

Diiodosilane. 4.¹ Direct Reduction of Ketals and Acetals in the Presence of Unprotected Carbonyls. A Case of Inverted Chemoselectivity

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Ketals and acetals are selectively reduced by diiodosilane to iodoalkanes in preference to ketones and aldehydes. This inversion of the normal order of reactivity of the “protected” and “unprotected” carbonyls allows partial reduction of polycarbonyl compounds with unusual regio- and chemoselectivity. Thus, 8,8-(ethylenedioxy)octan-2-one, 7,7-(ethylenedioxy)octanal, 3,3-(ethylenedioxy)-androstan-17-one and 3,3-(ethylenedioxy)pregnane-11,20-dione are converted to the corresponding iodo compounds.

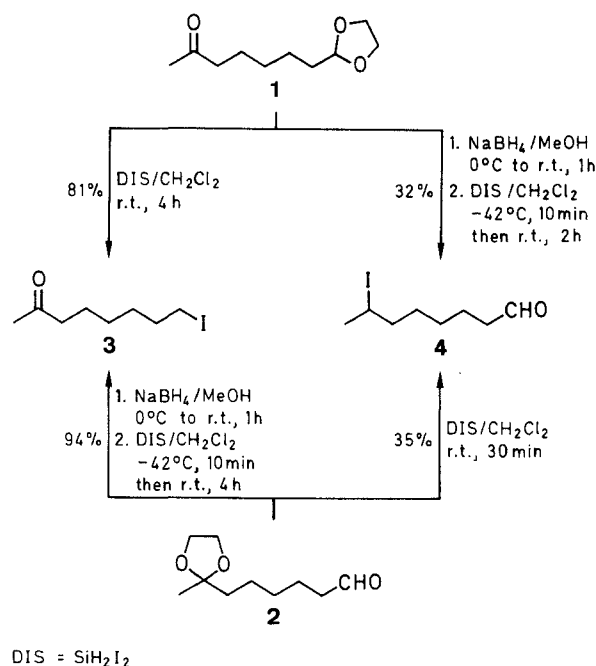
Ketals, acetals, and particularly dioxolane derivatives are the most useful and generally employed protecting groups for ketones and aldehydes. Selective masking of one carbonyl function in a molecule containing several carbonyl functionalities allows selective manipulation, e.g. reduction of the unprotected carbonyls. We report here that when using diiodosilane (SiH_2I_2 , DIS) reduction,^{3,4} the normal order of reactivity of the “protected” and “unprotected” carbonyls may be inverted. Ketals and acetals are selectively reduced by this reagent to iodoalkanes in preference to unprotected ketones and aldehydes.

We have recently studied the reaction patterns of DIS with ketals, acetals, ketones and aldehydes and found that this reagent may be used for mild cleavage of ketals and acetals either hydrolytically to give the parent carbonyl functionality or reductively to produce the corresponding iodoalkane.⁴ At low temperatures (-42°C) and short reaction times (a few minutes), catalytic amounts (5–10 mole %) of DIS provide clean deprotection of various ketals and acetals to yield ketones and aldehydes, with no apparent reduction of these products. Nevertheless, at temperatures above 0°C , DIS effectively reduces ketals and acetals to iodoalkanes.

Although this reduction is quite general with respect to ketals and acetals as well as unprotected ketones and aldehydes, reaction rates are strikingly dependent on the substrate. For example, at room temperature ketals and acetals are rapidly reduced to iodoalkanes, while free aldehydes, and particularly ketones, react very sluggishly. These observations suggest that a polyfunctional molecule containing both free and protected carbonyl functionalities could react preferentially at the protected site.

