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Metathesis

Iodonium Metathesis Reactions**

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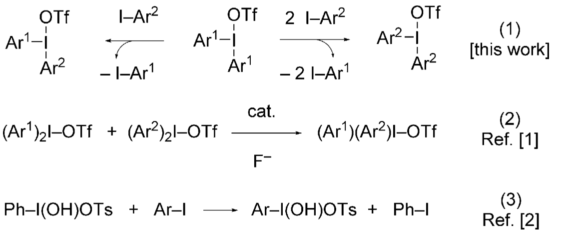
Dedicated to Dr. James Trotter

Abstract: *A metathesis reaction occurs when a diaryliodonium triflate is heated with an aryl iodide, resulting in the formation of a new diaryliodonium triflate.*

We describe a thermally induced, metal-free metathesis reaction between diaryliodonium triflates and certain aryl iodides according to Equation (1) (Scheme 1). Whereas DiMagno observed fluoride-catalyzed aryl–ligand exchange between diaryliodonium species [Eq. (2)][1] and Koser reported oxygen–ligand exchange between PhI(OH)OTf and aryl iodides [Eq. (3)],[2] the chemistry of Equation (1) appears to be undocumented.



Scheme 1. Iodonium metathesis reactions.

Diaryliodonium species are carriers of electrophilic aryl synthons, hence they arylate a diversity of nucleophiles,[3] even very weak ones.[4] For that reason, they are of significant interest in organic chemistry.[5] On the other hand, Yamamoto and co-workers have shown that organic iodides possess appreciable I-nucleophilicity.[6] This raises the question of whether diaryliodonium agents might be able to I-arylate aryl iodides, i.e., whether an iodonium metathesis reaction might be possible. The ability to prepare diaryliodonium complexes by this method would have a favorable impact on organic, materials, and medicinal chemistry;[3–5] however, the prognosis for the feasibility of the transformation seemed poor. For instance, Olofsson and co-workers, detected no aryl group exchange between bis(4-tolyl)iodonium triflate and 2,6-dimethyl-iodobenzene upon heating in DMF.[7]

In contrast with the foregoing, we found that 4-iodotoluene, 4-iodoanisole, and 1-iodonaphthalene displace PhI from Ph_2IOTf, leading to mixtures of products of mono- and bis-substitution. With low-melting[8] aryl iodides, the reaction may be induced by melting a mixture of the reactants.[9] However, incomplete consumption of Ph_2IOTf was consistently observed under these conditions. Generally better results were obtained by operating in 1,2-dichloroethane (DCE) solution, in which case most of the starting Ph_2IOTf was consumed (Table 1). The solution protocol is thus the method of choice. Interestingly, such metathesis reactions failed in donor solvents such as $(CF_3)_2CHOH$, MeCN, dimethylformamide (DMF), or dimethyl sulfoxide (DMSO). This stands in contrast with DiMagno's report that the chemistry of Equation (2) takes place in MeCN solution,[1] but it is consistent with Olofsson's observation that no aryl group exchange between diaryliodonium triflates and aryl iodides occurs in DMF.[7] A rationale for all this follows from a possible mechanism for the metathesis reaction proposed herein.

Table 1: Solution metathesis reactions of Ph_2IOTf.

$$\underset{\mathbf{1}}{Ph_2I\text{–}OTf} + \underset{\mathbf{2}}{Ar'\text{–}I} \xrightarrow{\text{conds.}^{[a]}} \underset{\mathbf{3}}{Ar'(Ph)I\text{–}OTf} + \underset{\mathbf{4}}{(Ar')_2I\text{–}OTf}$$

Entry	Ar′	t [h]	Ratio **3**:**4**:**1**[b]	Yield[c]
a	4-Me-C_6H_4	24	9.8:28.5:1.0	48
b	4-MeO-C_6H_4	25	27.3:23.1:1.0	78
c	1-naphthyl	26	2.0:1.0:0.0	14

[a] Conditions: 0.2 M solution of Ph_2IOTf in $(CH_2Cl)_2$, 5 equiv aryl iodide, thick-walled glass tube sealed with a Teflon screwcap and immersed in an oil bath kept at 120–125 °C. [b] Molar ratios calculated by the integration of ^1H NMR spectra. [c] Percent yield after silica gel column chromatography (gradient 10→40% acetone–CH_2Cl_2) to remove non-polar byproducts. The stated value is the sum of the yields of individual compounds present in the product mixture. A comparison of ^1H NMR spectra of crude and purified reaction mixtures indicated that insignificant changes in the ratio of iodonium triflate products had occurred upon chromatography.

