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Synthesis, Structure, and Chemoselective Reactivity of *N*-(2-Iodylphenyl)acylamides: Hypervalent Iodine Reagents Bearing a Pseudo-Six-Membered Ring Scaffold**

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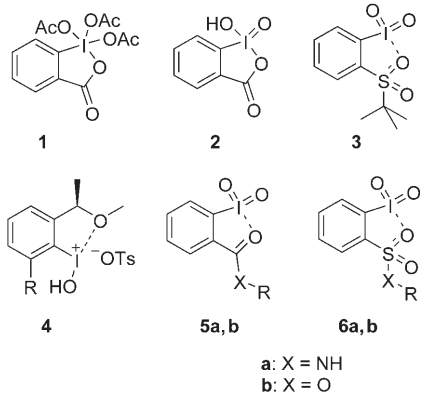
During the past decade, hypervalent iodine compounds have gained significant attention as mild, selective, and environmentally benign reagents in synthetic organic chemistry.[1,2] The oxidation of sensitive and complex alcohols[2a,b] and amines,[2c] the cyclization of anilides,[2d] the introduction of α,β unsaturation into carbonyl compounds,[2e] and the aromatization of tetrahydronaphthalene-1,4-diones[2f] are among elegant synthetic transformations effected by organic iodine(v) compounds (λ^5-iodanes). However, the major reagents used for these unique protocols, Dess–Martin periodinane (DMP, **1**)[2a] and its precursor 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one (IBX, **2**; see Scheme 1,[2b] suffer from a number of drawbacks, namely, DMP is highly sensitive towards moisture[3a] and unstable to prolonged storage, whereas IBX is explosive under impact or on heating to $>200\,^{\circ}C$,[3b] is nonrecyclable, and has limited solubility in most organic solvents except dimethyl sulfoxide (DMSO).



Scheme 1. Cyclic and pseudocyclic hypervalent iodine reagents.

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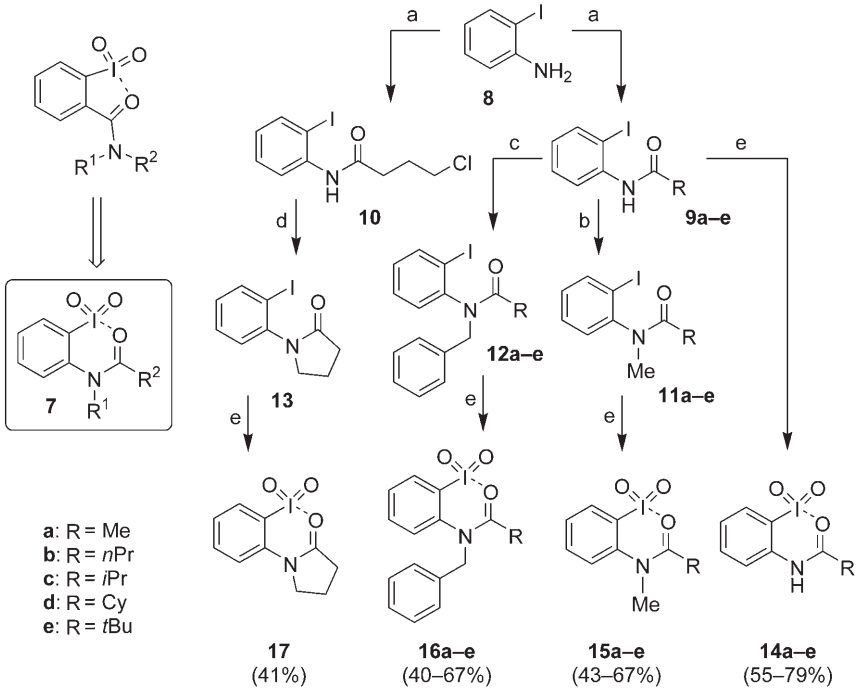
The low solubility of **2**, which restricts its practical application, arises from strong intermolecular secondary I···O, hydrogen-bonding, and π-stacking interactions observed for IBX in the solid state.[4] Several research groups have tried to overcome this preparative limitation by performing oxidation at elevated temperatures,[5a] using an ionic liquid and water as a reaction medium,[5b] or functionalizing the IBX aromatic core.[5c] Also, a number of solid-supported reagents in which the IBX scaffold is linked to a polymer have been reported.[6] Another fruitful approach coined by Protasiewicz, Wirth, and co-workers[7a–e] involves the incorporation of an *ortho*-substituent into λ^5- and λ^3-iodanes (e.g., sulfone **3** and benzyl ether **4**), thus resulting in intramolecular secondary bonding interactions. This *ortho*-stabilization leads to a partial disruption of the polymeric network, and consequently enhances solubility. More recently, investigations from our group have resulted in a series of stable and soluble IBX analogs: IBX amides **5a**,[7f] IBX esters **5b**,[7g] as well as IBX sulfonamides **6a** and IBX sulfonate esters **6b**.[7h] A planar pseudo-benziodoxole moiety that arises from the intramolecular nonbonding iodine–oxygen interaction is a key structural feature present in this series of compounds, as shown by X-ray crystallographic analysis. The readily available hypervalent iodine reagents **5**–**6** possess reactivity similar to IBX and DMP and have proved to be useful oxidizing reagents towards alcohols[8a] and sulfides.[8b] The synthesis of polymer-supported IBX esters and amides has been reported as well.[8c]