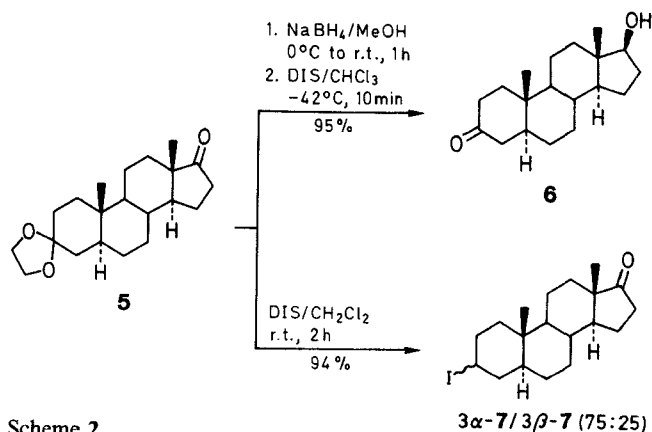
To check this opportunity we prepared two monoprotected derivatives of an aliphatic dicarbonyl compound: 8,8-(ethylenedioxy)octan-2-one (**1**) and 7,7-(ethylenedioxy)octanal (**2**) and examined their reactivity towards DIS (Scheme 1). Indeed, the acetal functionality of ketoacetal **1** is selectively reduced to 8-iodooctan-2-one (**3**) upon reaction with DIS at room temperature. Conversely, the isomeric product, 7-iodooctanal (**4**) is expectedly obtained from **1** by sodium borohydride reduction of the unprotected ketone, followed by iodination and acetal cleavage with DIS. Accordingly, ketal–aldehyde **2** is converted into the same products, either **3** or **4**, by switching procedures. Reaction with DIS at room tem-

perature gives rise to iodoaldehyde **4**, whereas the conventional sodium borohydride reduction followed by ketal cleavage and iodination with DIS affords iodoketone **3**. Obviously, reduction of a cyclic ketal in the presence of free aldehyde represents a rare case of inverted chemoselectivity. Nevertheless, yields of **4**, obtained either from **1** or **2**, are somewhat disappointing, due to its limited stability under the reaction conditions.



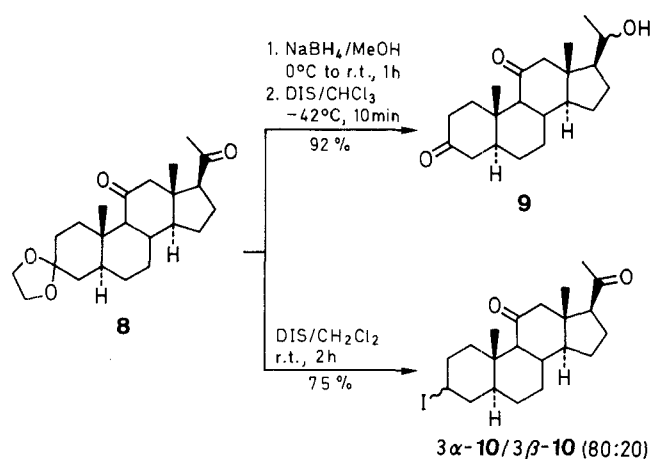
Scheme 1

With less sensitive substrates, such as steroidal diones, the above described modes of reactivity are illustrated in high yields. Conventional reduction of 3,3-(ethylenedioxy)androstan-17-one (**5**) with sodium borohydride, followed by low temperature ketal cleavage with DIS affords 17β -hydroxyandrostan-3-one (**6**). Conversely, reaction of the same substrate with DIS at room temperature gives rise to 3-iodoandrostan-17-one (**7**) (Scheme 2).



Scheme 2

This complementary chemoselectivity is further demonstrated by reduction of 3,3-(ethylenedioxy)pregnane-11,20-dione (**8**) with either sodium borohydride or DIS (Scheme 3). Selective reduction of the unprotected carbonyl at position 20 is achieved by borohydride reduction, affording 20-hydroxypregnane-3,11-dione (**9**) while the protected carbonyl at position 3 is preferentially reduced by DIS to give 3-iodopregnane-11,20-dione (**10**). Few attempts to convert the secondary alcohols in either **6** or **9** to iodoalkanes by reaction with DIS at room temperature resulted in unclear products. We did not try to optimize these transformations.