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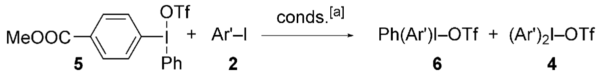
As seen in Table 1, the reaction tends to afford mixtures of products. In an effort to improve the selectivity, we examined the metathesis chemistry of mixed iodonium triflates, in which one of the aryl ligands is electron-poor and the other electron-rich.[10] Such species react with common nucleophiles by what appears to be an S_NAr mechanism, resulting in the transfer of the more electron-deficient aryl group[11]—at least in the absence of transition metal catalysts.[12] Improved aryl group transfer selectivity might be obtained if such a preference were maintained in the context of the metathesis reaction.

The foregoing complexes did react selectively, but, contrary to expectations, they preferentially transferred the more electron-rich group to 1-iodonaphthalene, 4-I-C_6H_4Me, 4-I-C_6H_4OMe, and Ph-I (Tables 2 and 3), indicating that the metathesis reaction is unlikely to proceed by an S_NAr mechanism.[13] On the other hand, thienyliodonium triflate **8** transferred the 4-MeOOCC_6H_4 group selectively (Table 4), leading to mixtures of products **9** and **4**, but only traces of **10**.

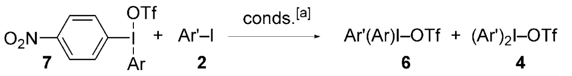
Table 2: Metathesis reactions of iodonium triflate **5**.



Entry	Ar′	t [h]	Ratio **6**:**4**:**5**:(other)[b]	Yield[c]
a	Ph	15	13.9[d] : 1.0 : (–)[e]	51
b	4-MeC_6H_4	15	6.0 : 35.7 : 1.0 : (–)[e]	59
c	4-MeOC_6H_4	15	2.3 : 2.2 : 1.0 : (–)[f]	80
d	1-naphthyl	24	6.6 : 1.8 : 1.0 : (–)[e]	35

[a], [b], [c] Same as for Table 1. [d] Compounds **7** and **4** are identical in this case. [e] Other products—if at all detectable—were present in insignificant amounts. [f] A trace amount of Ph_2IOTf, too small to be measured accurately and perhaps arising as described in Ref. [1], was apparent by ^1H NMR and MS.

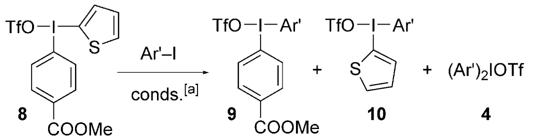
Table 3: Metathesis reactions of iodonium triflates **7**.



Entry	Ar	Ar′	Ratio **6**:**4**:**7**:(other)[b]	Yield[c]
a[d]	Ph	Ph	12.9[e] : 1.0 : (–)[f]	65
b[d]	Ph	4-MeC_6H_4	1.0 : 1.3 : 0.0 : (–)[f]	73
c[d]	Ph	4-MeOC_6H_4	60.1 : 35.1 : 1.0 : (–)[f]	76
d[d]	Ph	1-naphthyl	33.3 : 5.9 : 1.0 : (–)[f]	59
e[d]	4-MeOC_6H_4	Ph	11.5 : 8.2 : 1.0 : (1.0)[g]	60
f[d]	4-MeOC_6H_4	4-MeC_6H_4	1.3 : 1.0 : 0.0 : (–)[f]	79
g[d]	4-MeOC_6H_4	4-MeOC_6H_4	6.9[e] : 1.0 : (–)[f]	89
h[d]	4-MeOC_6H_4	1-naphthyl	8.4 : 1.2 : 1.2 : (1.0 + 0.6)[h]	64
i[d]	mesityl	4-MeC_6H_4	1.0 : 7.0 : 0.0 : (–)[f]	26
j[d]	mesityl	4-MeOC_6H_4	1.0 : 13.0 : 0.0 : (–)[f]	37
k[d]	mesityl	1-naphthyl	1.0 : 8.4 : 8.4 : (–)[i]	27

