared with **1a** having a solubility of 0.186 mmol/mL in acetonitrile for **1a**. The difference in solubility indicates that **2a** is sparingly soluble in both hexanes and acetonitrile. Since **2b** to **2d** were all liquid reagents, miscibilities were measured instead of solubilities. These three liquid reagents (**2b**, **2c**, **2d**) were combined with either acetonitrile or hexanes in reagent:solvent ratios of 2:1, 1:1, or 1:2 by volume of reagent to solvent by volume. All three reagents **2b** – **2d** were completely miscible in both polar acetonitrile and nonpolar hexanes regardless of the ratio of reagent to solvent.

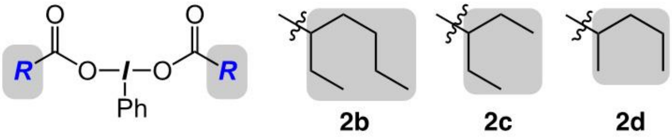


[a] Average of four experiments. See supporting information for details.

Figure 2. Solubility and miscibility of α-branched hypervalent iodines.

To get another idea of the relative ease with which these liquid reagents dissolve in polar and non-polar solvents, the partition coefficients of reagents **2b** – **2d** were measured in a mixture of acetonitrile and hexanes (Table 2). The biphasic solutions were rigorously stirred at 20 °C for at least 24 h before aliquots from each layer were taken, the solvent was removed in vacuo, and the concentration of reagent in each layer was determined. Reagent **2b**, derived from 2-ethylhexanoic acid, had a partition coefficient of 0.47, meaning that 47% of the reagent was found in the hexanes layer, with 53% found in the acetonitrile layer. Reagent **2b** having the strongest preference of the three for the non-polar layer was not surprising as **2b** was predicted to be the least polar reagent of the three liquid hypervalent iodides. Both reagents **2c** and **2d** had partition coefficients of 0.12. Although this indicates that each of the reagents are more soluble in acetonitrile than hexanes, the fact that all three were miscible in hexanes demonstrates their ability to be utilized in non-polar solvents.

Table 1. Partition coefficients of liquid hypervalent iodines



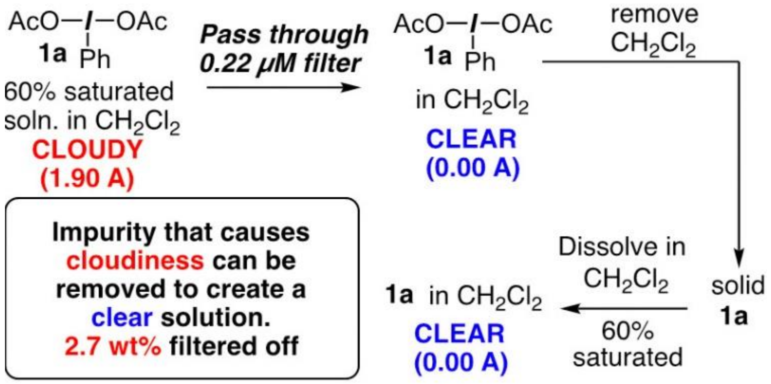
Partition Coefficient (P)
measured at 20 °C with neither layer saturated

$$= \frac{\left[\text{concentration in } \textbf{hexanes}\right]}{\left[\text{concentration in } \textbf{MeCN}\right]}$$

entry	substrate	partition coefficient [a]	% RSD
1	**2b**	0.47	11.7
2	**2c**	0.12	7.1
3	**2d**	0.12	8.7

[a] Average of two experiments.

A cloudy solution was observed while studying the solubility of hypervalent iodide compound **1a.** Namely taking a 60% saturated solution of commercially available **1a** and dissolving it in CH_2Cl_2 led to a solution with an absorbance of 1.90 A at 525 nm. When the cloudy solution was passed through a 0.22 µM syringe filter, it would transform from a cloudy solution into a clear solution with an absorbance 0.00 A at 525 nm (Scheme 1). Removal of the solvent afforded solid phenyliodine diacetate **1a**. We were curious if the filtered **1a** would again form a cloudy solution once it was redissolved in CH_2Cl_2, perhaps due to **1a** being in equilibrium with an insoluble impurity. Taking this purified solid and creating another 60% saturated solution in dichloromethane resulted in a clear solution (0.00 A at 525 nm). Redissolving the filtered **1a** that had been stored in a vial at least a week still resulted in a clear solution. When analyzing the mass recovered of **1a** following filtration, there was approximately 2.7% by weight of impurity removed by filtration through a 0.22 µM filter. Importantly, the established method for purifying **1a** involves washing the solid with hexanes to remove phenyl iodide and/or acetic acid.[26] Washing **1a** with hexanes does not remove the impurity that causes cloudiness. Likely due to the relatively small amount of this impurity we could recover from the filter paper, we were not able to determine the identity of this impurity. However, we wish to disclose the presence and a way to remove the impurity from a solution of phenyliodine diacetate.[27]