Scheme 3

In summary, regioselective partial reduction of polycarbonyl compounds often requires long sequence of protection and deprotection of the appropriate carbonyl functions.^{5,6} In this paper we have shown that many of these procedures may be shortened by direct transformation of the appropriate ketals with DIS, reactions occurring with unusual regio- and chemoselectivity. Several other examples of this inverted selectivity are known. For example, trimethylsilyl triflate preferentially promotes the aldol-type condensation of acetals with enol silyl ethers in competing reactions with carbonyl compounds.⁷ Analogous condensations were also observed with dibutyltin bis(triflate).⁸

IR spectra were measured on the neat compounds with an FT Infrared Nicolet MX-1 spectrophotometer. ¹H-NMR spectra were recorded in CDCl₃ on a Bruker AM-400 or Bruker AC-E200 NMR spectrometer. Thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60, F₂₅₄, Art 5549). Preparative TLC was performed on glass plates precoated with silica gel (Merck, Kieselgel 60 F₂₅₄, Art 5717). Column chromatography separations were performed on silica gel (Merck, Kieselgel 60, 230–400 mesh, Art. 9385). Distillations were usually performed with a Büchi kugelrohr apparatus, the temperatures presented are pot temperatures. THF, benzene and toluene were distilled over sodium benzophenone ketyl. CHCl₃ was dried over active alumina prior to use. DIS was prepared from phenylsilane and I₂, as we described earlier.³ All starting materials were purchased from either Aldrich or Fluka.

3,3-(Ethylenedioxy)androstan-17-one (**5**) and 3,3-(Ethylenedioxy)pregnane-11,20-dione (**8**):

The steroidal ketals are prepared according to literature procedures⁹ from the corresponding ketones by overnight reflux in benzene together with excess ethylene glycol and oxalic acid, with continuous removal of H₂O by a Dean-Stark trap. The cooled

mixture is filtered through a short alumina column, solvent is removed under reduced pressure and the product is purified by column chromatography and crystallization. Compound **5**¹⁰ is thus obtained in 83% yield and compound **8**¹¹ in 37% yield, together with 3,3-(ethylenedioxy)-20,20-(ethylenedioxy)pregnan-11-one (**11**) (51%).

8,8-(Ethylenedioxy)octan-2-one (**1**):

Synthesis is carried out as described for the homologous compound.¹² Methyl 5-bromopentanoate is reduced with LiAlH₄ to give the corresponding primary alcohol, which is oxidized with pyridinium chlorochromate (PCC). The resultant aldehyde is ketalized with ethylene glycol to produce 1-bromo-5,5-(ethylenedioxy)pentane. The latter is slowly added to a solution of methyl sodioacetoacetate in benzene/DMF (4:1), and the resultant mixture is heated for 40 h at 55°C.¹¹ Product **1**¹³ is finally obtained by demethoxycarbonylation with thiophenol and K₂CO₃ in DMF at 85°C, 3 h.¹⁴

HRMS: *m/z* calc. for C₁₀H₁₈O₃: 186.1255, found: 186.1247 (M⁺).

IR (neat): ν = 2940, 2880, 1710, 1410, 1360, 1140, 1090, 1040, 950.

¹H-NMR (CDCl₃/TMS): δ = 1.32 (m, 4H), 1.56 (m, 4H), 2.06 (s, 3H), 2.36 (t, 2H, *J* = 8 Hz), 3.84 (m, 4H), 4.77 (t, 1H, *J* = 5 Hz).

MS: *m/z* (%) = 186 (M⁺ 16), 185 (29), 143 (7), 141 (10), 125 (10), 124 (46), 109 (8).

7,7-(Ethylenedioxy)octanal (**2**):

Methyl 5-bromopentanoate is added to a methyl sodioacetoacetate at 25–30°C in benzene/DMF (4:1), and the mixture is heated at 55°C for 40 h. Demethoxycarbonylation of the resultant methyl ester as described above, yields methyl 7-oxooctanoate. Ketalization of the latter with ethylene glycol followed by reduction with LiAlH₄ affords 7,7-(ethylenedioxy)octan-1-ol. Its oxidation with PCC affords **2** in high yield.

HRMS: *m/z* calc. for C₉H₁₅O₃ (M⁺ – CH₃) 171.1021; found: 171.1005 (98.6%).

