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FACILE SYNTHESIS OF STABLE URACIL-IODONIUM(III) SALTS WITH VARIOUS COUNTERIONS

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Abstract – Aryliodonium(III) salts, one of the useful and important classes of hypervalent iodine compounds, have a wide range of applicability, i.e., photoacid generator, active bactericides, and coupling agents for reacting a wide range of nucleophiles even under metal-free conditions. In this report, we present an approach to the design of stable uracil-iodonium(III) salts with various counterions. Uracil is an important substructure that exists in many biologically active compounds and the introduction of such a moiety in iodonium(III) salts would be of high utility in organic chemistry.

This paper is dedicated to Professor Kiyoshi Tomioka on the occasion of his 70th birthday.

Nucleobases such as purines and pyrimidines are unique heteroaromatic compounds that constitute the basic subunit of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Apart from these natural nucleosides, many chemically modified nucleoside analogues have been successfully developed in recent years as DNA virus and retrovirus therapeutic agents.[1] In particular, 5-substituted uracil bases and nucleosides have a wide variety of applications as part of antivirals, anticancer agents, biological probes, and other biologically active molecules.[2] The synthesis of these molecules often includes cross-coupling reactions of halogenated or metallated uracils.[3] Although this approach represents a versatile and reliable

synthetic method, these functionalized uracil derivatives are sometimes difficult to prepare. Therefore, the preparation of an alternative synthetic technique is required for the further advancement of the uses of these molecules in the development of new reactions.

Iodonium(III) salts bearing carbon ligands have recently attracted significant amount of attention in organic chemistry as photoacid generator for cationic polymerization processes in material sciences, supramolecules, active bactericides, and efficient coupling agents that react with a wide range of nucleophiles even under metal-free conditions.[4] Several synthetic methods and broad applications of diaryliodonium(III) salts (Figure 1, left) have been intensively investigated so far.[5,6] In addition to the conventional diaryl and *N*-heteroaryl-iodonium(III) salts (Figure 1, center), other compounds bearing nucleobase and nucleoside moieties have recently appeared in literature.[7] In 1998, Kim and co-workers reported the preparation of phenyluracil-iodonium(III) triflates (Figure 1, right) via a reaction of uracil with phenyliodine(III) diacetate (PIDA) in the presence of triflic acid, and applied it to palladium-catalyzed alkenylations.[7a,7b] Recently, the group of Gaunt also introduced aryl *N*,*N*'-dimethyluracil-iodonium(III) triflates for the organocatalytic arylation of aldehydes.[7c] However, the isolation and application of uracil-iodonium(III) salts were mostly limited to treating triflate ($^{-}$OTf) salts,[8] and the relationship between their stability and the structural feature of uracil-iodonium(III) salts have not yet been explored, probably due to their hygroscopic charactersitics,[9] causing gradual decomposition as claimed in previous reports.[7]

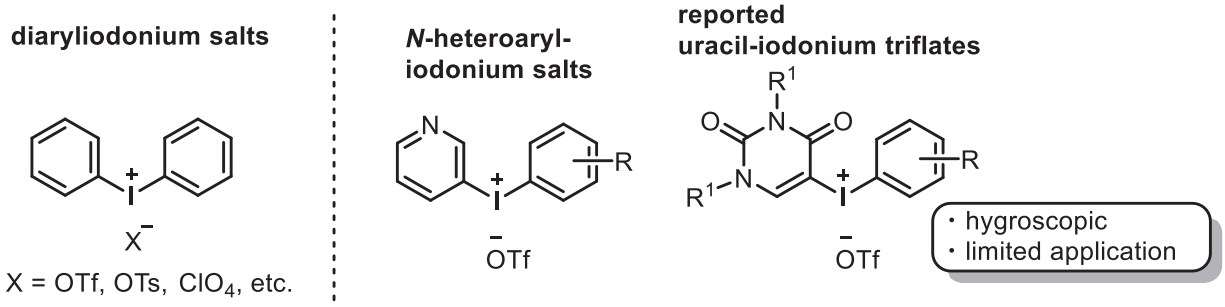
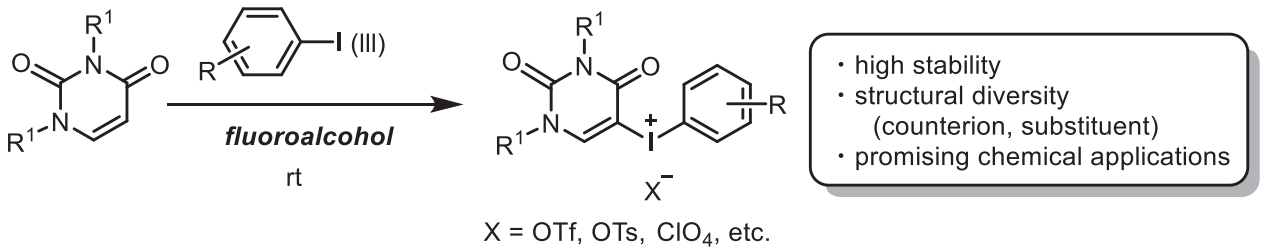


