# Reductive deuteration of ketones, benzhydrols, α,β–unsaturated ketones, and aryl alkenes by deuterium iodide in acetic acid

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**Abstract**

Reduction of substituted benzophenones, benzhydrols, diaryl alkenes, and benzylideneacetophenones with $D_3PO_2$ in DOAc in the presence of a small amount of iodine results in reduction to the corresponding alkanes efficiently, relatively inexpensively, and with regioselective incorporation of deuterium. Isotopic exchange results in incorporation of more than the expected amount of deuterium with the last two classes of compound.

**Keywords:** Deuterium iodide, hydrogen iodide, deuteration

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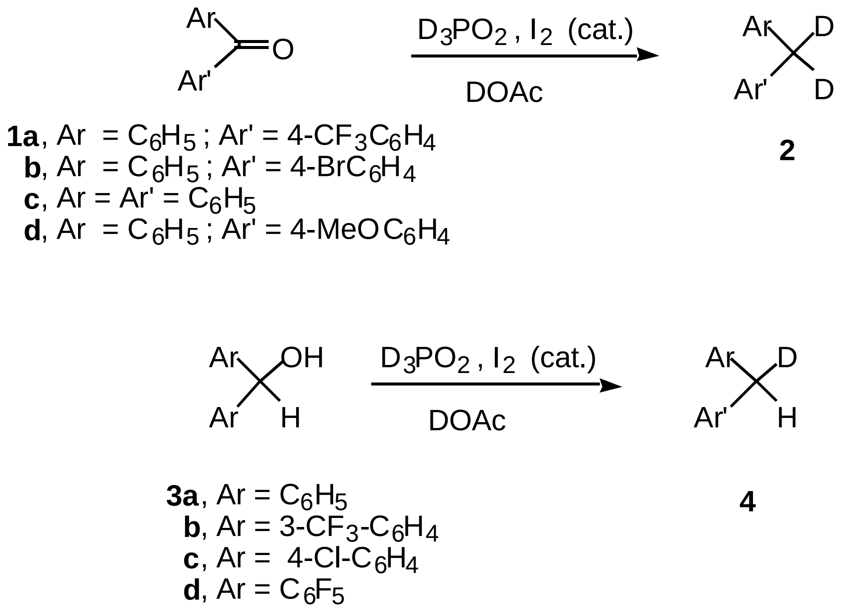
## Introduction

We have reported that substituted benzophenones[1] and benzhydrols[2] are reduced to the corresponding diarylmethanes by hydrogen iodide catalytically generated by a mixture of hypophosphorous acid ($H_3PO_2$) and iodine. We have since extended the range of substrates which are reduced efficiently by this reagent system to aryl alkenes[3,4] and α,β-unsaturated ketones.[1,5] Since $D_3PO_2$ and DOAc are commercially available, it seemed to us that this chemistry could be applied to the regioselective introduction of deuterium into organic substances. We report here the successful realization of this methodology, together with some mechanistically informative polydeuteration results with certain substrates.