[a], [b], [c] Same as in Table 1. [d] Reaction time: 12 h. [e] Compounds **7** and **4** are identical in this case. [f] Other products—if at all detectable—were present in insignificant amounts. [g] This other product was bis(4-anisyl)iodonium triflate (^1H NMR, MS), perhaps arising as described in Ref. [1]. [h] The major other product was 1-naphthyl-4-nitrophenyl-iodonium triflate; the minor other product was bis(4-anisyl)iodonium triflate (^1H NMR, MS). [i] A trace amount of 1-naphthyl-4-nitrophenyl-iodonium triflate, too small to be measured accurately, was apparent by ^1H NMR and MS.

Table 4: Metathesis reactions of thienyliodonium triflate **8**.



Entry	Ar′	Ratio **9**:**10**:**4**:**8**:(other)[b]	Yield[c]
a[d]	Ph	1.0 : trace : 15.1 : 0.0 : (–)[e]	40
b[d]	4-MeC_6H_4	1.0 : trace : 7.0 : 0.0 : (–)[e]	66
c[d]	4-MeOC_6H_4	1.3 : trace : 1.0 : trace : (–)[e]	91
d[d]	1-naphthyl	1.0 : trace : 4.1 : trace : (–)[e]	38

[a], [b], [c] Same as in Table 1. [d] reaction time: 12 h. [e] Other products—if at all detectable—were present in insignificant amounts.

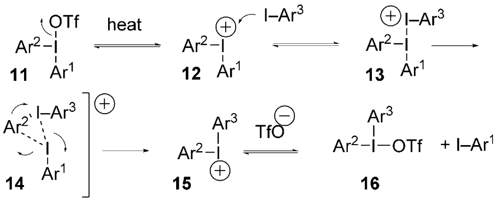
In light of precedent,[11] Coenen and co-workers, who also observed the preferential expulsion of 2-iodothiophene in S_NAr reactions of mixed 2-thienyliodonium salts,[14] ascribed this selectivity to the electron-rich character of the thienyl group. In the present case, such an explanation would be untenable, given the results of Tables 2 and 3. A more satisfactory rationale for aryl group transfer selectivity in iodonium metathesis emerged from a computational estimation of the fractional positive charge on the I atom of various aryl iodides (Table 5). Halides at the top of the list exhibit a smaller (+)-charge on the I atom, and may thus be expected to be better I-nucleophiles than those at the bottom of the table, for which, increased I-(+)-charge translates into greater nucleofugality. A diaryliodonium triflate based on an aryl iodide with a greater extent of (+)-charge on the I atom is likely to be destabilized relative to one centered on a less I-positive iodide, because the I atom must acquire additional (+)-character in the hypervalent state.[17] Such an accumulation of (+)-charge on an already positive I atom is surely energetically unfavorable. Therefore, iodonium metathesis occurs so that the extent of (+)-charge on the hypervalent I atom decreases; i.e., so that a more I-nucleophilic iodide displaces a less I-nucleophilic one. Table 5 seems to rationalize the formation of mixtures in reactions of Ph_2IOTf with 4-I-C_6H_4Me, 4-I-C_6H_4OMe, and 1-iodonaphthalene, given the similar charges on the I atom of nucleophiles and nucleofuge

Table 5: Calculated charge on the I atom of various aryl iodides.

substance	charge on the I atom[a]	
4-iodotoluene	+0.068	I-nucleophilicity
iodobenzene	+0.068	
1-iodonaphthalene	+0.070	↑
4-iodoanisole	+0.071	
4-bromo-1-iodobenzene	+0.088	
methyl 4-iodobenzoate	+0.093	
2-chloro-5-iodopyridine	+0.120	
4-nitro-1-iodobenzene	+0.120	
5-iodo-1-methyluracil	+0.162	↓
2-iodothiophene	+0.166	I-nucleofugality

[a] Geometric mean (Ref. [15]) of values (units of electron charge, e) calculated by MNDO, MNDO-d, AM1 and PM3 after geometry optimization (Ref. [16]).