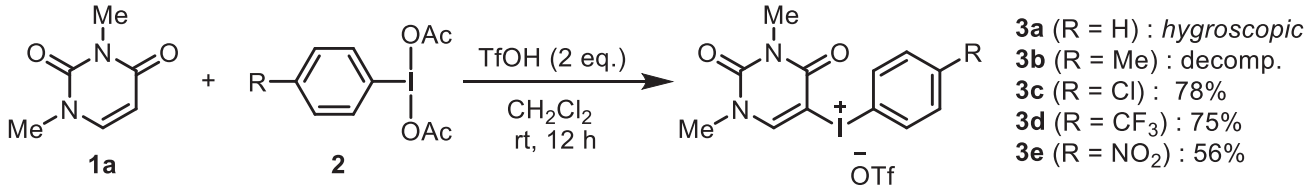
Figure 1. Conventional diaryliodonium(III) salts and their new heterocyclic series

Therefore, there is a room for improvement in the development of facile synthetic methods toward uracil-iodonium(III) salts with a large structural diversity and various counterions. In general, the chemical and physical properties of iodonium(III) salts are known to highly depend on both the nature of the aryl moiety and anionic counterpart (X^{-}).[4] Therefore, it reminds us to design stable uracil-aryliodonium(III) salts with more favorable physical characteristics for practical and easy-to-handle synthetic uses that can expand the applicability of these nucleobase salts for coupling reactions (Scheme 1).



Scheme 1. Our approach to the design and synthesis of stable uracil-aryliodonium(III) salts

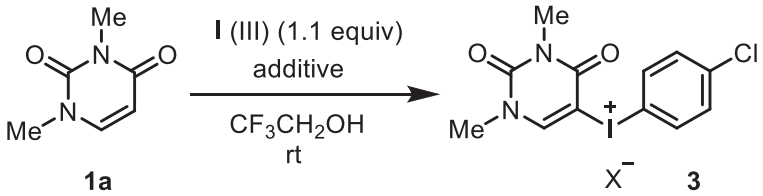
In order to determine the influence of substituent on the benzene ring,[10] we first examined the synthesis of uracil-aryliodonium(III) triflate salts bearing electron-donating or electron-withdrawing aryl moieties. Here, PIDA derivatives bearing different *para*-substituents, **2a** (R = H), **2b** (R = Me), **2c** (R = Cl), **2d** (R = CF_3), and **2e** (R = NO_2), were employed and a procedure previously reported by Kim[7a] was used (Scheme 2). In this pilot experiment, the reported triflate **3a** was produced in a seemingly good yield and precipitated in diethyl ether as fine powder. However, it was found that salt **3a** was too hygroscopic and could not be easily isolated and stored during the experiment without strict care against air and moisture. Similar behavior was previously pointed out by Gaunt et al., who reported that some uracil-aryl-iodonium(III) triflates are very difficult to handle and should be promptly dried under vacuum.[7c] Moreover, triflate **3b**, which was derived from *p*-tolyl-PIDA, was unstable, and thus its preparation resulted in decomposition during the reaction and workup. In contrast, salts **3c-e** having electron-withdrawing aryl moieties were obtained in good to moderate yields as white powders. The formation of these new uracil-iodonium(III) compounds that are stable under air was confirmed by nuclear magnetic resonance (NMR), infrared (IR), and high resolution mass (HRM) spectroscopies. Considering the result from this screening, it was apparent that the presence of an electron-donating group decreased the stability of uracil-aryliodonium(III) triflates. In fact, uracil-iodonium(III) salts applied to different synthetic methods were usually limited to triflates with electron-deficient aryl moieties such as 5-(2-chloropyridyl),[7c] 8-quinolyl,[7c] and 4-fluorophenyl[7e] group, which is in good accordance with our present observations.