IR (neat): ν = 2960, 2925, 2870, 2720, 1725, 1460, 1410, 1390, 1380.

¹H-NMR (CDCl₃/TMS): δ = 1.27 (s, 3H), 1.28 (m, 4H), 1.60 (m, 4H), 2.45 (t, 2H, *J* = 8 Hz), 3.89 (s, 4H), 9.77 (t, 1H, *J* = 0.2 Hz).

8-Iodooctan-2-one (**3**) from **2**:

NaBH₄ (50 mg, 1.3 mmol) is added, in portions, to a cooled solution (ice bath) of **2** (133 mg; 0.71 mmol) in MeOH (10 mL) during 15 min. The resultant mixture is stirred for an additional period of 1 h. Usual workup and removal of solvents furnished 7,7-(ethylenedioxy)octan-1-ol (132.5 mg, 99%) in the form of a colorless oil.

¹H-NMR (CDCl₃/TMS): δ = 1.27 (s, 3H), 1.32 (m, 6H), 1.55 (m, 4H), 1.85 (br, 1H), 3.59 (t, 2H, *J* = 6.7 Hz), 3.89 (s, 4H).

DIS (205 mg, 0.72 mmol) is added to a cooled solution of the above described crude alcohol in CH₂Cl₂ (3 mL) at –42°C. H₂O (2 drops) is added after 10 min. The mixture is removed from the bath and stirred at r.t. for 4 h. Additional CH₂Cl₂ (10 mL) and sat. aq NaHCO₃ (2 mL) is added. The organic layer is separated, washed with H₂O, dried and solvent is removed under reduced pressure to give **3**¹⁵; yield: 168.7 mg (94%), in the form of a colorless oil. C₈H₁₅IO (254.1).

¹H-NMR (CDCl₃/TMS): δ = 1.36 (m, 4H), 1.58 (quint, 2H, *J* = 7.1 Hz), 1.62 (quint, 2H, *J* = 7.3 Hz), 2.14 (s, 3H), 2.44 (t, 2H, *J* = 6.8 Hz), 3.19 (t, 2H, *J* = 6.9 Hz).

7-Iodoctanal (**4**) from **1**:

A reaction similar to the one described above is carried out with **1** (24 mg, 0.13 mmol) and NaBH₄ to produce the corresponding alcohol, which is reacted with DIS (37 mg, 0.2 mmol) in CH₂Cl₂ (2 mL). The mixture is worked up after 2 h, followed by preparative TLC (R_f 0.3, hexane/EtOAc, 9:1) gives **7**; yield: 10.3 mg (32%). C₈H₁₅IO (254.1).

¹H-NMR (CDCl₃/TMS): δ = 1.38 (br s, 2H), 1.62 (m, 2H), 1.92 (d, 3H, *J* = 6.8 Hz), 2.45 (td, 2H, *J* = 7.1, 0.2 Hz), 4.18 (m, 1H), 9.77 (t, 1H, *J* = 0.2 Hz).

8-Iodoctan-2-one (3) from 1:

DIS (300 mg, 1.06 mmol) is added to a solution of **1** (108 mg, 0.86 mmol) in CH₂Cl₂ (4 mL), and the mixture is stirred for 4 h at r.t. The mixture is quenched with 20% aq K₂CO₃ (0.5 mL) and CH₂Cl₂ (15 mL) and worked up to give **3**; yield: 118 mg (81%).

7-Iodoctanal (4) from 2:

DIS (340 mg, 1.2 mmol) is added to a stirred solution of **2** (112.5 mg, 0.6 mmol) in CH₂Cl₂ (4 mL), and the mixture is stirred for 30 min at r.t. The mixture is quenched with 20% aq K₂CO₃ (0.5 mL) and CH₂Cl₂ (15 mL) and the organic layer is washed, dried and solvent is removed under reduced pressure to give an oily residue. Separation by preparative TLC (R_f 0.3, hexane/EtOAc, 9:1) affords 7-oxooctanal (69.8 mg, 81%) (R_f 0.5) and 7-iodooctanal (**4**) (10.1 mg, 7%, 35% based on recovered oxooctanal). Attempts to increase the yield of **4** by driving the reaction to higher conversions proved unsuccessful.

