On the mechanism of α-phenylation of β-keto esters with diaryl-λ^3-iodanes: evidence for a non-radical pathway

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Dedicated to Professor Anastasios Varvoglis on his 65th birthday

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Abstract

Reaction of [(*o*-allyloxy)phenyl](phenyl)-λ^3-iodane with the potassium enolate of 2-(methoxycarbonyl)-1-indanone in *t*-BuOH at room temperature afforded a mixture of α-phenylation and α-(*o*-allyloxy)phenylation products in 61 and 7% yields, with no evidence for the formation of 3-substituted dihydrobenzofuran derivatives. A mechanism involving the intermediacy of aryl radicals in the α-arylation of β-keto ester enolates with diaryl-λ^3-iodanes is not compatible with the intramolecular aryl radical trapping experiments. A tandem ligand exchange-ligand coupling mechanism is proposed.

Keywords: Iodane, iodonium salt, phenylation, ligand exchange, ligand coupling

Introduction

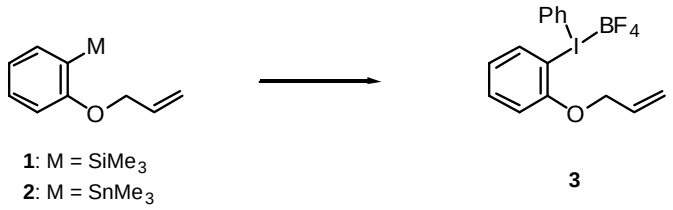
Since the first preparation of phenyl(*p*-iodophenyl)(bisulphato)-λ^3-iodane by Hartmann and Meyer in 1894, a large number of substituted and unsubstituted diaryl-λ^3-iodanes (diaryliodonium salts) have been synthesized.[1,2] They are versatile reagents in organic synthesis and act as highly reactive species in nucleophilic aromatic substitutions, which occur regioselectively at the *ipso* positions.[2] Their high reactivity is mostly due to the excellent nucleofugality of the aryl-λ^3-iodanyl group, which shows a leaving group ability about 10^6 times greater than that of triflate.[3] Diaryl-λ^3-iodanes undergo direct transfer of one of the aryl groups to enolate anions under mild conditions, yielding the α-arylated carbonyl compounds.[4] Recently we reported the asymmetric α-phenylation of cyclic β-keto esters using 1,1'-binaphthyl-2-yl(phenyl)-λ^3-iodane.[5]

Extensive studies by Beringer and his coworkers on arylation of enolate anions derived from 1,3-dicarbonyl compounds with diaryl-λ^3-iodanes suggest the involvement of aryl radicals;[4] however, the modest levels of asymmetric α-phenylation (up to 53% ee) using 1,1'-binaphthyl-2-

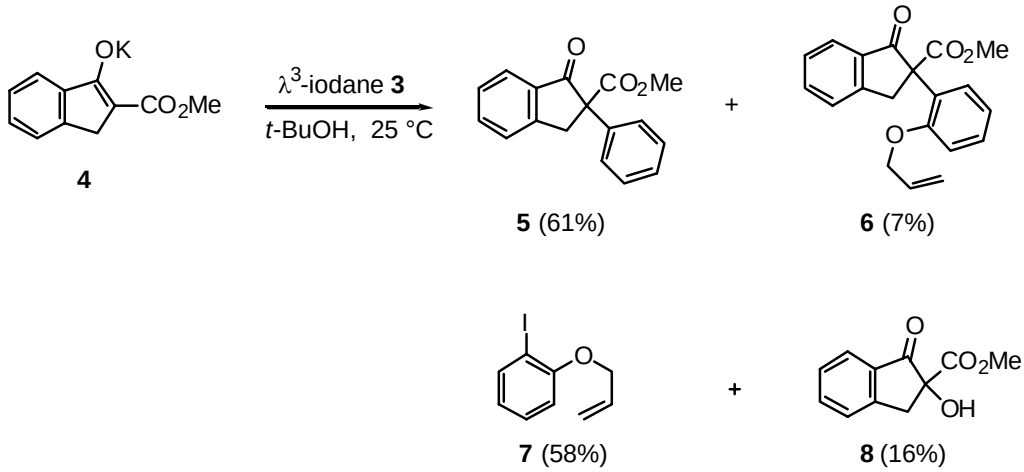
yl(phenyl)-λ^3-iodane is not compatible with a mechanism involving generation of a free phenyl radical.[5] To investigate the possibility of the involvement of a free radical process in this α-phenylation, an intramolecular aryl radical trapping experiment was carried out by using the well-established radical probe (*o*-allyloxy)phenyl radical.[6] We report herein that aryl radicals are not involved in the α-arylation of carbonyl compounds with diaryl-λ^3-iodanes.

