One-Pot Regioselective Synthesis of Chromanyl(phenyl)- λ^3 -iodanes: Tandem Oxidative Cyclization and λ^3 -lodanation of 3-Phenylpropanols

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ABSTRACT



Reaction of 3-phenylpropanol with an activated iodosylbenzene–18-crown-6 complex [Phl(OH)BF₄–18C6] in dichloromethane in the presence of BF₃–Et₂O afforded directly the 6-chromanyl(phenyl)- λ^3 -iodane–18C6 complex through tandem oxidative intramolecular cyclization yielding chroman and its regioselective phenyl- λ^3 -iodanation.

Diaryl- λ^3 -iodanes are versatile arylation agents in organic synthesis.¹ Because of their highly electron-deficient nature and the hyperleaving group ability of aryl- λ^3 -iodanyl groups,² they serve as highly activated species of aryl halides in nucleophilic aromatic substitution reactions and undergo transfer of the aryl group to a variety of organic substrates including carbon, nitrogen, phosphorus, and group 16 element-centered nucleophiles under mild conditions. They are also viable alternatives to aryl halides for copper- and palladium-catalyzed cross-coupling reactions with amines, alkenes, terminal alkynes, organoboranes, silanes, and stannanes.³ 2-(Trimethylsilyl)-phenyl- λ^3 -iodanes serve as useful progenitors for the quantitative generation of benzynes.⁴ Chromium(II)-mediated reactivity umpolung of diaryl- λ^3 iodanes was recently developed.⁵ Furthermore, some diaryliodanes are effective catalysts for the cationic and/or the free radical polymerizations and have found many practical applications as photoinitiators for polymerizations.⁶

Diaryl- λ^3 -iodanes are prepared by the reaction of arenes with iodosyl-, (diacyloxyiodo)arenes, or their derivatives in the presence of an acid catalyst.¹ Use of the activated arene with a silyl, stannyl, or boryl group makes it possible to

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synthesize diaryliodanes in an exclusively regioselective manner under mild conditions.⁷ Double ligand exchange on iodine(III) of inorganic λ^3 -iodanes such as (OI)₂SO₄, OIOTf, (RCO₂)₃I, and (NC)₂IOTf with arylsilanes and stannanes directly affords diaryliodanes.⁸ β -Chlorovinyl- and β -(triflyloxy)vinyl- λ^3 -iodanes also undergo ligand exchange on iodine(III) by the reaction with aryllithiums, yielding diaryliodanes.⁹ We report herein a direct synthesis of 6-chromanyl(phenyl)- λ^3 -iodanes from 3-phenylpropanols by the reaction with aryl- λ^3 -iodanes, which involves the oxidative intramolecular cyclization yielding chromans, followed by their regioselective phenyl- λ^3 -iodanation. Interestingly, an intermediate spirocyclohexadiene **5** favors the 1,2-shift of a carbon–carbon bond over that of a carbon–oxygen bond.

Recently, we reported a synthesis of a protonated iodosylbenzene monomer-18-crown-6 complex 1 as crystals, in which intermolecular hypervalent I(III) •••• O interactions play an essential role in the complexation¹⁰ and dramatically increase the stability of the highly labile hydroxy(phenyl)- $\lambda^3\text{-iodane}$ PhI(OH)BF4.11 The complex 1 serves as an efficient oxidant for a broad range of functional groups such as olefins, alkynes, enones, silyl enol ethers, sulfides, and phenols under mild conditions, especially in water as a solvent. Very interestingly, exposure of 3-phenyl-1-propanol (2) to the hydroxy- λ^3 -iodane complex 1 (1.2 equiv) in dichloromethane at room temperature resulted in the oxidative intramolecular cyclization yielding chroman, followed by the phenyl- λ^3 -iodanation of the aromatic ring, with formation of 6-[phenyl(tetrafluoroborato)- λ^3 -iodanyl]chroman (3) as a 2:1 complex with 18-crown-6 (18C6) albeit in a low yield (13%) (Scheme 1).^{12,13} Aryl- λ^3 -iodanes undergo oxidation of alcohols to carbonyl compounds;¹ however, in

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this reaction, formation of 3-phenylpropanal was found to be a minor process with less than 2% yield.