Scheme 2. Synthesis of 1,3-dimethyluracil-iodonium triflates with different aryl moieties

Then, we found that the stabilizing effect of the 4-chlorophenyl moiety furnishes the preparation of uracil-iodonium(III) derivatives carrying different types of counterions (Table 1). In the reported various methods for iodonium(III) salt synthesis, we conducted the dehydrative condensation of uracil with Koser-type reagent (ArI(OH)OTs) for the preparation of uracil-aryliodonium(III) tosylate in fluoroalcohol medium according to the established protocol.[6] The reaction was carried out with 1,3-dimethyluracil (**1a**) and stoichiometric 4-$ClC_6H_4I(OH)OTs$ (**2f**) in 2,2,2-trifluoroethanol (TFE), which successfully gave the desired tosylate salt **3f** in a high yield (entry 1). The use of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) instead of TFE resulted in the small decrease in yield (entry 2). The extensive number of Koser-types reagents that are readily available and their variation in the dehydrative condensation can expand the structural motif of the obtained iodonium(III) product. One example of this phenomenon is the preparation of mesylate **3g** (entry 3). Similar modification of the counterion was possible by the utilization of PIDA derivative **2c** (entry 4). Therefore, trifluoroacetate and perchlorate anions were conveniently introduced as counterions to the products, **3i** and **3j**, in good yields under similar reaction conditions (entries 5 and 6). All these uracil-iodonium(III) salts **3f-j** with different counterions obtained in this study were totally non-hygroscopic, stable under air, and thus tolerable to prolonged storage.

Table 1. Facile synthesis of uracil-iodonium(III) salts with various counterions

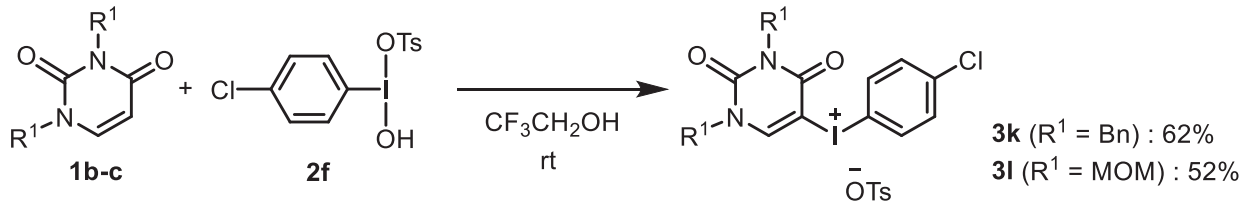


Entry	I(III)	Additive	Time	X	Product	Yield
1	4-ClC_6H_4 I (OH)OTs (**2f**)	none	24 h	OTs	**3f**	98%
2[a]	4-ClC_6H_4 I (OH)OTs (**2f**)	none	18 h	OTs	**3f**	89%
3	4-ClC_6H_4 I (OH)OMs (**2g**)	none	12 h	OMs	**3g**	74%
4	4-ClC_6H_4 I $(OAc)_2$ (**2c**)	(+)-10-OCs (1.1 eq.)	12 h	(+)-10-OCs	**3h**	74%
5	4-ClC_6H_4 I $(OAc)_2$ (**2c**)	CF_3CO_2H (2.0 eq.)	24 h	$OCOCF_3$	**3i**	72%
6	4-ClC_6H_4 I $(OAc)_2$ (**2c**)	$HClO_4$ (2.0 eq.)	24 h	ClO_4	**3j**	68%

[a] 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was used instead of 2,2,2-trifluoroethanol (TFE).
OMs = methanesulfonyloxy, OCs = camphorsulfonyloxy

Next, we briefly explored the availability of *N*-protecting groups for the uracil molecule in the condensation reactions with 4-$ClC_6H_4I(OH)OTs$ (**2f**) leading to the corresponding iodonium(III) salts. Hence, *N*-protected uracil derivatives containing benzyl (R^1 = Bn, **1b**) and methoxymethyl (R^1 = MOM,

1c) groups were subjected to the optimized reaction conditions, producing the desired iodonium(III) tosylates **3k** and **3l** in acceptable yields. To our delight, these modified salts (**3k** and **3l**) were also not sensitive to air and easy-to-handle solids suitable for further synthetic use.