Results and Discussion

Among the most general methods for the regioselective synthesis of organo-λ^3-iodanes is Lewis acid-catalyzed group 14 element-iodine(III) exchange.[7] Attempts at Si-I(III) exchange of (*o*-allyloxy)trimethylsilylbenzene **1** with iodosylbenzene in the presence of BF_3-Et_2O, however, did not result in formation of the desired [(*o*-allyloxy)phenyl](phenyl)-λ^3-iodane **3**, and a large amount of the silylbenzene **1** was recovered unchanged. However, use of the more reactive organostannane dramatically changed the reaction course and resulted in Sn-I(III) exchange under mild conditions. Exposure of (*o*-allyloxy)trimethylstannylbenzene **2** to iodosylbenzene (1.6 equiv) in the presence of BF_3-Et_2O (1.3 equiv) in dichloromethane at room temperature for 26 h in nitrogen afforded the (*o*-allyloxy)phenyl-λ^3-iodane **3** as colorless crystals in 70% yield (Scheme 1).

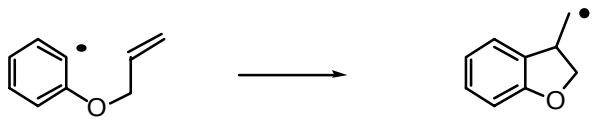


Scheme 1



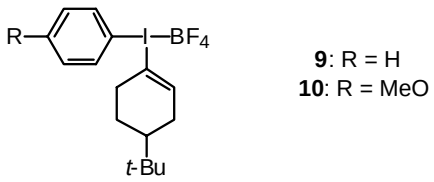
Scheme 2

With the functionalized λ^3-iodane **3** in hand, we examined the phenylation of 2-(methoxycarbonyl)-1-indanone. Exposure of (*o*-allyloxy)phenyl-λ^3-iodane **3** to the potassium enolate **4** in *t*-BuOH at room temperature for 7 days afforded a mixture of α-phenylation **5** and α-(*o*-allyloxy)phenylation products **6** in 61 and 7% yields (Scheme 2). 2-(2-Propenyloxy)iodobenzene (**7**) (58%) and 2-(methoxycarbonyl)-2-hydroxy-1-indanone (**8**) (16%) were also obtained, but no evidence for the formation of 3-substituted dihydrobenzofuran derivatives, the expected radical cyclization products according to the reaction shown in Scheme 3, was observed to the limits of ^{1}H NMR (400 MHz) detection of the crude reaction mixture.



Scheme 3

Predominant α-phenylation over α-(*o*-allyloxy)phenylation in a ratio of 9:1 is not unexpected. We have reported that, compared to the reaction of alkenyl(phenyl)-λ^3-iodane **9**, use of alkenyl-λ^3-iodane **10** with *p*-methoxyphenyl group as a carbon ligand on the iodine(III) tends to increase the selectivity for α-vinylation of 1,3-dicarbonyl compounds at the expense of the competing α-arylation.[8] Thus, the presence of an electron-releasing *para* methoxy group decelerates the nucleophilic aromatic substitution at the *ipso* position. Similar electronic effects of substituents in determining selectivity were reported in the nucleophilic *ipso* substitution of unsymmetrical diaryl-λ^3-iodanes.[2,9]