Use of 3 equiv of λ^3 -iodane complex 1 in refluxing dichloromethane afforded the 2:1 complex 3_2 -18C6 in 37% yield (Table 1, entry 2). A good yield of the product was

Table 1. Direct Synthesis of 6-Chromanyl(phenyl)- λ^3 -iodane **3** from Alcohol **2**^{*a*}

entry	iodane	additive (equiv)	temp (°C)	time (h)	yield (%) ^b
1	1		25	24	23^c
2	1		40	23	37^c
3	1		81	5	41^c
4	1	$BF_3-Et_2O(3)$	40	7	$51(63)^{c,e}$
5	PhIO	$Tf_2NH(3)$	40	7	38
6	PhIO	$HBF_4-Me_2O(3)$	25	5	(41)
7	PhIO	$BF_3-Et_2O(3)$	40	3	61

^{*a*} Unless otherwise noted, reactions were carried out using 3–3.1 equiv of λ^3 -iodanes in dichloromethane under Ar. ^{*b*} Isolated yields. Parentheses are ¹H NMR yields. ^{*c*} Yields of the 2:1 complex **3**₂–18C6. ^{*d*} In MeCN. ^{*e*} Diaryl- λ^3 -iodane **4** (20%) was obtained.

obtained by using a Lewis acid additive, BF_3-Et_2O , which probably increases the reactivity of λ^3 -iodane complex **1** via the coordination to the oxygen atom of the hydroxy group (entry 4). In this reaction, simple λ^3 -iodanation of the aromatic ring in **2** competes with the oxidative cyclization and afforded the byproduct diaryl- λ^3 -iodane **4** in 20% yield. Instead of the crown ether complex **1**, use of iodosylbenzene in the presence of BF_3-Et_2O (3 equiv) increased the yield of **3** to 61% (entry 7).

Figure 1 illustrates solid-state structures of the 2:1 complex 3_2-18C6 , in which two independent molecular complexes A and B exist.¹⁴ In each complex A or B, chromanyl(phenyl)- λ^3 -iodanyl groups protrude face of the 18C6, providing a perching type of host-guest relationship. The 2:1 complex A adopts a distorted trigonal bipyramidal geometry about the iodines with a phenyl group and an oxygen O5 occupying apical positions and with a chromanyl group and two oxygens

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Figure 1. ORTEP structures of the 2:1 complex 3_2-18C6 (thermal ellipsoids drawn at the 50% probability level). Left, the complex A; right, the complex B. Selected interatomic distances (Å) and angles (°): I1-C1 2.110(2); I1-C7 2.095(2); I2-C22 2.109(2); I2-C28 2.087(2); C1-I1-C7 95.04(10); C22-I2-C28 95.85(10). Symmetry operations: ¹⁾ -X + 1/2, -Y + 1/2 - 1, Z; ²⁾ -X + 1/2, -Y + 1/2, Z.

O3¹⁾ and O4¹⁾ in equatorial sites. On the other hand, the complex B shows a distorted pentagonal planar coordination around the iodines, in which each iodine atom contacts with the three adjacent oxygen atoms of 18C6, O7, O8, and O8²⁾, for I2. The I1•••O5, I2•••O7, and I2•••O8²⁾ distances (3.242-(4), 2.9669(19), and 2.9227(18) Å) are shorter than the van der Waals distance (3.50 Å),¹⁵ and all of the C1–I1•••O5, C22–I2•••O7, and C28–I2•••O8²⁾ triads are near-linear (164.51(8), 165.70(8), and 171.31(9)°). Therefore, these close contacts are indicative of the hypervalent secondary interactions, in which each oxygen atom donates an electron pair into the I–C σ^* orbital.¹⁰

Scheme 2 illustrates a reaction pathway leading to the formation of 6-chromanyl- λ^3 -iodane 3. Nucleophilic attack of 3-phenyl-1-propanol (2) at the para position to the positively charged iodine(III) of λ^3 -iodane 1, followed by internal cyclization via nucleophilic attack of the intramolecular hydroxy group, will produce the spiro-1,4-cyclohexadiene 5. On the other hand, instead of the intramolecular cyclization, simple aromatization through deprotonation gives the diaryl- λ^3 -iodane **4** regioselectively. A 1,2-shift of a carbon-carbon bond in 5 (path a) with reductive elimination of iodobenzene, evoked by the excellent nucleofugality of the phenyl- λ^3 -iodanyl group which shows a leaving group ability about 10⁶ times greater than triflate,² produces chroman (8). An alternative 1,2-shift of a carbon-oxygen bond in 5 (path b) will also afford chroman (8). In addition to these concerted ring-expanding rearrangements of 5,



