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Straightforward Syntheses of Hypervalent Iodine(III) Reagents Mediated by Selectfluor

Chengfeng Ye, Brendan Twamley, and Jean'ne M. Shreeve*

Department of Chemistry, University of Idaho, Moscow, Idaho 83844-2343

jshreeve@uidaho.edu

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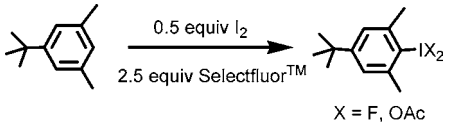
ABSTRACT



Use of Selectfluor allows hypervalent iodine(III) species such as aryl iodine(III) difluoride, diacetate, and di(trifluoroacetate) and Koser's salt to be easily prepared. Aryl iodine(III) difluoride and diacetate can be synthesized from the corresponding arene and elemental iodine in one-pot procedures.

The incorporation of fluorine into molecules results in dramatic changes in their physical, chemical, and biological properties.[1] Constantly expanding commercial products ranging from anticancer agents to agrochemicals to lubricants for spaceships to toothpaste contain C−F bonds. Among the dozens of fluorinating reagents, Selectfluor (**1**) continues to be one of the most powerful tools of choice as "tamed fluorine." In less than two years, **1** has been the subject of three major reviews.[2] Although **1** is most often employed as an extremely effective electrophilic fluorinating reagent, it also plays an important role as mediator or catalyst in organic syntheses. For example, Stavber and Zupan demonstrated that **1** was the effective mediator for direct iodination of arenes and ketones using iodine with **1** where only one-half equivalent each of I_2 and **1** was necessary for this task.[3] On the other hand, due to the very useful oxidizing properties of hypervalent iodine(III), exemplified by iodine(III) difluoride and diacetate and Koser's salt, it has attracted surging interest in organic synthesis.[4] Although aryl iodine(III) difluoride has been considered for use as a fluorinating reagent, this application was usually limited by its synthesis and storage difficulties. Previously, the iodine(III) difluoride compounds were prepared by one-step procedures that involved elemental fluorine (at −100 °C),[5] SF_4,[6] XeF_2,[7] or an electrochemical process,[8] as well as some recently improved routes involving multiple-step protocols (Scheme 1).[9]

(1) (a) Olah, G. A.; Chambers, R. D.; Prakash, G. K. S. *Synthetic Fluorine Chemistry*; John Wiley: New York, 1992. (b) Hudlicky, M.; Pavlath, A. E.; *Chemistry of Organic Fluorine Compounds II*; American Chemical Society: Washington, DC, 1995. (c) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell Publishing: Oxford, 2004.

(2) (a) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31−44. (b) Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2004**, *44*, 192−212. (c) Stavber, S.; Zupan, M. *Acta Chim. Slov.* **2005**, *52*, 13−26.

(3) (a) Zupan, M.; Iskra, J.; Stavber, S. *Tetrahedron Lett.* **1997**, *38*, 6305−6306. (b) Stavber, S.; Kralj, P.; Zupan, M. *Synlett* **2002**, 598−600. (c) Stavber, S.; Kralj, P.; Zupan, M. *Synthesis* **2002**, 1513−1518. (d) Stavber, S.; Jereb, M.; Zupan, M. *Chem. Commun.* **2002**, 488−489.

(4) (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523−2584. (b) Wirth, T. *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis*; Springer-Verlag: Berlin, 2003. (c) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893−2903. (d) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656−3665.

(5) Naumann, D.; Ruther, G. *J. Fluorine Chem.* **1980**, *15*, 213−222.

(6) Lyalin, V. V.; Orda, V. V.; Alekseeva, L. A. *Zh. Org. Khim.* **1970**, *6*, 329−332. CAN 72, 110915.

(7) (a) Zupan, M.; Pollak, A. *Chem. Commun.* **1975**, 715−716. (b) Zupan, M. *Collect. Czech. Chem. Commun.* **1977**, *42*, 266−274.

(8) Hara, S.; Hatakeyama, T.; Chen, S. Q.; Ishi-I, K.; Yoshida, M.; Sawaguchi, M.; Fukuhara, T.; Yoneda, N. *J. Fluorine Chem.* **1998**, *87*, 185−192.