We report herein the elaboration of the *ortho*-stabilization concept with regard to λ^5-iodanes. Our initial aim was to furnish an aryl iodyl species with a pseudo-six-membered ring unit such that the iodine(v) atom and *ortho*-sustituent donor atom were located in the 1,6-position. To obtain the required scaffold, we decided on an amide group as the *ortho* sustituent. Indeed, changing the aryl amide function in the substituted IBX amide to an aryl carbamoyl group yields *N*-(2-iodylphenyl)acylamides **7** with the required pseudo-benziodoxazine structure (Scheme 2). Assuming that an isosteric switch will not substantially change the molecular electronic parameters of the system when carried out, one can expect **7** to be close to the IBX amides in oxidative properties. Furthermore, the *ortho*-amide group offers a large variety of structural modifications, which may allow control over the reactivity profile of the title compounds.

A set of sixteen pseudo-benziodoxazines **14**–**17** was prepared to investigate the influence of the structure of the *ortho* sustituent on the oxidative activity of the target *N*-(2-iodylphenyl)acylamides and to explore the chemistry of these novel reagents (Scheme 2). Synthesis of **14**–**17** was performed by acylation of the commercially available 2-iodoaniline (**8**) with a range of acyl chlorides. Subsequent treatment of the obtained amides **9a**–**e** and **10** with NaH in dry THF, followed by alkylation with MeI and BnBr in the case of **9a**–**e**, led to pyrrolidinone **13** and substituted amides **11a**–**e** and **12a**–**e**. Oxidation of iodoarenes **11**–**13** with 3,3-dimethyldioxirane afforded **14**–**17** in good yields. All the products were isolated in the form of stable, white solids.[9]

Compounds **14**–**17** were identified by spectroscopic and ESI-mass-spectrometric analysis; single-crystal X-ray analysis



Scheme 2. Preparation of target aryl iodyl derivatives **14a–e**, **15a–e**, **16a–e**, and **17**. a) RCOCl (1.0 equiv), Et_3N (1.1 equiv), THF, 0°C→RT, 30 min; b) 1. NaH (1.1 equiv), THF, 0°C, 30 min; 2. MeI (1.3 equiv), THF, 0°C→RT, 3 h; (c) 1. NaH (1.1 equiv), THF, 0°C, 30 min; 2. BnBr (1.3 equiv), THF, 0°C→RT, 3 h; d) NaH (1.1 equiv), THF, 0°C→RT, 3 h; e) 3,3-dimethyldioxirane (3.0 equiv, 0.1 M in acetone), CH_2Cl_2, 0°C→RT, 3 h. Cy = cyclohexyl.

was also used in the case of **15e**. IR spectra of all compounds showed a strong absorption for I=O at 760–780 cm^{-1}. With a few exceptions (amides **14e**, **15c–e**, **16e**, and **17**), the expected carbonyl absorption appeared as two strong bands: the first band at 1640–1675 cm^{-1} (characteristic amide C=O stretch)[10] and the second at 1600–1620 cm^{-1} (C=N–Ar stretch).[10] Compounds **14e** and **15c–e** showed a single band at 1600–1620 cm^{-1}, whereas **16e** and **17** were characterized by a sole band at 1643 cm^{-1}. ^1H NMR analysis indicated practically no downfield shift for the proton *ortho* to the iodine atom relative to iodo derivatives **9–13**. In the ^{13}C NMR spectra of iodyl arenes **14a–e** and **17**, the signal for C–IO_2 was observed at approximately $\delta = 133$ ppm, whereas for amides **15–16** this signal emerged at $\delta = 142$ ppm. The ESI-HRMS spectra of **14–17** demonstrated strong peaks that correspond to dimers $[2M+Na]^+$, as well as weaker $[M+Na]^+$ peaks. These data will be rationalized later during the discussion of the reactivity profile of compounds **7**.