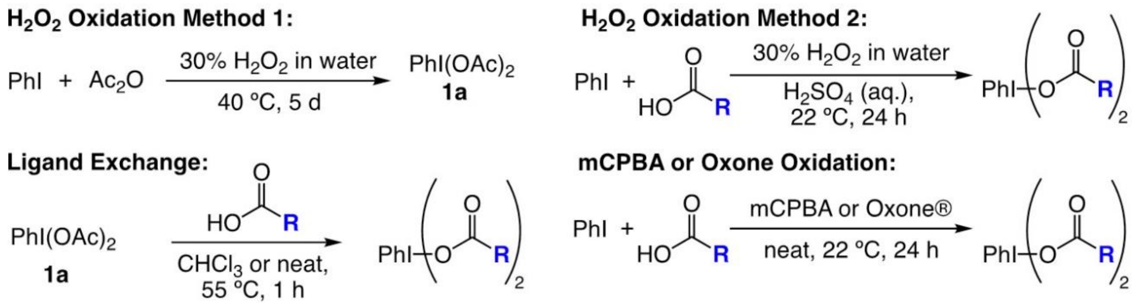


Scheme 1. Impurity in commercial **1a** can be removed.

Phenyliodine dicarboxylates were synthesized via the oxidation of phenyl iodide in neat or solvated carboxylic acids using various oxidants. Table 2 shows the results of each oxidation reaction. The purity of the products obtained via the oxidation method was typically better than using ligand exchange. The purities in Table 2 were calculated from NMR analysis in which the major impurities were excess carboxylic acid. Further bicarbonate extractions always increased purity and the purities reported in Table 2 are specifically what was acquired from the specified five extractions. While methods involving oxidants of peroxyacids[27] and Oxone[23,24,28,29] are well-known, their application to synthesizing liquid-state phenyliodide dicarboxylates required alterations due to the constraints of physical properties and the number of carboxylic acid equivalents used. For instance, less equivalents of carboxylic acid would lead to m-chlorobenzoic acid (the byproduct of mCPBA oxidation) undergoing ligand exchange and bonding to the iodine atom (this asymmetric compound was not isolated but was observed via NMR).

Exploring oxidation reagents led us to formulate two new hydrogen peroxide oxidation methods,[30] which we believe occur through a radical process.[31] The novel reaction using 30% hydrogen peroxide with acetic anhydride required specific volumetric (not stochiometric) ratios and proceeded without the use of polymer-support (Tables 3).[32] The biphasic nature of the mixture has a narrow window in which the reaction reaches the desired product, all of which is governed by solubility equilibria. The hydrogen peroxide method was unsuccessful in synthesizing the liquid-state phenyliodide dicarboxylates, presumably due to varying the carboxylic acid changing the polarity of the biphasic reaction mixture to prevent successful mixing of the phases. Our results in Tables 1 and 2 showed that it is at least possible to synthesize compound **1a** from phenyl iodide with hydrogen peroxide and acetic anhydride.

Table 2. Yields and purities phenyliodine dicarboxylates through various synthetic methods



entry	product	method	yield	purity[a]
1	**1a**	H_2O_2 (Method 1)	57%	99%
2	**1a**	H_2O_2 (Method 2)	99%	99%
3	**1a**	Oxone	91%	99%
4	**2a**	Ligand Exchange	65%	73%
5	**2b**	Ligand Exchange	88%	75%
6	**2b**	mCPBA	60%	93%
7	**2b**	Oxone	0%	N/A
8	**2b**	H_2O_2 (Method 2)	0%	N/A
9	**2c**	mCPBA	60%	93%
10	**2c**	Oxone	0%	N/A
11	**2c**	H_2O_2 (Method 2)	0%	N/A
12	**2d**	Ligand Exchange	66%	86%
13	**2d**	mCPBA	78%	90%
14	**2d**	Oxone	trace	N/A
15	**2d**	H_2O_2 (Method 2)	0%	N/A

[a] The purity values listed can be increased with subsequent extractions but those reported are specifically from the procedure described in the experimental section.