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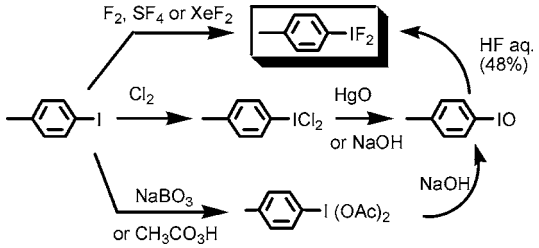
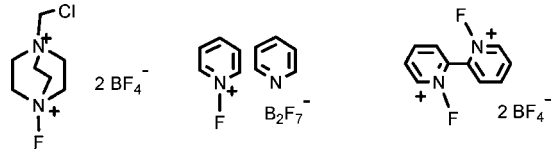
Scheme 1



Herein, we report a facile and straightforward synthesis of hypervalent iodine(III) reagents using Selectfluor.

Selectfluor (**1**), Accufluor NFPY (**2**), and MEC-31 (**3**) are very common electrophilic reagents of choice, but there are no reports on the reactions of such fluorinating reagents with aryl iodides[10] (Scheme 2).

Scheme 2

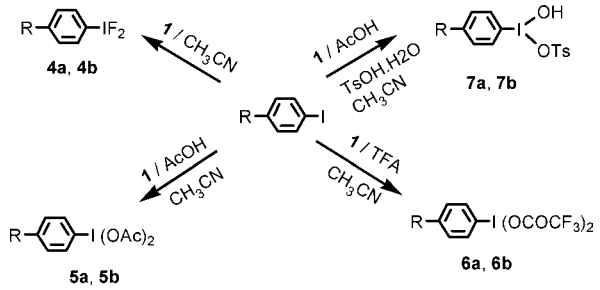


As a matter of fact, the reaction of 2 equiv of Selectfluor (**1**) with iodobenzene or 4-iodotoluene led to the facile and quantitative syntheses of hypervalent aryl iodine difluorides (**4a**, **4b**) as determined by NMR spectra in CD_3CN. The isolated yield, however, can be low (ca. 30%) due to the intrinsic instability of iodine(III) difluoride compounds. This can be greatly improved by the addition of trace amounts of $Et_3N{\cdot}3HF$ before workup, as the presence of HF may stabilize the aryl iodine(III) difluoride. Excess quantities of Selectfluor did not lead to fluorination of the phenyl ring. The reactions of other fluorinating reagents under the same conditions, e.g., Accufluor NFPY and MEC-31, with iodoarenes did not produce hypervalent iodine difluoride compounds.

When CH_3CN/AcOH or CH_3CN/trifluoroacetic acid (TFA) was used as a solvent, the corresponding aryl iodine(III) diacetate or di(trifluoroacetate) was the sole product. Moreover, when the solvent of CH_3CN/AcOH contains another equivalent of $TsOH{\cdot}H_2O$, the products of Koser's salt (**7a**, **7b**) precipitated from the solution in good yield and high purity (Scheme 3).

On the basis of Stavber and Zupan's endeavor devoted to the syntheses of iodoarenes mediated by **1**,[3] we found that when the stoichiometry of **1** used in the reaction was increased to 2.5 equiv, the aryl-IF_2 or -$I(OAc)_2$ could be easily obtained under the given conditions. As shown in

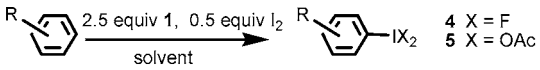
Scheme 3

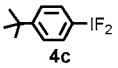
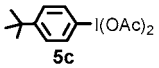
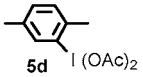
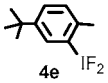
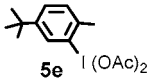
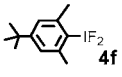
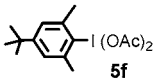
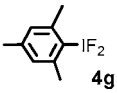
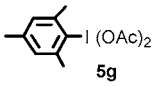


a: R = H; b: R = Me

Table 1, good regioselectivity and yields were achieved for

Table 1. One-Pot Synthesis of Aryl-IF_2 or -$I(OAc)_2$ from Arene[a]



Substrate	4	Yield (%)	5	Yield (%)
	 **4c**	71	 **5c**	-[b]
	 **4d**	74	 **5d**	86
	 **4e**	64	 **5e**	84
	 **4f**	78	 **5f**	89
	 **4g**	83	 **5g**	91

[a] For **4**, solvent = CH_3CN. For **5**, solvent = CH_3CN (AcOH). [b] Impure.

mono-, di-, and tri-substituted benzenes.

It is noteworthy that this is the first report of straightforward synthesis of hypervalent iodine(III) difluoride and diacetate from arene and elemental iodine, while the previous methods start from the corresponding iodoarene. Furthermore, this method is fairly mild and easy to handle; no special precautions or equipment were needed.