Single crystals of **15e** of X-ray-diffraction quality were obtained by slow evaporation from a methanol solution.[11] As anticipated, the structure of **15e** exhibits a strong I(1)···O(4) intramolecular interaction which affords the pseudo-benziodoxazine ring (Figure 1). The observed I(1)···O(4) distance of 2.647 Å is a typical for I^v pseudocyclic moieties.[7a–h] The resulting pseudo-benziodoxazine scaffold is not planar and a torsion angle of 41.33° was observed for the C(6)-C(11)-N(5)-C(13) fragment. This observation is rather intriguing because all known five-membered pseudocyclic iodine(v)-containing compounds have a planar geometry. Such a dramatic difference can be explained by the steric interaction between the hypervalent iodine center and the carbonyl oxygen atom. Indeed, the rotation of the C(6)-C(11)-N(5)-C(13) fragment to a zero-degree torsion angle results in a I(1)···O(4) distance of 1.86 Å, which is typical for the I=O bond, and therefore a planar geometry in the case of **15e** cannot be achieved. Another important feature of the crystal structure of **15e** is an unusual arrangement of the 3D polymeric network. As with the previously reported IBX analogues,[7a–h] molecules of **15e** form infinite polymeric chains in the bis-μ-oxo motif. This structure, however, differs from those observed earlier in two ways: First, the I(1)···O″(2) and I(1)···O′(3) distances are unusually different, with the latter close to the intramolecular I(1)···O(4) distance, whereas the former is close to the sum of the iodine and oxygen van der Waals radii (Figure 1). Second, the observed polymeric chain is spiral shaped along the principal *c* axis, whereas in previously reported IBX analogs such polymer motifs were close to a linear geometry. Overall, the formation of a six-membered pseudocycle in **15e** leads to several unique features in the solid-state structure.

The solubility of **14–17** varies appreciably depending on the nature of the substituents. Specifically, **14a–d** and pyrrolidinone **17** have very limited solubilities in polar organic solvents, such as dichloromethane, 1,2-dichloroethane (DCE), and acetonitrile. In contrast, **15a–e** and especially **16** exhibit

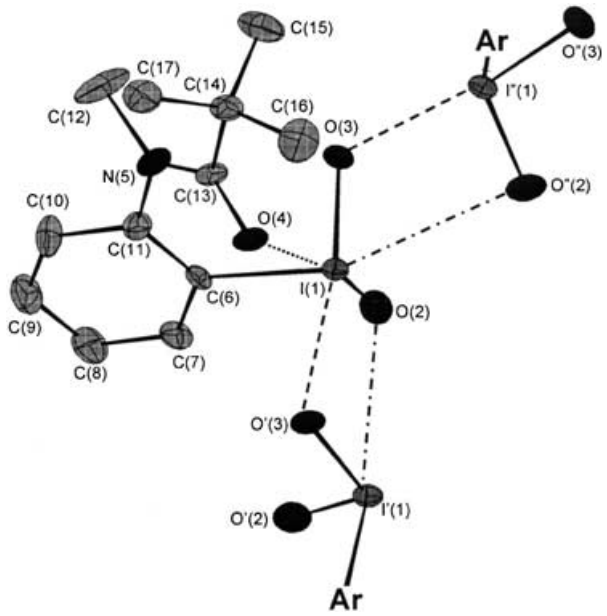


Figure 1. CAMERON drawing of a polymeric chain in the solid-state structure of **15e** at the 30% probability level (hydrogen atoms are omitted for clarity, Ar = 2-$C_6H_4NMeCOtBu$). Selected distances [Å] and angles [°]: I(1)–O(2) 1.791, I(1)–O(3) 1.832, I(1)···O″(2) 3.226, I(1)···O′(3) 2.627, I(1)–C(6) 2.115, I(1)···O(4) 2.647, N(5)–C(13) 1.349, O(4)–C(13) 1.225, O(2)-I(1)-O(3) 103.88, O(2)-I(1)-C(6) 99.01, O(3)-I(1)-C(6) 94.38, O(2)-I(1)···O(4) 166.31, C(6)-C(11)-N(5)-C(13) 41.33.