Table 3. Demonstration of the Specific Volumetric Ratios Required for H_2O_2 Oxidation Method 1

1a (yield)	Temp.	Time	PhI	Ac_2O	H_2O_2 (30%)
92%	40 °C	5 Days	0.134 mL	14.5 mL	4 mL
91%	40 °C	5 Days	0.134 mL	10 mL	4 mL
16%	40 °C	5 Days	0.134 mL	6 mL	4 mL
Trace	40 °C	5 Days	0.134 mL	3 mL	4 mL

A second method that relied on specific volumetric ratios of acetic acid, phenyl iodide, hydrogen peroxide**,** and sulfuric acid afforded desired product when using acetic acid but not with other carboxylic acids. Method 2's use of sulfuric acid and acetic acid (as opposed to Method 1 using acetic anhydride and no sulfuric acid or carboxylic acid) successfully synthesized **1a** at lower temperature and time, but also did not work for compounds **2b-2d** the other compounds. Perhaps delicate tuning to each carboxylic acid volume ratio could result in the liquid-state phenyliodine dicarboxylates via Method 2 by hydrogen peroxide oxidation. Using hydrogen peroxide as the oxidant instead of others could have significant implications for industrial production and *in situ* use of phenyliodine dicarboxylates.

Previous methods employing Oxone in the synthesis of hypervalent iodides required a strong acid as an activating agent.[23,24,28,29] As seen in entry 3 of Table 3, **1a** was obtained in 91% yield from phenyl iodide using only Oxone and acetic acid. However, when we tried this same procedure with the branched carboxylic acids, the desired products **2b** – **2d** were not obtained. We did not attempt the Oxone oxidation with these carboxylic acids in the presence of strong acid activators. Of all the oxidation methods attempted for the long chain carboxylic acids, oxidation with mCPBA appeared to be the most successful although the obtained product was sometimes contaminated with m-chlorobenzoic acid. Optimal equivalents of carboxylic acid were 8; less equivalents led to purities below 80%.

Conclusions

Three of the new hypervalent iodide reagents we report here are liquids and are miscible in both hexanes and acetonitrile. These reagents should expand the types of solvents that can be screened when optimizing reactions that use hypervalent iodides. Synthesis of these compounds in high purity required developing new synthetic reactions which should find use in other research groups. Also of general use to the synthetic community is the discovery of an impurity in commercially available phenyliodine diacetate and the disclosure of a method to remove this impurity.

Experimental Section

General. All reactions were performed in oven-dried glassware. All solubility, miscibility, and partition coefficient measurements were carried out in undried glassware without special precaution to exclude air. Unless otherwise noted, all solvents and reagents were obtained from commercial sources and used without further purification. In the solubility studies, acetonitrile (99.8%, anhydrous; Fisher Scientific) was sparged with nitrogen gas and passed through two columns of activated alumina on an LC Technology solvent purification system prior to use, though we used this acetonitrile open to the atmosphere. NMR data of synthesized compounds matched what was previously reported. All reactions were performed in standard fume hoods in oven-dried glassware under an atmosphere of N_2 in the reaction vessels. Unless otherwise noted, all solvents and reagents were obtained from commercial sources and used without further purification. Absorbances were measured with a Genesys 10S Vis Spectrophotometer equipped with Thermo electron quartz cuvettes with a 10 mm path length. NMR data of synthesized compounds matched what was previously reported. A Bruker Avance III 500 MHz spectrometer was used to record the ^1H and ^{13}C NMR spectra in $CDCl_3$. The solvent resonance was used as the internal standard with $CDCl_3$ δ 7.26 ppm for ^1H NMR and δ 77.16 ppm for ^{13}C NMR. ^1H NMR data is reported as chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), integration, and coupling constant (Hz), while ^{13}C is reported as chemical shift (δ, ppm).