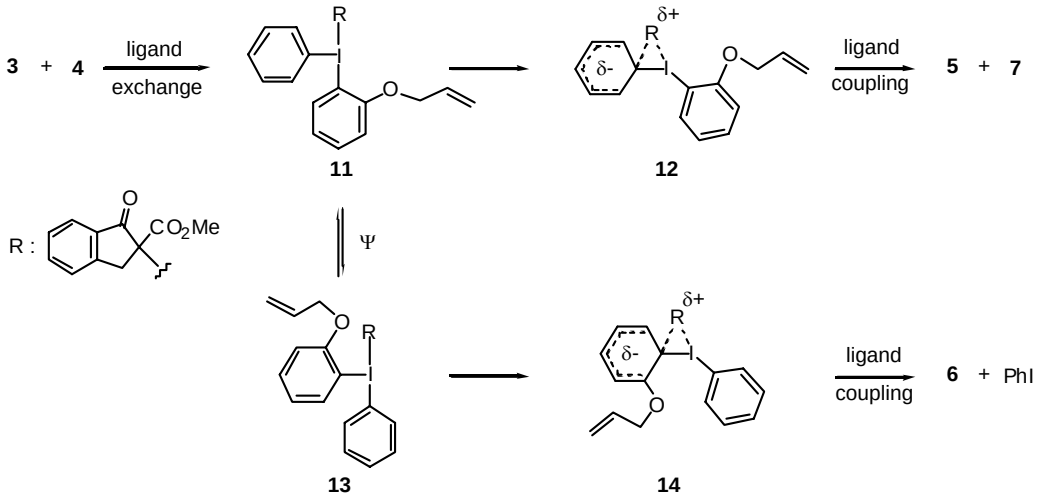


9: R = H
10: R = MeO

No formation of the radical cyclization products, dihydrobenzofurans, in the reaction of the (*o*-allyloxy)phenyl-λ^3-iodane **3** with the potassium enolate **4** appears to exclude the intermediacy of aryl free radicals in the α-arylation. This is in good agreement with Barton's spin-trapping experiments.[10] We propose that the reaction probably proceeds via an initial ligand exchange on the iodine(III) with the enolate anion, followed by a ligand coupling (Scheme 4).[8]

Ligand exchange on the iodine of λ^3-iodanes with nucleophiles is a well-established process and generally proceeds very rapidly via the intermediacy of tetracoordinated [12-I-4][11] species with a square-planar arrangement.[2] This process produces the λ^3-iodane **11**, which exists as an equilibrium mixture with **13** through rapid pseudorotation on iodine(III).[5b] Of the two possible transition states for the subsequent ligand coupling, **12** is more favorable than **14**, because both the negative charge on the aromatic ring and the enhanced positive charge on the iodine(III) are

stabilized by the substituents more effectively. These polarized transition states account for the preferred coupling of enolates with the more electron-deficient phenyl group in λ^3-iodane **3**.



Scheme 4

Experimental Section

General Procedures. For general experimental details, see ref. 3. Preparative thin-layer chromatography (TLC) was carried out on precoated plates of silica gel (Merck, silica gel F-254).

Synthesis of [2-(2-propenyloxy)phenyl](phenyl)(tetrafluoroborato)-λ^3-iodane (3). To a stirred mixture of (*o*-allyloxy)phenylstannane **2**[12] (337 mg, 1.14 mmol) and iodosylbenzene (422 mg, 1.82 mmol) in dichloromethane (15 mL) was added BF_3-Et_2O (210 mg, 1.48 mmol) at 0 ˚C in nitrogen and the mixture was stirred for 26 h at room temperature. After the addition of a saturated aqueous sodium tetrafluoroborate solution, the mixture was stirred for 30 min. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was concentrated under aspirator vacuum to give a solid residue, which was washed several times with hexane by decantation at -78 ˚C. Recrystallization from hexane-dichloromethane gave the (*o*-allyloxy)phenyliodane **3** (338 mg, 70%) as colorless crystals: mp 182-183 ˚C; IR (KBr) 1587, 1567, 1473, 1444, 1282, 1057 (br), 990, 739, 679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00 (br d, *J* = 8.5 Hz, 2H), 7.81 (br d, *J* = 8.3 Hz, 1H), 7.68-7.42 (m, 4H), 7.10-7.0 (2H), 6.03 (ddt, *J* = 17.6, 10.3, 5.4 Hz, 1H), 5.45-5.32 (m, 2H), 4.71 (br d, *J* = 5.4 Hz, 2H); FAB MS *m/z* 337 [$(M\text{-}BF_4)^+$]. Anal. Calcd for $C_{15}H_{14}BF_4IO$: C, 42.49; H, 3.33. Found: C, 42.53; H, 3.42.