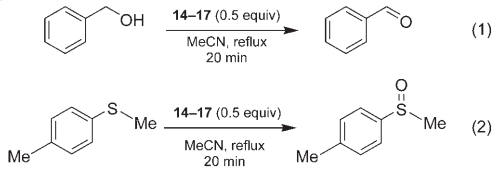
excellent solubility in polar organic solvents, for example, the solubilities of **15d**, **15e**, and **16e** in CH_2Cl_2 are 0.97, 0.12, and 1.4 M, respectively. The plausible reason for the low solubility of **14** is the formation of intermolecular hydrogen bonds through amide hydrogen atoms which cause extra reinforcement of the polymeric network. In the case of **17**, the low solubility could be explained by the presence of a compact pyrrolidinone ring which offers minor steric demand and, thus, causes no disruption of the polymeric structure.

The oxidation activity of **14**–**17** was evaluated by studying the oxidation of benzyl alcohol and methyl *para*-tolyl sulfide. Preliminary reactivity investigations with **16d** (reagent/substrate = 1:2) showed that these oxidations proceed quantitatively at reflux within 1.5 hours and with MeCN or DCE as the optimal reaction solvents. Reaction at reflux is essential for fast conversions; for example, full conversion requires 36–48 hours at room temperature in DCE as the solvent. To compare reactivity, **14**–**17** were reacted under uniform conditions (the results are presented in Table 1).

The experimental results show that the oxidative activity of **14**–**17** depends on the nature of the *ortho*-substituent to a significant extent. On examination of the oxidative ability of **14**–**17**, a clear pattern emerges: First, unsubstituted amides **14**, with the exception of pivalamide **14e**, exhibit virtually no oxidative activity. This fact appears to arise from the negligible solubility of these compounds in MeCN. Compound **14e** renders moderate solubility and, hence, oxidizes benzyl alcohol. Interestingly, amide **14e** is not reactive towards methyl *para*-tolyl sulfide. Furthermore, series **15**, with **15d** displaying the optimal activity, also demonstrates similar selective oxidative behavior. In series **16**, the selectivity vanishes and both benzyl alcohol and methyl *para*-tolyl sulfide were oxidized effectively. In both sets of compounds, the acetamide derivatives (**15a** and **16a**) display considerable reactivity towards methyl *para*-tolyl sulfide. Finally, **17** does not oxidize alcohols, but reacts slowly with the sulfide functionality.

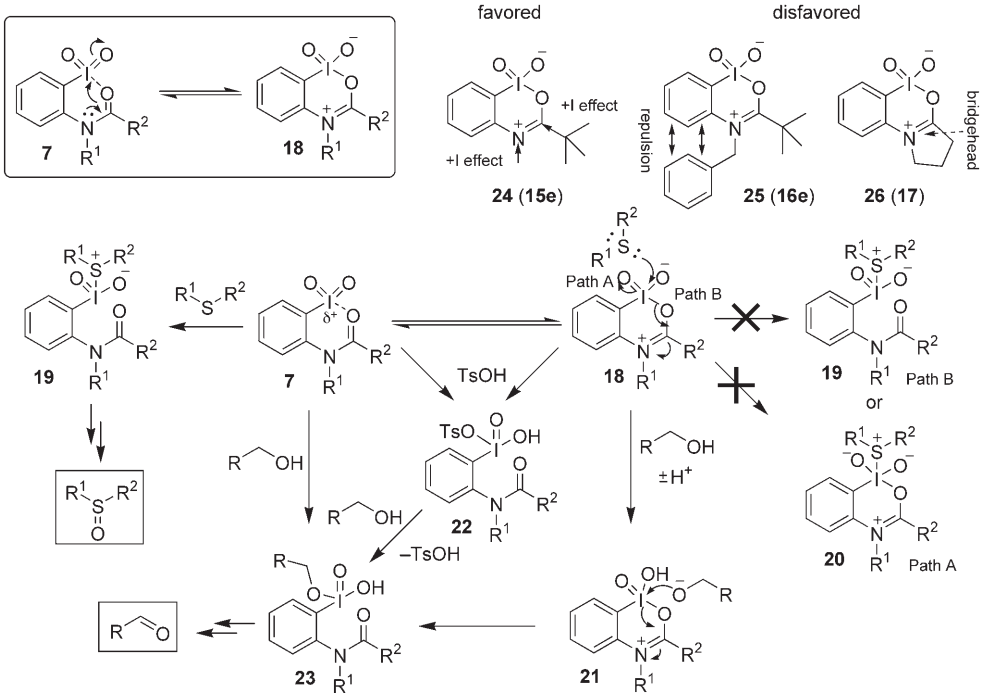
The character of such a structure–activity relationship can be explained by examination of the equilibrium between amide **7** and benziodoxazine **18** (Scheme 3). The cyclic form **18** apparently has decreased electrophilic reactivity because of its zwitterionic structure with the negative charge on the iodyl moiety and is, thus, not able to react with sulfides to form either intermediates **19** or **20**. On the other hand, the iodyl moiety in benziodoxazine **18** is possibly basic enough to abstract a proton from an alcohol to yield the protonated cyclic form **21**. Subsequent attack by an alkoxide leads to alkoxyiodane **23**, which undergoes decomposition to form