Scheme 3. Availability of uracil *N*-protecting groups

In summary, we successfully synthesized a series of stable uracil-iodonium(III) salts that include various structural motives and counterions and are suitable for isolation and storage. Moreover, this study has clarified that designing aryl moieties on the salts is definitive for manipulating their physical properties. Additionally, the introduction of an electron-withdrawing group is a significant beneficial for their isolation and storage. The new uracil-iodonium(III) salts could become unique compounds and attractive synthetic modules in material sciences, supramolecular chemistry, biological applications, and organic synthesis in constructing unique functionalized molecules containing nucleobases. Therefore, further investigation on their utilization is in progress in our laboratories.

EXPERIMENTAL

Melting point (mp) is uncorrected. All ^{1}H- and ^{13}C-NMR spectra of the products were measured in CD_3OD by spectrometers operating at 600 MHz (150 MHz for ^{13}C NMR) at 25 ^{o}C. Data are reported as follows: chemical shift in ppm (δ), integration, multiplicity (s = singlet, d = doublet, m = multiplet), and coupling constant (*J*) in Hz. Absorptions of infrared spectra (IR) are reported in reciprocal centimeters (cm^{-1}) for representative peaks.

Materials

Hypervalent iodone(III) reagents **2b-g** were synthesized from the corresponding commercial iodoarenes by oxidations according to the literature procedures.[11] The *N*-protected uracils **1b** and **1c** were prepared from uracil by the known methods.[12]

General procedure for the synthesis of uracil-iodonium(III) tosylates (Table 1)

To a solution of 1,3-dimethyluracil **1a** (0.20 mmol) in 2,2,2-trifluoroethanol (TFE) (3 mL), (4-chlorophenyl)(hydroxy)iodonium tosylate **2f** (0.20 mmol) was added and it was stirred at room

temperature. After completion of the reaction, the solvent was removed under vacuum. The product was then precipitated by the addition of Et_2O with stirring. The precipitate was filtered to give uracil-iodonium(III) salt **3f** as white powder.

Characterization of the new uracil-iodonium(III) salts 3

(4-Chlorophenyl)(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)iodonium triflate (3c)

white powder; mp 154-155 ºC; ^{1}H-NMR (600 MHz, CD_3OD): 3.34 (3H, s), 3.48 (3H, s), 7.55 (2H, d, J = 9.0 Hz), 8.13 (2H, d, J = 9.0 Hz), 8.92 (1H, s) ppm; ^{13}C-NMR (150 MHz, CD_3OD): 29.8, 38.3, 89.5, 113.6, 133.0, 138.1, 140.4, 152.3, 155.9, 160.8 ppm; IR: 1717, 1662, 1514, 1251, 1227, 1024, 631 cm^{-1}; HRMS (FAB): calcd for $C_{12}H_{11}ClIN_2O_2$ $[M\text{-}OTf]^+$: 376.9548, found: 376.9546.

(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(4-(trifluoromethyl)phenyl)iodonium triflate (3d)

white powder; mp 190-191 ºC; ^{1}H-NMR (600 MHz, CD_3OD): 3.34 (3H, s), 3.49 (3H, s), 7.85 (2H, d, J = 8.4 Hz), 8.35 (2H, d, J = 8.4 Hz), 8.96 (1H, s) ppm; ^{13}C-NMR (150 MHz, CD_3OD): 28.4, 37.0, 88.1, 118.6, 128.0, 128.1, 128.2, 135.7, 150.9, 154.8, 159.4 ppm; IR: 1723, 1680, 1614, 1325, 1229, 1025, 639 cm^{-1}; HRMS (FAB): calcd for $C_{13}H_{11}F_3IN_2O_2$ $[M\text{-}OTf]^+$: 410.9812, found: 410.9816.