Iodine(III) compounds have been widely used as oxidants or catalysts for organic transformations. For the ease of the recycling of iodoarene, polymers[7,11] or ionic liquid-supported[12] hypervalent iodine(III) reagents continue to be of

(10) (a) Lal, G. S. *J. Org. Chem.* **1993**, *58*, 2791−2796. (b) Syvret, R. G.; Butt, K. M.; Nguyen, T. P.; Bulleck, V. L.; Rieth, R. D. *J. Org. Chem.* **2002**, *67*, 4487−4493.

(11) Tohma, H.; Takizawa, S.; Maegawa, T.; Kita, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 1306−1308.

(12) (a) Qian, W.; Jin, E.; bao, W.; Zhang, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 2−5. (b) Handy, S. T.; Okello, M. *J. Org. Chem.* **2005**, *70*, 2874−2877.

considerable interest. Our protocol also proceeds smoothly for direct synthesis of polymer-supported iodine(III) diacetate, with nearly one-third of the phenyl rings of the copolymer being loaded with $I(OAc)_2$ based on elemental analysis.[13]

Solid-State Structures of 4b, 4f. There are only three reported single-crystal structures of hypervalent RIF_2 species. Compound **4b** is the most common aryl-IF_2 reagent, and the original report of its structure indicated that the I−F bond lengths were quite different (2.1 and 1.5 Å).[14] As the material is easily crystallized, we reinvestigated this structure as well as the structure of **4f**. A thermal ellipsoid plot of **4b** is shown in Figure 1a. This compound crystallizes in an orthorhombic

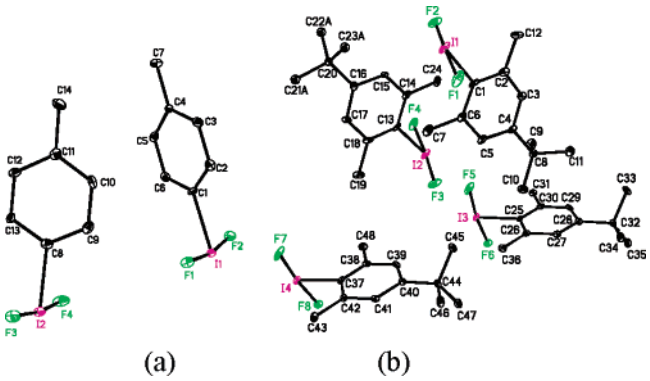


Figure 1. Thermal ellipsoid plot (30%) of (a) **4b** and (b) **4f**. Hydrogen atoms have been removed for clarity. Only one conformation of the disordered methyl group is shown in **4f**.

system, with two crystallographically independent molecules in the asymmetric unit.[15] The I−F bond lengths are approximately equal (2.025(3), 1.995(3) Å and 2.023(3), 1.992(3) Å to each independent iodine atom). These bond lengths are very similar to those in $C_6F_5IF_2$ (2.029, 1.954 Å)[16] and CF_3IF_2 (1.982(2) Å),[17] which clearly demonstrates that the structure of **4b** is not unusual as previously thought. The F−I−F array is not linear (171.0 and 174.4°) and is a result of the large space requirements of the lone pairs and intermolecular interactions (vide infra). This angle is less acute than that in CF_3IF_2 (164.5°) but similar to those in $C_6F_5IF_2$ (171.6, 170.5°). The bonded fluorine atoms are apical, and the distorted equatorial plane consists of the *ipso* arene carbon atom and two intermolecular I···F interactions (I1···F1^{i}, 3.050(3), I1···F2^{ii}, 3.101(3) Å, and I2···F3^{i}, 3.253(3), I2···F4^{ii}, 2.895(3) Å; $i = 1/2 - x, y, -1/2 + z$, ii = $1/2 - x, y, 1/2 + z$). The structure of **4f**,[18] Figure 1b, has less symmetry (triclinic, *P*-1), and has four crystallographically independent molecules in the asymmetric unit. The I−F bond lengths and angles are similar to those in **4b** (I−F av = 2.019, 1.991 Å; F−I−F = 172.5−174.4°); however, the iodine atoms are now only four coordinate with a distorted square planar geometry. There is only one intermolecular I···F interaction (I···F = 2.856(3), 2.829(3), 2.989(3), and 3.026(3) Å) per molecule. In both **4b** and **4f**, the most notable feature is the I···F supramolecular synthon. The I···F interaction is short and in **4b**, together with some extra I···F interactions (I1−F3iii, 3.389(3) Å; iii = $x, y, -1 + z$) and CH···F close contacts, generates an interesting zigzag double-chain motif (Figure 2a). In **4f**, the synthon is localized