(PhI). The selective transfer of the 4-MeOOCC$_6$H$_4$ group from **5** is consistent with the greater extent of (+)-charge on the I atom of 2-iodothiophene (better nucleofuge) relative to methyl 4-iodobenzoate. Finally, the fact that no metathesis occurred between Ph$_2$IOTf and 5-iodouridine triacetate,[18,19] 2-chloro-5-iodopyridine, or 4-Br-C$_6$H$_4$-I may be ascribed to the unfavorable change in (+)-charge on the hypervalent I atom that would be incurred during the reaction.[20] On the basis of the foregoing, a possible mechanism for the iodonium metathesis reaction may be ventured as outlined in Scheme 2.



Scheme 2. Mechanistic hypothesis for the iodonium metathesis reaction.

Reversible dissociation of the starting complex **11** and addition of a nucleophilic aryl iodide to the iodonium ion **12** yields **13**. The latter would form only in polar, nonnucleophilic media such as DCE: donor solvents (DMF, MeCN, etc.), surely more nucleophilic than aryl iodides, would outcompete Ar^{3}I for **12**, thus retarding/suppressing metathesis. Kinetically faster expulsion of the more nucleofugal aryl iodide from **13**, perhaps via transition state **14**,[7] leads to the iodonium ion **15**, which then combines with TfO$^-$ to give the final **16**.

In summary, iodonium metathesis reactions are feasible. This engenders numerous opportunities that are actively being researched. Pertinent results will be disclosed in due time.

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[2] G. F. Koser, R. H. Wettach, *J. Org. Chem.* **1980**, *45*, 1542.

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[7] J. Malmgren, S. Santoro, N. Jalalian, F. Himo, B. Olofsson, *Chem. Eur. J.* **2013**, *19*, 10334. See especially p. 10337.

[8] The aryl iodide should melt below ca. 120°C: most diaryliodonium triflates are stable at or below this temperature: a) K. M. Lancer, G. H. Wiegard, *J. Org. Chem.* **1976**, *41*, 3360; b) W. E. McEwen, J. W. DeMassa, *Heteroatom Chem.* **1996**, *7*, 349.

[9] Two examples are provided as Supporting Information.

[10] The diaryliodonium triflates employed in this study were prepared as described by: M. Bielawski, M. Zhu, B. Olofsson, *Adv. Synth. Catal.* **2007**, *349*, 2610, and recrystallized before use (see the Supporting Information for details).

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[12] Ref. [3] as well as: N. R. Deprez, M. S. Sanford, *Inorg. Chem.* **2007**, *46*, 1924.

[13] Diaryliodonium species with two electron-rich aryls were less reactive. Thus, the reaction of bis(4-anisyl)iodonium triflate with 4-iodotoluene went to only 65% conversion after 16 h to give a 1.6:2.0:1.0 mixture of starting complex, 4-anisyl-4-tolyliodonium triflate, and bis-4-tolyliodonium triflate. Therefore, no further work was done with such electron-rich complexes.

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[15] The geometric mean better reflects the "true" value (the actual (+)-charge on the I atom) toward which a set of numbers (calculated charges) tend: P. J. Fleming, J. J. Wallace, *Commun. ACM* **1986**, *29*, 218.

[16] MNDO, MNDO-d, AM1, PM3 as provided in the Hyperchem package.

[17] This finds support in semiempirical calculations (see the Supporting Information), which, however, tend to be imprecise for hypervalent halogen compounds (e.g. J. J. P. Stewart, *J. Comput. Chem.* **1989**, *10*, 221). Calculated values should only be taken for reflecting a trend.

[18] The significance of this reaction derives from the fact that aryl(5-uridinyl)iodonium complexes are precursors of 5-^{18}F-uridine, which is of considerable interest in PET imaging: Ref. [14] as well as M. S. Yusubov, D. V. Svitich, M. S. Larkina, V. V. Zhdankin, *ARKIVOC* **2013**, 364.

[19] Iodouridine triacetate was computationally modeled with the structurally simpler 5-iodo-1-methyluracil.

[20] Metathesis also failed with highly electron-rich aryl iodides such as 4-iodoveratrole, *N*-(4-iodophenyl)phthalimide, and *N,N*-dimethyl-4-iodo-aniline, which upon contact with diaryliodonium complexes developed blue-green colors and yielded intractable mixtures of products, perhaps due to the occurrence of competing single-electron transfer (SET) processes.