General procedures for ligand exchange methods

(a) Ligand exchange: PhI(OAc)$_2$. (3.1 mmol) and 2-ethylhexanoic acid (6.2 mmol) are dissolved in $CHCl_3$ in a round-bottomed flask equipped with a stir bar. A rubber septum affixed to a flow of N_2 gas is added and the reaction is heated to 55 ℃, and the reaction allowed to stir for 1 hour under nitrogen. Once the hour has elapsed, the mixture is quenched with $NaHCO_3$ (aq.) and extracted with $CHCl_3$. The extracted organic layer is dried over anhydrous Na_2SO_4, the Na_2SO_4 is removed via filtration through a plug of cotton, and the solvent is removed under vacuum.

General procedures for oxidation methods

Oxidation with mCPBA. PhI (3.0 mmol) and 2-ethylhexanoic acid (18.8 mmol) are combined at room temperature in a round-bottomed flask equipped with a stir bar. mCPBA (3.3 mmol) is added followed by a rubber septum affixed to a flow of N_2 gas and the reaction is allowed to stir for 24 hours. After the 24 hours has elapsed, the reaction mixture is dissolved in hexane (30 mL) and the organic layer is washed in a separatory funnel five times with a 1:1 mixture of $NaHCO_3$ (aq.) and deionized water (20 mL each extraction). The extracted organic layer is dried over anhydrous Na_2SO_4, the Na_2SO_4 is removed via filtration through a plug of cotton, and the solvent is removed under vacuum.

Oxidation with Oxone using long-chain carboxylic acids. PhI (3.0 mmol) and 2-ethylhexanoic acid (18.8 mmol) are combined at room temperature in a round-bottomed flask equipped with a stir bar. Oxone (3.3 mmol) is added followed by a rubber septum affixed to a flow of N_2 gas, and the reaction is allowed to stir for 24 hours. After the 24 hours elapsed, the reaction mixture is dissolved in hexane (30 mL) and the organic layer is washed in a separatory funnel five times with a 1:1 mixture of $NaHCO_3$ (aq.) and deionized water (20 mL each extraction). The extracted organic layer is dried over anhydrous Na_2SO_4, the Na_2SO_4 is removed via filtration through a plug of cotton, and the solvent is removed under vacuum. *Note: All reactions failed with this method except when the carboxylic acid was acetic acid. Heating the reaction led to trace product formation for the long chain carboxylates.*

Oxidation with Oxone using acetic acid: PhI. (3.0 mmol) and acetic acid (53 mmol) are combined at room temperature in a round-bottomed flask equipped with a stir bar. Oxone (3.3 mmol) is added followed by a rubber septum affixed to a flow of N_2 gas, and the reaction is allowed to stir for 24 hours. After the 24 hours elapsed, the reaction mixture is dissolved in hexanes (30 mL) and is washed in a separatory funnel five times with a 1:1 mixture of $NaHCO_3$ (aq.) and deionized water (20 mL each extraction). The extracted organic layer is dried over anhydrous Na_2SO_4, the Na_2SO_4 is removed via filtration through a plug of cotton, and the solvent is removed under vacuum.

Oxidation with H_2O_2, method 1. Warning!: There are reports of explosions in the synthesis of hypervalent iodides using peroxides and anhydrides.[33] We had no such issues during our studies but still recommend performing these syntheses on the small scales reported below before scaling up.

PhI (3.0 mmol) was added via syringe to a round-bottomed flask equipped with a stir bar and a rubber septum affixed to N_2 gas. Then, Ac_2O (385 mmol) was added via syringe. The mixture is allowed to stir for ~1 minute and 30% H_2O_2 (15 mmol, 0.46 mL) in water is added via syringe. The mixture is heated to 40 ℃ and allowed to stir for 5 days. CH_2Cl_2 (20 mL) is added to the reaction mixture, followed by 30 mL of saturated $NaHCO_3$ (aq.). The layers are separated and then the aqueous layer is washed with two more 30 mL portions of CH_2Cl_2. The combined organic layers are dried over anhydrous Na_2SO_4, and the solvent is removed under vacuum.