17β-Hydroxyandrostane-3-one (6) from 5:

NaBH₄ (50 mg) is added in portions over a period of 30 min to a cooled solution (ice bath) of **5** (92.4 mg, 0.3 mmol) in MeOH (25 mL), and the mixture is stirred for an additional period of 1 h. The mixture is worked up with H₂O and CH₂Cl₂. The organic phase is dried and the solvent is removed under pressure, affording 3,3-(ethylenedioxy)-17β-hydroxyandrostane¹⁶; yield: 91.2 mg (98%).

This crude product is dissolved in CHCl₃ (3 mL) and cooled to -42°C. DIS (85 mg, 0.3 mmol) is added, the mixture is stirred for 10 min and then quenched with H₂O. Extraction with Et₂O yields **6**¹⁷ yield: 75.8 mg (95%).

¹H-NMR (CDCl₃/TMS): δ = 0.73 (s, 3 H), 0.99 (s, 3 H), 3.62 (t, 1 H, J = 8.8 Hz).

(R,S)-20-Hydroxypregnan-3,11-dione (9) from 8:

An experiment similar to the one described above is carried out with **8** (37.5 mg, 0.1 mmol), affording hydroxydione **9**⁵ (yield: 30.5 mg (92%), C₂₁H₃₂O₃ (332.5).

¹H-NMR (CDCl₃/TMS): δ = 0.68 (s, 3 H), 1.15 (d, 3 H, J = 6.4 Hz), 1.21 (s, 3 H), 3.65 (br m, 1 H).

(R,S)-3-Iodoandrostane-17-one (7) from 5:

DIS (26 mg, 0.09 mmol) is added to a solution of **5** (15.4 mg, 0.046 mmol) in CH₂Cl₂ (3 mL) at r.t. and the mixture is stirred for 2 h. More CH₂Cl₂ (10 mL) and 20% aq K₂CO₃ (0.1 mL) are added, and the organic layer is washed with H₂O and dried (Na₂SO₄). Removal of solvent under reduced pressure affords (R,S)-3-iodoandrostane-17-one (**7**)¹⁸; yield: 17.5 mg (94%), in the form of a white solid, which was found to be pure by TLC: R_f 0.43 (hexane/EtOAc, 85:15). ¹H-NMR shows a mixture of two epimers: 3α-iodoandrostane-17-one (δ = 4.95) and 3β-iodoandrostane-17-one (δ = 4.16) in the ratio of 75:25, respectively.

¹H-NMR (CDCl₃/TMS): δ = 0.83 (s, 3 H), 0.86 (s, 3 H), 4.16 (m, 0.25 H, W_{1/2} = 8.9 Hz), 4.95 (m, 0.75 H, W_{1/2} = 2.8 Hz).¹⁸

MS: m/z (%) = 400 (M⁺ 3.5), 318 (44), 273 (100), 272 (88, M-H1), 257 (18), 255 (55), 244 (6), 219 (9), 218 (53), 215 (19), 203 (6), 190 (19), 161 (19), 145 (17), 135 (18), 128 (3).

(R,S)-3-Iodopregnan-11,20-dione (10) from 8:

A reaction similar to the one described above is carried out with DIS (28 mg, 0.1 mmol) and **8** (18 mg, 0.05 mmol) yielding a mixture

of 3α- and 3β-iodopregnan-11,20-dione (16.2 mg, 75%) in a 80:20 ratio, respectively.

C₂₁H₃₁IO₂ HRMS: m/z calc. for C₂₁H₃₁O₂ (M⁺ - I, parent ion): 315.2324 found: 315.2304.

¹H-NMR (CDCl₃/TMS): δ = 0.58 (s, 3 H), 1.02 (s, 3 H), 2.10 (s, 3 H), 4.16 (br m, 0.2 H, 3β-iodo isomer), 4.95 (t, 0.8 H, J = 2.5 Hz, 3α-iodo isomer).¹⁹

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