Table 1: Oxidative activity of **14**–**17** towards benzyl alcohol and methyl *para*-tolyl sulfide.



Entry	Reagent[a]	Conversion[b] in reaction (1) [%]	Conversion[c] in reaction (2) [%]
1	**14a**	0	0
2	**14b**	0	0
3	**14c**	2	0
4	**14d**	3	0
5	**14e**	36	0
6	**15a**	32	9
7	**15b**	70	6
8	**15c**	22	0
9	**15d**	72	0
10	**15e**	39	0
11	**16a**	19	95
12	**16b**	68	81
13	**16c**	36	31
14	**16d**	66	64
15	**16e**	79	96
16	**17**	0	8
17	**15d**	77[d]	89[d]

[a] The ratio of BnOH and *para*-Tol SMe to reagents **14**–**17** was 2:1. [b] Determined by GCMS; benzaldehyde and the respective iodoarenes **9** and **11**–**13** were the only reaction products detected. [c] Determined by GCMS; methyl *para*-tolyl sulfoxide and the respective iodoarenes **9** and **11**–**13** were the only reaction products detected. [d] Reaction was performed in the presence of TsOH (10 mol%).

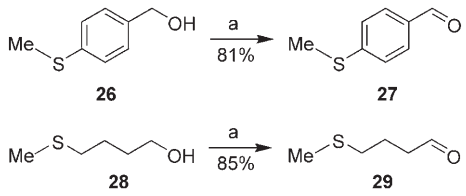


Scheme 3. Proposed mechanistic rationale for the reactivity of pseudo-benziodoxazines **14**–**17** towards alcohols and sulfides. I effect = inductive effect.

an aldehyde according to the conventional mechanism.[3a] In contrast, the open form **7** is more electrophilic and reacts unselectively with both the alcohol and sulfide groups. We can speculate that **14e** and **15c–e**, which are selective towards alcohol oxidation, have **18** as the major form in solution. The cyclic form **18** of **14e** and **15c–e** is possibly stabilized by the electron-donating effect of the R^1 group and especially the R^2 group through the decrease in the positive charge on the nitrogen atom (see **24**). In **15a**,**b**, the Me and *n*Pr substituents offer less stabilization, and minor amounts of the open form **7** is present in solution. Hence, partial oxidation of the sulfur atom is observed in **15a**,**b**. For series **16**, the cyclic form **18** is highly disfavored because of steric reasons (Scheme 3; see **25**), and no selectivity is observed. Compound **17** possesses lowered reactivity because of low solubility, and it is exclusively reactive towards the sulfide group. This behavior could be explained by the fact that the formation of benziodoxazine **26** is also highly disfavored because of the formation of a double bond at the bridgehead of a bicyclic system.