Oxidation with H_2O_2, method 2. AcOH (53 mmol), H_2O_2 (15 mmol, 30% in H_2O), concentrated H_2SO_4 (3.0 mmol) and PhI (3.0 mmol) are added sequentially via syringe to a round-bottomed flask affixed with a stir bar and a rubber septum affixed to N_2 gas. The reaction is allowed to stir for 24 h at room temperature or 40 ℃. After the 24 hours has elapsed, CH_2Cl_2 (20 mL) is added to the reaction mixture, followed by 30 mL saturated $NaHCO_3$ (aq.). The layers are separated and then the aqueous layer is washed with two more 30 mL portions of CH_2Cl_2. The combined organic layers are dried over anhydrous Na_2SO_4, and the solvent is removed under vacuum.

Phenyl-λ³-iodanediyl bis(1-adamantoate) (2a). ^{1}H NMR (500 MHz, CHLOROFORM-d) Shift ppm 1.54 - 1.69 (m, 12 H), 1.73 (d, *J* 2.84 Hz, 12 H), 1.84 - 1.90 (m, 6 H), 7.38 - 7.43 (m, 2 H), 7.47 (m, 1 H), 7.93 (m, 2 H).^{13}C NMR (126 MHz, CHLOROFORM-d) Shift ppm 28.16 (6 C), 36.50 (6 C), 39.41 (6 C), 41.25 (2 C), 121.98 (1 C), 130.59 (2 C), 131.15 (2 C), 134.24 (1 C), 182.65 (2 C).

Phenyl-λ³-iodanediyl bis(2-ethylhexanoate) (2b). ^{1}H NMR (500 MHz, CHLOROFORM-d) Shift ppm 0.80 - 0.86 (m, 12 H), 1.09 - 1.57 (m, 16 H), 2.23 (tt, *J* 8.83, 5.36 Hz, 2 H), 7.48 (m, 2 H), 7.57 (m, 2 H), 8.08 (m, 2 H). ^{13}C NMR (126 MHz, CHLOROFORM-d) Shift ppm 11.91 (2 C), 13.86 (2 C), 22.59 (2 C), 25.91 (2 C), 29.68 (2 C), 32.24 (2 C), 47.45 (2 C), 121.98 (1 C), 130.59 (2 C), 131.45 (2 C), 134.86 (1 C), 181.19 (2 C).

Phenyl-λ³-iodanediyl bis(2-ethylbutanoate) (2c). ^{1}H NMR (500 MHz, CHLOROFORM-d) Shift ppm 0.81 (t, *J* 7.5 Hz, 12 H), 1.38 – 1.59 (m, 8 H), 2.17 (tt, *J* 8.80, 5.40 Hz, 2 H), 7.47 (m, 2 H), 7.57 (m, 1 H), 8.08 (m, 2 H). ^{13}C NMR (126 MHz, CHLOROFORM-d) Shift ppm 11.88 (4 C), 25.46 (4 C), 49.05 (2 C), 122.28 (1 C), 130.68 (2 C), 131.44 (2 C), 134.84 (1 C), 181.10 (2 C).

Phenyl-λ³-iodanediyl bis(2-methylpentanoate) (2d). ^{1}H NMR (500 MHz, CHLOROFORM-d) Shift ppm 0.84 (t, *J* 7.25 Hz, 6 H), 1.06 (d, *J* 6.94 Hz, 6 H), 1.17 - 1.34 (m, 2 H), 1.51 - 1.59 (m, 2 H), 2.41 (sxt, *J* 6.94 Hz, 2 H), 7.49 (m, 2 H), 7.58 (m, 1 H), 8.07 (m, 2 H). ^{13}C NMR (126 MHz, CHLOROFORM-d) Shift ppm 13.93 (2 C), 17.57 (2 C), 20.46 (2 C), 36.46 (2 C), 39.36 (2 C), 122.08 (1 C), 130.7 (2 C), 131.43 (2 C), 134.68 (1 C), 181.79 (s, 2 C).

General procedure for solubility measurements. Following a procedure by Malwade et *al.*,[20] a saturated solutions of the hypervalent iodide being investigated was allowed to stir for at least 24 h in an isothermal bath at 20 ± 0.1 °C controlled by a PolyScience LM Series 1/3 HP benchtop chiller. The solution was quickly removed from the isothermal bath via a syringe and filtered through a PTFE 0.22 µm porosity syringe filter into a 20 mL vial. Aliquots of the filtered solution were then measured into tared vials. The samples were concentrated in vacuo and dried on a high-vacuum pump until the masses remained constant. The mass of the compound obtained was divided by the volume added to determine the solubilities.