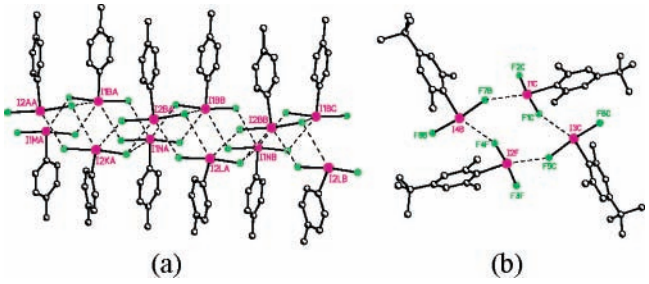


Figure 2. (a) Zigzag double-chain synthon formed via I···F intermolecular interactions in **4b**. (b) Chair conformation ring synthon in **4f**. Hydrogen atoms and some labeling omitted for clarity.

and forms an unusual eight-membered chair I−F ring (Figure 2b). There are weak CH···F contacts (ca. 2.45 Å) between these localized synthons and adjacent synthons.

Reaction Behavior of $PhIF_2$ vs Selectfluor. We also explored the reaction properties of iodobenzene difluoride prepared in situ (coded as [$PhIF_2$]) rather than the isolated pure compound ($PhIF_2$), using 1,1-diphenylethene as a model substrate. Under the conditions outlined in Scheme 4, a rearranged ketone was the major product when aqueous HF (50%), $Et_3N{\cdot}3HF$, or pyridinium polyhydrogen fluoride (PPHF)[19] was employed as a catalyst for [$PhIF_2$] (conditions a). The typical rearranged product, 1,1-difluoro-1,2-diphenylethane,[7] was only observed when $PhIF_2$/PPHF was used (conditions c), indicating that the side-product of Selectfluor, which would be present when $PhIF_2$ is not purified, may interfere with the rearrangement reaction. In sharp contrast,

(13) ACROS, Polystyrene: 2% divinylbenzene copolymer beads, 200−400 mesh. A 0.1 g amount of this copolymer was treated with I_2 (1 mmol) and Selectfluor (5 mmol) in acetonitrile for 24 h, filtered, and washed with acetic acid and acetonitrile, 0.19 g. Elemental analysis: C, 50.44; H, 4.62; I, 24.46. Nearly one-third of the phenyl rings were loaded with -$I(OAc)_2$ based on iodine content.

(14) Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505−519.

(15) Crystal data for **4b**: $C_7H_7F_2I$, MW = 256.03, orthorhombic, *Pca*2(1), T = 87(2) K, Bruker SMART APEX, Mo Kα, λ = 0.71073 Å, a = 17.9460(7) Å, b = 11.4823(5) Å, c = 7.3257(3) Å, V = 1509.54(11) Å^3, Z = 8, size 0.33 × 0.12 × 0.06 mm^3, ρ_{calcd} = 2.253 Mg/m^3, μ = 4.196 mm^{-1}, reflections collected/unique 23 053/2737, R(int) = 0.0291, R_1 = 0.0228, wR_2 = 0.0568 ($I > 2\sigma I$), GOF = 1.057.

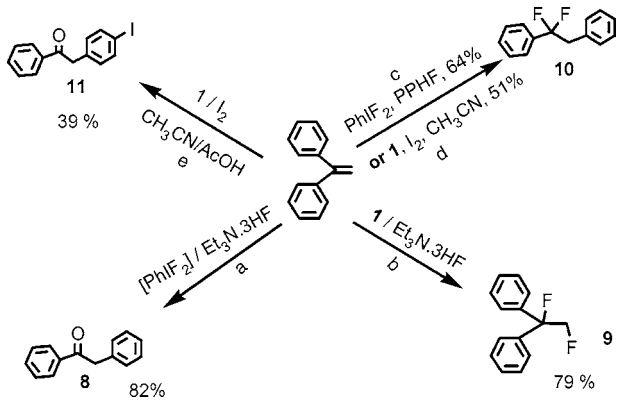
(16) Bailly, F.; Barthen, P.; Breuer, W.; Frohn, H.-J.; Giesen, M.; Helber, J.; Henkel, G.; Priwitzer, A. *Z. Anorg. Allg. Chem.* **2002**, *626*, 1406−1413.

(17) Minkwitz, R.; Berkei, M. *Inorg. Chem.* **1998**, *37*, 5247−5250.