The proposed mechanism is supported by experimental and spectral data. In their IR spectra, **14e** and **15c–e** showed a single band at 1600–1620 cm^{-1}, which is a typical C=N–Ar stretch. Compounds **16e** and **17** were characterized by a single band at 1643 cm^{-1}, thus indicating an amide carbonyl function. All other compounds showed carbonyl absorptions in both of these regions. The ^{13}C NMR spectra of **15a** in [D_6]DMSO revealed pairs of close signals for C=O, C–NRCO, and C–IO_2 (Figure 2). We assume that this phenomenon results from the coexistence of forms **7** and **18** in solution. The same type of spectrum is observed for **15b** and **16a–d** in [D_6]DMSO and CD_3CN (but not in CD_3OD). Addition of MsOH (Ms = methanesulfonyl; approximately 1.0 equiv) led to upfield signals for C–NRCO and C–IO_2, whereas the upfield signal for C=O vanished, thus putatively yielding the mesylate species similar to the open form **7** (Figure 2). Indeed, no selectivity was observed when oxidations were carried out with **15d** in the presence of a catalytic amount of TsOH (Ts = *para*-toluenesulfonyl; Table 1, entry 17). Conceivably, the formation of electrophilic species **22**, which is close to **7** in reactivity, is responsible for such a major change in the oxidative behavior. The ^{13}C NMR spectra of **15e** and **16e** correspond to the cyclic and open forms of **15a**, respectively (Figure 2). The latter spectroscopic data match the reactivity profile of **15e** and **16e** perfectly but contradict the X-ray data obtained for **15e**. This data can be rationalized by the supposition that the zwitterionic cyclic form **18** exists only in solution, in which charge separation is stabilized by polar solvent molecules, and thus could not be observed in the solid state.

To validate the chemoselective reactivity of **15d**, the oxidation reactions of thioalcohols **26** and **28** were studied (Scheme 4). However, when 0.5 equivalents of oxidant in DCE at reflux were used, considerable amounts (approximately 30% by GCMS) of the respective sulfoxides were formed along with the main products **27** and **29**. Probably, the



Scheme 4. Site-selective oxidation of thioalcohols **26** and **28**. a) **15d** (1.0 equiv), MeSEt (1.0 equiv), DCE, reflux, 2.5 h.

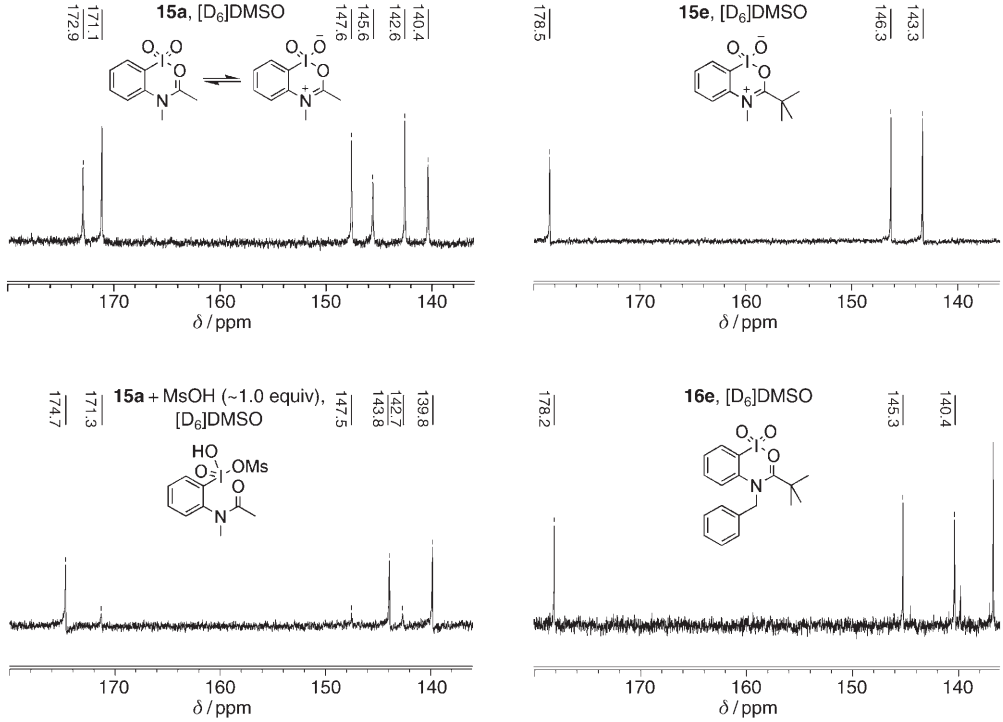


Figure 2. ^{13}C NMR spectra (δ = 136–180 ppm) of iodylarenes **15a**, **15a** + MsOH (1.0 equiv), **15e**, and **16e** in [D_6]DMSO.