## Results and Discussion

A number of organic substrates were heated in DOAc containing a small amount of iodine and excess $D_3PO_2$ in $D_2O$ (Table 1). Deuterium content was determined by mass spectrometry and, in some cases, $^1$H NMR spectroscopy. Benzophenones (**1**) and benzhydrols (**3**) complement each other nicely: reductive deuteration of **1** affords doubly deuterated diarylmethanes (**2**), whereas substrates **3** afford the corresponding monodeuterated analogs (**4**) (Scheme 1). However, reduction of benzophenones bearing electron-supplying groups on at least one ring does result in introduction of additional deuterium atoms, presumably by electrophilic exchange of protons on the aromatic ring (runs 3 and 4). Indeed, when diphenylmethane itself was subjected to the reaction conditions, it was found to have incorporated *ca.* 12% $d_1$ and 1% $d_2$ after 24 hours. Ring exchange is not observed in the reduction of benzhydrols because of the milder conditions used for reduction of these substrates,[2] but a small amount of dehalogenation to 4-chlorodiphenylmethane (**9**) did take place with the dichloro compound **3c** (run 8). 1,4-Dibenzoylbenzene (**10a**) can be reduced completely to 1,4-dibenzylbenzene (**10c**)[1] but at shorter times, a mixture is produced in which the major product is 4-benzylbenzophenone (**10b**), with clean introduction of four or two deuterium atoms, respectively (run 5). Reduction of diaryl alkenes (**5**) typically requires 24 hr at reflux (Scheme 2).[3,4] Under these more vigorous conditions, extensive and in some cases complete, exchange of protons of the starting alkene for deuterium occurs competitively with reductive dideuteration of the double bond (runs 10-12).[4] In one case, perdeuteration of a thiophene ring was observed together with alkene exchange and reduction, resulting in introduction of seven deuterium atoms (run 13).[6] Finally, chalcones **7** are reduced with predominant overall introduction of three deuterium atoms (Scheme 2); the regiochemistry was established as shown by $^1$H NMR spectroscopy.[5] Yields are not as high as with the other substrates, however. We presume that reduction adds two deuterium atoms across the double bond, and that exchange of an proton *alpha* to the carbonyl then takes place to introduce the third deuterium.[5] *Ca.* 10-20% of the product contains one proton *alpha* to the carbonyl group, indicating that this exchange is not complete under our standard reaction conditions**.** Compound **7b** exchanges further (onto the methoxy-substituted aromatic ring) under the reaction conditions to afford primarily a tetradeuterio product (run 17).



**1a**, Ar = $C_6H_5$ ; Ar' = 4-$CF_3C_6H_4$
**b**, Ar = $C_6H_5$ ; Ar' = 4-$BrC_6H_4$
**c**, Ar = Ar' = $C_6H_5$
**d**, Ar = $C_6H_5$ ; Ar' = 4-MeO$C_6H_4$

