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REGIOSPECIFIC REDUCTION OF UNSATURATED CONJUGATED KETONES WITH SODIUM DITHIONITE UNDER PHASE TRANSFER CATALYSIS[1]

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Abstract: Selective double bond reduction of unsaturated conjugated ketones has been achieved in excellent yields by use of sodium dithionite in a two phase benzene-water system with Adogen as phase transfer catalyst. However, this reduction was unsatisfactory for hydrophilic ketones; in this case, competitive reactions led to the predominant formation of water soluble sulfur derivatives, similar to those obtained in the reaction of unsaturated conjugated ketones with sodium dithionite in aqueous dimethylformamide.

Several reports have appeared in the literature on the application of aqueous solutions of sodium dithionite in the presence of cosolvents, such as dimethylformamide or dioxane, as advantageous alternative for reduction of aldehydes and ketones to alcohols.[2-4] In this context, we have extended this reduction procedure to a two phase benzene-water system by the use of phase transfer catalysts, with results comparable or even superior to those obtained under the above homogeneous conditions.[5]

Likewise, we have also described the regiospecific reduction of 2,4-alkadienoic acids and esters with sodium dithionite to afford Z:E isomeric mixtures of the corresponding 3-alkenoic acids and esters, respectively, in good yields. A moderate stereoselectivity (Z:E, 3:1) was observed in the reduction of the above acids in aqueous solution, while approximately the same amounts of both isomeric monoene esters were obtained in the presence of phase transfer catalysts.[6]

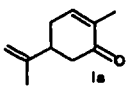
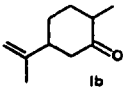
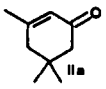
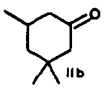
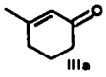
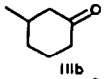
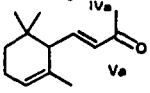
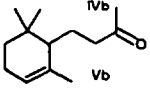
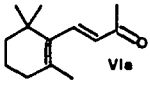
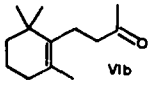
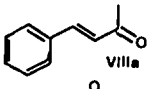
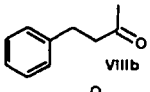
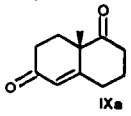
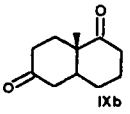
Although Chung[7] had claimed that α,β-unsaturated ketones were resistant to the reduction by sodium dithionite in aqueous DMF, our interest to broaden the scope of application of this reagent in general organic synthesis led us to restudy that reaction.

A recent preliminary report[8] along this line has prompted us to present here our detailed experimental procedure for regiospecific reduction of double bonds in conjugated unsaturated ketones with sodium dithionite under phase transfer catalysis.

RESULTS AND DISCUSSION

As shown in Table 1, reduction of unsaturated ketones to the corresponding dihydroderivatives was generally achieved in excellent yields, using 2.25 or 9 fold molar excesses of sodium dithionite in a water-benzene two phase system, containing sodium bicarbonate and a commercial mixture of methyl trialkyl [C_8-C_{10}] ammonium chlorides (Adogen 464®). As a rule, stepwise addition of the reductant led to an improvement of the yields obtained, presumably, by avoidance of the fast

Table 1. Sodium dithionite reduction of unsaturated ketones under phase transfer catalysis.

Entry	Substrate	Product	Yield[1]	Mole substrate (mmole scale): PTC:HCO_3^-:$S_2O_4^{2-}$	Method[2]
1	 Ia	 Ib	91(4:96)	1(4):0.3:18:9	A
2	 IIa	 IIb	81	1(5):0.3:18:9	B
3	 IIIa	 IIIb	30	1(5):0.3:18:9	A
4	 IVa	 IVb	0	1(4):0.3: 5:2.25	A
5	 Va	 Vb	76	1(6):0.3: 5:2.25	B
6	 VIa	 VIb	65	1(3):0.3: 5:2.25	B(1h)
7	 VIIa	 VIIb	63	1(4):0.3: 5:2.25	B
8			25	1(12):0.3: 5:2.25	B
9	 VIIIa	 VIIIb	56	1(6):0.3:18:9	B
10			56	1(6):0.3: 5:2.25	B[3]
11	 IXa	 IXb	80(61:39)	1(3):0.3: 5:2.25	B(15 min)

1) Isolated yields. Numbers in parentheses correspond to cis:trans isomer ratio.
2) A: Sodium dithionite added in one single lot. B: Stepwise addition of reductant. Reaction time 2 h, unless otherwise stated.
3) BHT was added to the reaction mixture. GLC analysis showed a formation of 63% VIIIb along with 15% VIIIa.

decomposition of the dithionite, which is favored at high concentrations. However, for reduction of some substrates the use of concentrated sodium dithionite solutions also proved to be advantageous. Unexpectedly, ketones IIIa and IVa afforded poor or negligible yields of reduced compounds with both concentrations (cf. entries 3 and 4).

As far as the stereoselectivity of the reduction is concerned, it is worth of note that in the reduction of carvone (Ia) the trans isomer was predominant (Ib, cis:trans 4:96) (entry 1). On the other hand, the reaction of Wieland-Miescher ketone (IXa) afforded a 61:39 cis:trans mixture of saturated dione IXb after 15 min (entry 11). However, when this reduction was continued for 4 hours, hydroxyketones and diols were also present with concurrent changes in the cis:trans isomer ratio (84:21) and yield (36%) of dione IXb.