initially formed alkoxyiodane **23** can oxidize the sulfur atom to yield the sulfoxide functionality. To avoid this complication, MeSEt (1.0 equiv) was added to the reaction mixture and the quantity of **15d** was increased to 1.0 equivalent. This alteration in the protocol afforded target aldehydes **27** and **29** (sole oxidation products of **26** and **28** as determined by GCMS) in good preparative yields (Scheme 4); furthermore, small amounts of MeSOEt were also isolated. It is notable that oxidation of the thioalcohol **28** using DMP gives only 20% yield of the aldehyde **29**.[12]

In conclusion, the design, preparation, structure, and oxidative properties of novel *N*-(2-iodylphenyl)acylamides **14**–**17** have been described herein, and a mechanistic proposal that accounts for the reactivity pattern of **14**–**17** has also been sufficiently espoused. X-ray studies of **15e** revealed a unique pseudo-benziodoxazine structure, the first reported example of a six-membered pseudocyclic scaffold for iodine(v), with intramolecular secondary I···O bonding interactions. Preliminary experiments indicate that the reagents **14**–**17** can oxidize alcohols and sulfides and that the reactivity largely depends on the substitution pattern of the amide group adjacent to the iodyl moiety. This discovery suggests that the pseudo-benziodoxazine scaffold is a promising lead structure for the design of new regio- and stereoselective hypervalent iodine oxidants. Investigations into mechanistic and reactivity aspects of **14**–**17**, as well as the design of a polymer-supported derivative of the described reagents is ongoing and will be reported in due course.

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[9] Representative procedure for the preparation of **15e**: A freshly prepared solution of 3,3-dimethyldioxirane in acetone (0.1M, 30 mL, 3.0 mmol) was added to a stirred solution of amide **11e** (0.317 g, 1.0 mmol) in CH_2Cl_2 (5 mL) at 0°C (ice bath). The reaction mixture was stirred for 1 h at 0°C, the ice bath was removed, and the solution was additionally stirred for 2 h at room temperature. The solvent was removed under reduced pressure, the remaining white solid was stirred with Et_2O (5 mL) for 15 min, filtered, washed with cold Et_2O (2 × 2.5 mL), and dried in vacuum to afford analytically pure **15e** (0.293 g, 84%) as a snow-white solid. M.p. 172°C (decomp.); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 8.00$ (dd, $^3J = 8.0$ Hz, $^4J = 1.5$ Hz, 1H, Ar), 7.69 (td, $^3J = 7.7$ Hz, $^4J = 1.5$ Hz, 1H, Ar), 7.51–7.59 (m, 2H, Ar), 3.68 (s, 3H, CH_3), 1.43 ppm (s, 9H, $3CH_3$); ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 182.0$, 147.0, 144.7 (C–IO_2), 134.9, 128.4, 128.3, 127.0, 41.5, 41.0, 28.2 ppm; IR (NaCl): $\tilde{\nu} = 1602$ (C=O), 760 cm^{-1} (I=O); ESI-HRMS: *m*/*z* (%) 372.0075 (23) $[M+Na]^+$, 721.0684 (100) $[2M+Na]^+$. Refer to the Supporting Information for additional synthetic protocols and spectral data.

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[11] X-ray diffraction data were collected on Rigaku AFC-7R diffractometer using graphite-monochromated molybdenum Kα radiation ($\lambda = 0.71073$ Å) at 293 K. Psi-scan absorption corrections were applied to the data using TeXsan 10.3b program (Rigaku Inc. 1997). The structure was solved by direct methods (SIR-92) and refined by full-matrix least-squares refinement on F^2 using Crystals for Windows program. Crystal data for **15e** $C_{12}H_{16}INO_3$: $M_r = 349.17$, tetragonal, space group $I4_1$, $a = b = 14.268(2)$, $c = 12.832(3)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 2612.3(7)$ Å^3, $Z = 8$, $\mu = 2.448$ mm^{-1}, 1685 reflections measured, 1568 unique ($R_{int} = 0.10$); final $R_1 = 0.040$, $R_w = 0.101$. CCDC-279792 (**15e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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