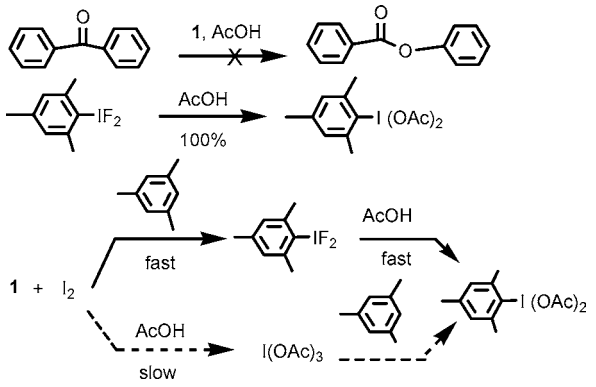
(18) Crystal data for **4f**: $C_{12}H_{17}F_2I$, MW = 326.16, triclinic, space group *P*-1, T = 87(2) K, Bruker SMART APEX, Mo Kα, λ = 0.71073 Å, a = 11.5263(7) Å, b = 12.7649(8) Å, c = 17.7467(11) Å, α = 76.027 (1)°, β = 81.454 (1)°, γ = 88.146 (1)°, V = 2505.7(3) Å^3, Z = 8, size = 0.42 × 0.24 × 0.11 mm^3, ρ_{calcd} = 1.729 Mg/m^3, μ = 2.548 mm^{-1}, reflections collected/unique 38 176/9078, R(int) = 0.0319, R_1 = 0.0485, wR_2 = 0.1269 ($I > 2\sigma I$); GOF = 1.032.

(19) Reddy, V. P.; Alleti, R.; Perambuduru, M. K.; Welz-Biermann, U.; Buchholz, H.; Prakash, G. K. S. *Chem. Commun.* **2005**, 654−656.

Scheme 4



Scheme 5



Selectfluor (in the absence of any iodine(III) moiety) gives the *vic*-difluorinated compound (conditions b). In other words, 1 equiv of iodobenzene changes the reaction behavior of Selectfluor.

Interestingly, when 1,1-diphenylethene was directly treated with Selectfluor and I_2 in acetonitrile (conditions d) without addition of arene to produce aryl-IF_2, the desired rearranged *gem*-difluorinated species can readily form. Thus, the tedious procedure of recycling of iodoarene under conditions c and preparation of XeF_2[20] were circumvented. Moreover, when the solvent contained acetic acid (conditions e), the product became very complex, in which 39% of the rearranged iodinated ketone (**11**)[21] was identified. Expansion of this method to other olefins is underway.

Mechanism Considerations. There are two plausible intermediates for aryl iodine(III) diacetate from reaction of **1** and iodoarene: (i) peroxyacetic acid formed in situ by reaction of **1** and AcOH or (ii) aryl iodine(III) difluoride. Under the same conditions, no Baeyer−Villiger products were detected by GC-MS for the diphenyl ketone, which indicates that peroxyacetic acid was not produced in situ. However, when treated with acetic acid, mesityl-IF_2 was quickly converted quantitatively into its diacetate. This result suggests that aryl-IF_2 may be the effective intermediate.

When elemental iodine is used for the direct formation of aryl iodine(III) diacetate (conditions in Table 1), $I(OAc)_3$ may also be an intermediate besides aryl-IF_2. Actually, I_2 could slowly be consumed just in the presence of 3 equiv of **1** in CH_3CN/AcOH. However, in our hands, reaction of $I(OAc)_3$[22] only with electron-rich arene was able to afford the corresponding aryl-$I(OAc)_2$ (**5f**, **5g**) in good yield; for **5c**−**e**, yields were very low. In addition, considering that the formation of $I(OAc)_3$ mediated by Selectfluor is a slow process, the aryl iodine(III) difluoride rather than $I(OAc)_3$ may be the intermediate in this case.

In conclusion, use of Selectfluor allows hypervalent iodine(III) species such as aryl iodine difluoride, diacetate, and di(trifluoroacetate) and Koser's salt to be easily prepared, and the former two iodine(III) reagents can be prepared from the corresponding arene and I_2 in one-pot procedures.

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Supporting Information Available: Experimental section and characterization data, ^1H NMR spectra for all compounds, as well as CIF files for crystal structures **4b**, **4f**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051446T

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(21) Futami, Y.; Nishino, H.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3182−3186.

(22) $I(OAc)_3$ is extremely sensitive to moisure and was prepared as described by: Birchall, T.; Frampton, C. S.; Kapoor, P. *Inorg. Chem.* **1989**, *28*, 636−639.