General procedure for determination of miscibility. Liquid hypervalent iodide (**2b-2b**) was added to a 10 x 75 mm test tube followed by either acetonitrile or hexanes in a 2:1, 1:1, or 1:2 ratio by volume of hypervalent iodide to solvent. Volumes of solvent and hypervalent iodide were either 0.50 or 0.25 mL. The mixture was stirred with a spatula to ensure a complete mixing and allowed to settle for five minutes. Miscibility was determined by visual inspection of the mixture. See supporting information for pictures of the mixtures after they were allowed to settle.

General procedure for determination of partition coefficient. A 8 mL glass vial is equipped with a Teflon-coated stir bar. Two immiscible solvents - acetonitrile (3.00 mL) and hexanes (3.00 mL) were added to the prepared vial using a syringe. Compound **2c** (0.10 mL) was then transferred into the vial via a syringe. Multiple concentrations (0.10 mL, 0.20 mL) used to ensure both layers are not saturated. When the amount of **2c** added was doubled and the amount in the layer also doubled, we determined that the layers at the lower concentration of **2c** were not saturated. The prepared vial was sealed with a PTFE-lined cap and further sealed with electrical tape. The solution was then stirred in an isothermal control bath at 20 ± 1 ℃ for 24 hours controlled by a PolyScience LM Series 1/3 HP benchtop chiller. The solution was transferred into a graduated cylinder and the total volume of each solvent layer was recorded (acetonitrile layer: 3.55 mL, hexanes layer: 2.45 mL). Even though Two aliquots (1 mL) of each solvent layer were transferred to the tared vials and further concentrated using rotovap and dried via a high vacuum pump until the mass has stabilized after being checked ~every 24 h. The leftover solution was also collected in a tared vial and resulted to be 49.3 mg after the removal of solvents. The mass of compound **2c** dissolved in acetonitrile was measured to afford 29.8 mg in the first vial and 28.5 mg in the second vial. The mass of **2c** dissolved in hexanes was measured to afford 4.7 mg in the first vial and 4.8 mg in the second vial. The total mass of **2c** recovered resulted to be 117 mg and the percent recovery of compound **2c** is 90%. Using the density and molar mass of **2c** (1.3 g/mL, 434.10 g/mol) as well as the volumes of the acetonitrile and hexanes layers after stirring, the concentration of **2c** in the acetonitrile layer resulted to be 0.069 mol/L and 0.069 mol/L respectively. The concentration of **2c** in the hexanes layer resulted to be 0.011 mol/L and 0.011 mol/L respectively. The partition coefficient of hexanes to acetonitrile layer is calculated by dividing the average concentration of the hexanes layer by the acetonitrile layer to afforded 0.16. See supporting information for data.

General procedure for purification of phenyliodine diacetate (PIDA) 1a. PIDA **1a** (1.00 g) and dichloromethane (6.00 ml) are added into a beaker and stirred for an hour to make a 60% saturated solution based on the solubility measured in previous work.[5] It is likely that an hour is not required, although the yield of purified compound may be lower due to incomplete dissolution. The cloudy solution (1.897 A at 525 nm) is filtered through a PTFE 0.22 µm porosity syringe filter to obtain a clear solution (0.000 A at 525 nm). The filter and syringe is then washed with an excess 2 x 0.5 mL of CH_2Cl_2. The filtered solution is concentrated in vacuo and dried on a high-vacuum pump until the mass was stable to afford 0.958 g of solid **1a** that can be redissolved in CH_2Cl_2 to make a 60% saturated solution with an absorbance of 0.000 A at 525 nm.

Filtered solid **1a** was stored in vials at 2 ^{o}C for a week both under an atmosphere of N_2 and an atmosphere of air. A 60% saturated solution of **1a** in CH_2Cl_2 was made after 10 days for the solid in each vial. Both solutions were clear by visual inspection. The **1a** stored under an atmosphere of N_2 had an absorbance of 0.000 A and the solid stored under an atmosphere of air had an absorbance of 0.001 A.

Acknowledgements

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Supplementary Material

Supplementary data associated with this article can be found in the online version.

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