(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(4-nitrophenyl)iodonium triflate (3e)

white powder; mp 212-213 ºC; ^{1}H-NMR (600 MHz, CD_3OD): 3.34 (3H, s), 3.50 (3H, s), 8.33 (2H, d, J = 9.0 Hz), 8.39 (2H, d, J = 9.0 Hz), 8.97 (1H, s) ppm; ^{13}C-NMR (150 MHz, CD_3OD): 28.4, 37.0, 88.2, 120.3, 125.9, 136.2, 150.2, 150.9, 155.0, 159.4 ppm; IR: 1716, 1663, 1352, 1248, 1023, 632 cm^{-1}; HRMS (FAB): calcd for $C_{12}H_{11}IN_3O_4$ $[M\text{-}OTf]^+$: 387.9789, found: 387.9791.

(4-Chlorophenyl)(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)iodonium tosylate (3f)

white powder; mp 186-187 ºC; ^{1}H-NMR (600 MHz, CD_3OD): 2.37 (3H, s), 3.33 (3H, s), 3.47 (3H, s), 7.23 (2H, d, J =7.8 Hz), 7.54 (2H, d, J = 9.0 Hz), 7.69 (2H, d, J = 7.8 Hz), 8.12 (2H, d, J = 9.0 Hz), 8.92 (1H, s) ppm; ^{13}C-NMR (150 MHz, MeOD): 19.9, 28.4, 36.9, 88.2, 112.3, 125.5, 128.4, 131.6, 136.7, 139.0, 140.3, 142.2, 150.9, 154.5, 159.4 ppm; IR: 1715, 1656, 1615, 1214, 1169, 997, 682 cm^{-1}; HRMS (FAB): calcd for $C_{12}H_{11}ClIN_2O_2$ $[M\text{-}OTs]^+$: 376.9548, found: 376.9569.

(4-Chlorophenyl)(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)iodonium mesylate (3g)

white powder; mp 185-186 ºC; ^{1}H-NMR (600 MHz, CD_3OD): 2.70 (3H, s), 3.34 (3H, s), 3.49 (3H, s), 7.56 (2H, d, J = 9.0 Hz), 8.13 (2H, d, J = 9.0 Hz), 8.94 (1H, s) ppm; ^{13}C-NMR (150 MHz, CD_3OD): 29.8,

38.3, 40.0, 90.0, 113.7, 133.0, 138.1, 140.4, 152.4, 156.0, 160.8 ppm; IR: 1739, 1715, 1662, 1218, 1158, 1033 cm^{-1}; HRMS (FAB): calcd for $C_{12}H_{11}ClIN_2O_2$ $[M\text{-}OMs]^+$: 376.9548, found: 376.9545.

(4-Chlorophenyl)(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)iodonium (+)-10-camphorsulfonate (3h)

white powder; mp 194-195 ºC; ^{1}H-NMR (600 MHz, CD_3OD): 0.87 (3H, s), 1.15 (3H, s), 1.41-1.44 (1H, s), 1.61-1.63 (1H, s), 1.91 (1H, d, J = 14.4 Hz), 2.05-2.08 (2H, m), 2.34-2.37 (1H, m), 2.67-2.69 (1H, m), 2.77 (1H, d, J = 14.4 Hz), 3.31-3.33 (1H, m), 3.36 (3H, s), 3.51 (3H, s), 7.57 (2H, d, J = 9.0 Hz), 8.15 (2H, d, J = 9.0 Hz), 8.96 (1H, s) ppm; ^{13}C-NMR (150 MHz, CD_3OD): 20.1, 20.4, 25.8, 27.8, 29.8, 38.4, 43.6, 44.0, 59.6, 89.6, 113.7, 132.9, 138.1, 140.3, 152.4, 156.1, 160.9, 218.2 ppm; IR: 1747, 1717, 1653, 1353, 1217, 1204 cm^{-1}; HRMS (FAB): calcd for $C_{12}H_{11}ClIN_2O_2$ $[M\text{-}OCs]^+$: 376.9548, found: 376.9552.

(4-Chlorophenyl)(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)iodonium trifluoroacetate (3i)

white powder; mp 174-175 ºC; ^{1}H-NMR (600 MHz, CD_3OD): 3.36 (3H, s), 3.50 (3H, s), 7.58 (2H, d, J = 8.4 Hz), 8.14 (2H, d, J = 8.4 Hz), 8.94 (1H, s) ppm; ^{13}C-NMR (150 MHz, CD_3OD): 28.4, 36.9, 88.2, 112.3, 130.2, 131.6, 136.6, 138.8, 139.0, 150.9, 154.4, 159.4 ppm; IR: 1714, 1652, 1609, 1191, 1137 cm^{-1}; HRMS (FAB): calcd for $C_{12}H_{11}ClIN_2O_2$ $[M\text{-}OCOCF_3]^+$: 376.9548, found: 376.9556.