intervention of a spirocyclohexadienyl cation **9** produced by a stepwise initial elimination of the phenyl- λ^3 -iodanyl group with hyperleaving group ability should be considered. Finally, phenyl- λ^3 -iodanation of chroman (**8**) with the hydroxy- λ^3 -iodane **1** would take place regioselectively at C6 yielding 6-chromanyl(phenyl)- λ^3 -iodane **3**. Use of BF₃-Et₂O (3 equiv) as an additive (entry 4) probably decreases the rate of intramolecular cyclization of a hydroxy group yielding spirocyclohexa-1,4-diene **5**, because of the decreased nucleophilicity of the hydroxy group by the coordination of the Lewis acid to the oxygen atom. Therefore, in the presence of the external BF₃-Et₂O, the direct aromatization yielding the diaryl- λ^3 -iodane **4** will compete with the tandem oxidative cyclization and λ^3 -iodanation of 3-phenyl-1-propanol (**2**) to a significant extent.

1,2-Migration of spiro-1,4-diene **5** with ring expansion was evaluated by the reaction of deuterated 3-phenylpropanol **11** with 88 and 58% deuterium contents at the ortho and benzylic positions, being prepared from dichlorocinnamic acid **10** (Scheme 3). Deuterium contents in the cyclization product **3-d** obtained were determined by ¹H NMR to be 12% at C5 and 78% at C8. These results clearly indicate a preference for the 1,2-shift of a carbon–carbon bond in spirocyclohexadiene **5-d** yielding chroman **8-da** over that of a carbon–oxygen bond affording **8-db** in a ratio of 87: 13. Stability differences between carbocations **6** and **7** will be reflected in the transition states for these 1,2-migrations of **5**.

In fact, 1-oxaspiro[4,5]deca-6,9-dien-8-one (**12**) exclusively undergoes the acid-catalyzed dienone—phenol rearrangement through a carbon—carbon bond migration and affords 6-methoxychroman (**13**) after methylation with MeI/NaOH (Scheme 4).¹⁶

Recent molecular orbital calculations of transition-state energies for the ring expansion of the spirocyclohexadienyl

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^{*a*} Parentheses are % deuterium contents. Some benzylic deuteriums were omitted for clarity.

cation **9** at ab initio (MP2/6-31G^{*}) and density functional (B3LYP/6-31G^{*}) levels show that migration of the carbon– carbon bond is favored by 24 kJ mol⁻¹ over that of the carbon–oxygen bond,¹⁷ which is in good agreement with our experimental results.¹⁸



The last step of the tandem oxidative cyclization and λ^3 iodanation of phenylpropanol **2**, i.e., introduction of the hypervalent phenyl- λ^3 -iodanyl group to chroman (**8**) at C6, was found to occur regioselectively as shown in Scheme 5. Both nitration of chroman (**8**) with 60% nitric acid¹⁹ and radical iodination with acetyl hypoiodite¹² have been shown to take place similarly at C6 and afford 6-nitro- and 6-iodochromans regioselectively.

(2-Methylphenyl)propanol 14 undergoes the tandem cyclization and λ^3 -iodanation by the reaction with iodosylbenzene and BF₃-Et₂O and afforded a 77:23 mixture of

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8-methyl- **15** and 5-methyl-6-chromanyl- λ^3 -iodane **16** in a moderate yield (Scheme 6). The structure of these λ^3 -iodanes



was determined by the conversion to the corresponding iodides **17** and **18**, through ligand exchange on iodine(III) with KI and the subsequent thermal nucleophilic aromatic substitution.²⁰ Predominant formation of the 8-methyl-6chromanyl- λ^3 -iodane **15** is compatible with a facile 1,2-shift of a carbon–carbon bond in spirocyclohexadiene **19** yielding 8-methylchroman (**20**).

In conclusion, both hydroxy- λ^3 -iodane-18-crown-6 complex **1** [PhI(OH)BF₄-18C6] and iodosylbenzene in the presence of BF₃-Et₂O serve as useful agents for tandem oxidative cyclization and λ^3 -iodanation of 3-phenylpropanols, which directly produces 6-chromanyl(phenyl)- λ^3 -iodanes with high regioselectivity.

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Supporting Information Available: Typical experimental procedures, spectral data for new compounds, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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