**2**

**3a**, Ar = $C_6H_5$
**b**, Ar = 3-$CF_3$-$C_6H_4$
**c**, Ar = 4-Cl-$C_6H_4$
**d**, Ar = $C_6F_5$

**4**

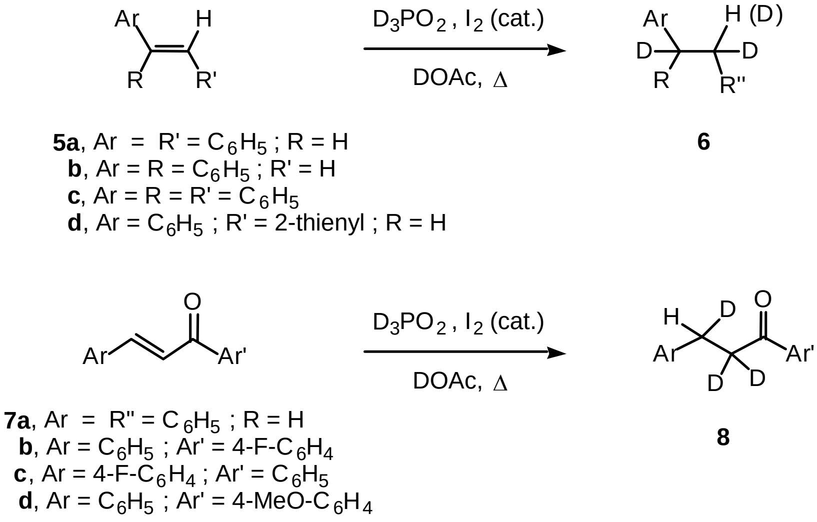
**Scheme 1**

**Table 1.** Reduction of Organic Substrates in $D_3PO_2$ /$D_2O$/DOAc

| Run | Substrate | Product | Yield (%) | Deuterium content (± 4%) |
|---|---|---|---|---|
| 1 | **1a** | **2a** | 98 | 100% $d_2$ |
| 2 | **1b** | **2b** | 95 | 100% $d_2$ |
| 3 | **1c** | **2c** | 96 | 79% $d_2$, 16% $d_3$ , 5% $d_4$ |
| 4 | **1d** | **2d** | 81 | 20% $d_2$, 20% $d_3$, 50% $d_4$, 10% $d_5$ |
|  |  | **10** | 19 | 20% $d_2$, 35% $d_3$, 45% $d_4$ |
| 5 | **10a** | **10b** | 87 | 100% $d_2$ |
|  |  | **10c** | 13 | 100% $d_4$ |
| 6 | **3a** | **4a** | 98 | 100% $d_1$ |
| 7 | **3b** | **4b** | 97 | 100% $d_1$ |
| 8 | **3c** | **4c** | 98 | 100% $d_1$ |
|  |  | **9** | 2 | 100% $d_1$ |
| 9 | **3d** | **4d** | 99 | 100% $d_1$ |
| 10 | **5a** | **6a** | 98 | 40% $d_1$, 44% $d_2$, 14% $d_3$, 1% $d_4$ |
| 11 | **5b** | **6b** | 97 | 35% $d_3$, 54% $d_4$, 11% $d_5$ |
| 12 | **5c** | **6c** | 99 | 100% $d_3$[a] |
| 13 | **5d** | **6d** | 97 | 100% $d_7$[b] |
| 14 | **7a** | **8a** | 74 | 13% $d_2$, 87% $d_3$ |
| 15 | **7b** | **8b** | 58 | 39% $d_2$, 61% $d_3$ |
| 16 | **7c** | **8c** | 92 | 17% $d_2$, 83% $d_3$ |
| 17 | **7d** | **8d** | 89 | 25% $d_3$, 75% $d_4$ |

[a] Product is 1,2,2-$d_3$-1,1,2-triphenylethane.

[b] Product is 1,1,2,2-$d_4$-1-phenyl-2-[3',4',5'-$d_3$]-thienylethane.



**5a**, Ar = R' = $C_6H_5$ ; R = H
**b**, Ar = R = $C_6H_5$ ; R' = H
**c**, Ar = R = R' = $C_6H_5$
**d**, Ar = $C_6H_5$ ; R' = 2-thienyl ; R = H

**7a**, Ar = R'' = $C_6H_5$ ; R = H
**b**, Ar = $C_6H_5$ ; Ar' = 4-F-$C_6H_4$
**c**, Ar = 4-F-$C_6H_4$ ; Ar' = $C_6H_5$
**d**, Ar = $C_6H_5$ ; Ar' = 4-MeO-$C_6H_4$

**Scheme 2**

## Experimental Section

### Representative experimental procedures

Benzalacetophenone (**7a**) (0.832 g, 4 mmol), iodine (1.016 g, 4.0 mmol), and acetic acid-d (20 mL) were stirred in a flask equipped with condenser. $D_3PO_2$ (50% $D_2O$ solution; 0.829 mL, 8.0 mmol) was added and the mixture was heated to 60 °C for 4 hr. It was then cooled, diluted with water, and extracted with ether. The ether solution was washed successively with saturated $NaHCO_3$ and $NaHSO_3$, dried over $Na_2SO_4$, and evaporated. Analysis by GC-MS showed a single constituent (**8a**) (0.630 g, 74%); $^1$H NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 2.95 (br s, benzyl H, 1H), and 3.2 (br s, $\alpha$–C$\underline{H}$CO, 0.15H), 7.1-7.9 (m, 10 H). Procedures for the reduction of substituted benzophenones[1] and benzhydrols[2] were followed except for substitution of $D_3PO_2/D_2O$ (Aldrich) and DOAc for their protio counterparts. Aryl alkenes were reduced by a procedure similar to that used for benzophenones.[5]

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## References and Notes

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6. The sequence in which the seven deuterium atoms are introduced is under investigation.