(4-Chlorophenyl)(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)iodonium perchlorate (3j)

white powder; mp 134-135 ºC; ^{1}H-NMR (600 MHz, CD_3OD): 3.34 (3H, s), 3.49 (3H, s), 7.54 (2H, d, J = 8.4 Hz), 8.13 (2H, d, J = 8.4 Hz), 8.91 (1H, s) ppm; ^{13}C-NMR (150 MHz, CD_3OD): 29.8, 38.4, 89.4, 113.6, 133.0, 138.1, 140.4, 152.4, 156.0, 160.9 ppm; IR: 1720, 1653, 1610, 1120, 1083 cm^{-1}; HRMS (FAB): calcd for $C_{12}H_{11}ClIN_2O_2$ $[M\text{-}ClO_4]^+$: 376.9548, found: 376.9563.

(4-Chlorophenyl)(1,3-dibenzyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)iodonium tosylate (3k)

white powder; mp 189-190 ºC; ^{1}H-NMR (600 MHz, CD_3OD): 2.36 (3H, s), 5.05 (2H, s), 5.12 (2H, s), 7.21 (2H, d, J = 7.8 Hz), 7.24-7.25 (3H, m), 7.28-7.29 (2H, m), 7.34-7.36 (5H, m), 7.52 (2H, d, J = 9.0 Hz), 7.69 (2H, d, J = 7.8 Hz), 8.09 (2H, d, J = 9.0 Hz), 9.04 (1H, s) ppm; ^{13}C-NMR (150 MHz, CD_3OD): 19.9, 45.8, 53.2, 89.8, 112.5, 125.6, 127.5, 127.9, 128.0, 128.1, 128.3, 128.7, 131.6, 135.0, 135.9, 136.6, 139.0, 140.3, 142.2, 150.5, 153.7, 158.9 ppm; IR: 1740, 1703, 1655, 1374, 1231, 1214, 1165 cm^{-1}; HRMS (FAB): calcd for $C_{24}H_{19}ClIN_2O_2$ $[M\text{-}OTs]^+$: 529.0174, found: 529.0183.

(1,3-Bis(methoxymethyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(4-chlorophenyl)iodonium tosylate (3l)

white powder; mp 148-149 °C; ^{1}H-NMR (600 MHz, CD_3OD): 2.39 (3H, s), 3.38 (3H, s), 3.44 (3H, s), 5.24 (2H, s), 5.37 (2H, s), 7.25 (2H, d, J = 7.8 Hz), 7.57 (2H, d, J = 9.0 Hz), 7.71 (2H, d, J = 7.8 Hz), 8.16 (2H, d, J = 9.0 Hz), 9.09 (1H, s) ppm; ^{13}C-NMR (150 MHz, CD_3OD):19.9, 56.5, 56.9, 73.6, 80.3, 90.4, 112.2, 125.6, 128.4, 131.7, 131.8, 132.6, 135.1, 136.4, 136.8 ppm; IR: 1738, 1670, 1366, 1216, 1164 cm^{-1}; HRMS (FAB): calcd for $C_{14}H_{15}ClIN_2O_2$ $[M\text{-}OTs]^+$: 436.9760, found: 436.9767.

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9. Water and other proton sources are known to accelerate the photo-induced degradation processes of iodonium salts. See: S.-S. Lin, Y.-J. Chan, and Y.-D. Lee, *J. Appl. Polym. Sci.*, 2013, **127**, 3269.

10. It is known that substituents on the benzene ring strongly affect the stability and other physical properties of hypervalent iodine(III) compounds. For example, (difluoroiodo)benzene ($PhIF_2$) is a potentially useful fluorinating agent, but has limited applications due to its excessively low stability. Thus, the more stable *p*-iodotoluene difluoride (*p*-$TolIF_2$), which is easier to handle, was instead employed for practical applications and commercialization. See, ref. 4c.

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