Reaction of 2-(methoxycarbonyl)-1-indanone with (*o*-allyloxy)phenyl-λ^3-iodane (3). To a stirred solution of freshly sublimed potassium *tert*-butoxide (10 mg, 0.08 mmol) in *tert*-butyl alcohol (2 mL) was added 2-(methoxycarbonyl)-1-indanone (15 mg, 0.08 mmol) under nitrogen

at room temperature, and the mixture was stirred for 1 h. (*o*-Allyloxy)phenyliodane **3** (33 mg, 0.09 mmol) was added to this mixture at room temperature, and the resulting pale yellow suspension was stirred for 7 days. Water was added and the mixture was extracted with dichloromethane three times, and the combined organic phase was washed with water and brine. The solution was dried over anhydrous Na_2SO_4 and concentrated to give an oil, which was purified by preparative TLC (8:1:1 hexane-ethyl acetate-dichloromethane) to give phenylated indanone **5** (12.9 mg, 61%), (*o*-allyloxy)phenylated indanone **6** (1.7 mg, 7%), allyl ether **7** (12 mg, 58%), and hydroxy-1-indanone **8** (2.4 mg, 16%).

2-(Methoxycarbonyl)-2-phenyl-1-indanone (5).[8] colorless oil; IR ($CHCl_3$) 3020, 2965, 1740, 1720 (br), 1610, 1500, 1465, 1435, 1230 (br), 1010, 965, 910, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.84 (br d, *J* = 7.7 Hz, 1H), 7.62 (br t, *J* = 7.7 Hz, 1H), 7.57-7.18 (m, 7H), 4.24 (d, *J* = 17.3 Hz, 1H), 3.75 (s, 3H), 3.56 (d, *J* = 17.3 Hz, 1H); MS *m/z* (relative intensity) 266 (55, M^+), 238 (90), 223 (31), 207 (100), 178 (100), 89 (36), 76 (29); HRMS calcd for $C_{17}H_{14}O_3$ (M^+) 266.0942, found 266.0936. Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.47; H, 5.34.

2-(Methoxycarbonyl)-2-[2-(2-propenyloxy)phenyl]-1-indanone (6). colorless oil; IR ($CHCl_3$) 2930, 1710, 1600, 1455, 1240 (br), 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.86 (br d, *J* = 7.0 Hz, 1H), 7.63 (br t, *J* = 6.8 Hz, 1H), 7.46-7.10 (m, 4H), 6.95-6.82 (m, 2H), 5.90 (ddt, *J* = 17.0, 10.5, 5.0 Hz, 1H), 5.33 (dq, *J* = 17.0, 1.5 Hz, 1H), 5.22 (dq, *J* = 10.5, 1.5 Hz, 1H), 4.55 (dt, *J* = 5.0, 1.5 Hz, 1H), 4.52 (dt, *J* = 5.0, 1.5 Hz, 1H), 4.45 (d, *J* = 17.8 Hz, 1H), 3.71 (s, 3H), 3.21 (d, *J* = 17.8 Hz, 1H); MS *m/z* (relative intensity) 322 (11, M^+), 249 (85), 205 (39), 165 (100), 90 (23); HRMS calcd for $C_{20}H_{18}O_4$ (M^+) 322.1205, found 322.1202.

2-(2-Propenyloxy)iodobenzene (7).[13] pale brown oil; IR ($CHCl_3$) 2920, 1580, 1470, 1275, 1250, 1015, 995 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.34-7.20 (m, 1H), 6.81 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.71 (td, *J* = 7.9, 1.4 Hz, 1H), 6.07 (ddt, *J* = 17.2, 10.5, 4.9 Hz, 1H), 5.52 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.31 (dq, *J* = 10.5, 1.7 Hz, 1H), 4.60 (dt, *J* = 4.9, 1.7 Hz, 2H); MS *m/z* (relative intensity) 260 (100, M^+), 220 (14), 133 (26), 83 (59); HRMS calcd for C_9H_9OI (M^+) 259.9698, found 259.9726.

2-Hydroxy-2-(methoxycarbonyl)-1-indanone (8). colorless crystals; mp 128-129.5 ˚C (recrystallized from dichloromethane-hexane, lit.[14] mp 131-132 ˚C; IR (KBr) 3417, 1752, 1713, 1605, 1466, 1441, 1258, 1217, 1183, 1128, 955, 933 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (br d, *J* = 7.6 Hz, 1H), 7.68 (br t, *J* = 7.3 Hz, 1H), 7.52-7.40 (4H), 3.96 (s, 1H), 3.75 (s, 3H), 3.74 (d, *J* = 17.3 Hz, 1H), 3.26 (d, *J* = 17.3 Hz, 1H); MS *m/z* (relative intensity) 206 (6, M^+), 147 (9), 118 (29), 90 (95), 77 (100) , 63 (93), 51 (68).

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