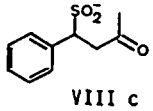
In agreement with our previous results in the reaction of α,β;γ,δ-dienic carboxylic acids and esters with sodium dithionite, eucarvone (VIIa) afforded dihydroderivative VIIb, resulting from the 1,4 reduction of the dienic system (entry 7). In contrast, β-ionone (VIa) was selectively reduced at the 1,2 position of this unsaturated system. This apparently anomalous result might arise from the isomerization of the exocyclic double bond, formed in the anticipated 1,4 reduction, or from the steric encumbrance of the γ,δ-tetrasubstitution that favors the alternative 1,2 reduction (cf. entries 5 and 6).

Table 2.- Reactivity of different substrates under alternative homogeneous (HR) and phase transfer (PT) reaction conditions.

Entry	Substrate	Method	Unreacted starting material at different reaction times 15'	30'	60'	90'	120'
1	Ia	PT1	91(1)	90(2)	89(3)	88(4)	86(4)
2	"	HR1	99(-)	99(-)	99(-)	98(--)	99(--)
3	"	PT2	82(-)	81(-)	79(-)	79(--)	78(--)
4	"	HR2	--(-)	--	--	--	--
5	"	HR3	1(2)	-(6)	-(9)	-(10)	--(13)
6	"	HR4	94(-)	86(-)	83(1)	82(2)	82(2)
7	IIa	PT1	99	97	96	89	87
8	"	PT2	95	94	92	90	88
9	IIIa	PT1	96	94	90	65	54
10	"	PT2	69	67	64	61	58
11	IVa	PT1	17	2	--	--	--
12	"	PT2	1	-	--	--	--
13	VIa	PT2	97	96	96	91	87
14	VIIIa	PT1	85(-)	68(-)	62(-)	53(--)	43(--)
15	"	HR1	3(-)	2(-)		--	--

a) PT1,HR1: Sodium hydroxymethanesulfinate as reagent. PT2,HR2: Sodium bisulfite as reagent. HR3: Sodium dithionite as reagent. HR4: Sodium dithionite/paraformaldehyde as reagent.
b) By glc analysis using internal standard (n-alkane: n=12 for entries 9-12; n=13 for 7,8,13; n=14 for 1-6; n=15 for 14,15). Numbers in parentheses correspond to reduction product formed.

As we have mentioned above, Chung had found benzalacetone (VIIIa) and other unsaturated conjugated ketones to be resistant to the reduction with sodium dithionite in the presence of sodium bicarbonate in aqueous solution. This author related this unreactivity with the formation of sulfinate adducts by 1,4 addition, which were characterized by ^{1}H NMR and methylation to give the corresponding sulfone derivatives[9]. In fact, when we repeated this reduction, in aqueous dimethyl formamide, we confirmed the formation of the sulfinate VIIIc as the major definite product[10]. On the other hand, the reduction of VIIIa to dihydroderivative VIIIb took place in moderate yield (25%), when a 2.25 molar excess of dithionite was used under standard phase transfer conditions. This yield, though, was increased up to 56% by stepwise addition of a nine fold molar excess of reductant. Remarkably, better results were obtained by performing the reaction in the presence of a catalytic amount of an antioxidant, such as 2,6-di-t-butyl-4-methylphenol (BHT) (cf. entries 8-10).



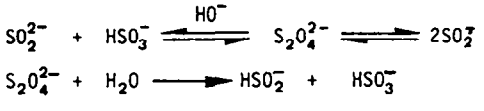
VIII c

At this stage, we carried out the alternative reactions summarized in Table 2 to ascertain some of our apparently anomalous results, as well as to shed light on the plausible mechanism of this reduction under phase transfer catalysis. The reaction of benzalacetone (VIIIa) with sodium hydroxymethanesulfinate, a source of sulfinate radicals[11], led to the disappearance of the starting ketone and to the formation of the aqueous soluble sulfinate derivative VIIIc as the major product (cf. entries 14 and 15), whereas other ketones remained practically unaffected by treatment with that reagent (cf. entries 1,2 and 7). On the other hand, while the reaction of sodium bisulfite with ketone IVa was almost complete after 15 min with concomitant formation of water-soluble bisulfite addition derivatives[12], carvone (Ia) reacted sluggishly under the same conditions (cf. entries 12 and 3).

As was shown by independent experiments, this variance was most likely related to the water-solubility differences of both ketones; the solubility in the aqueous layer would favour the fast reaction of the ketone with sodium bisulfite or other species derived from sodium dithionite (see Scheme 1).

Likewise, in contrast to the practically complete reduction of the conjugated double bond of carvone (Ia) with sodium dithionite under phase transfer conditions, when this reaction was carried out in aqueous dimethylformamide, an almost negligible yield (< 10%) of an isomeric mixture of dihydrocarvone (Ib) was obtained (entry 5). Also in this case, the formation of sulfinates was detected by conversion to the corresponding sulfones.

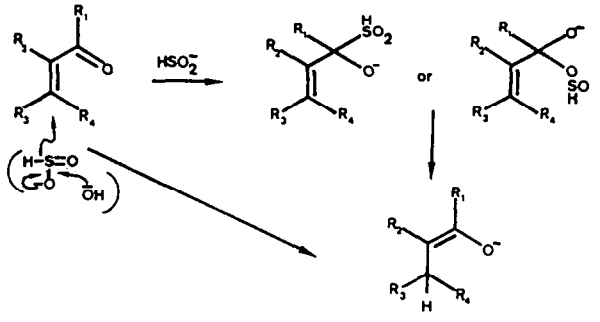
According to the literature data, as shown in Scheme 1, several reactive species might be responsible for the above diversity of results. In alkaline solution, sodium dithionite appears to exist in equilibrium with the species bisulfite anion and sulfur dioxide dianion[13] and also with the sulfur dioxide radical anion that is detectable by esr.[14] On the other hand, the presence of sulfoxylate anion has been postulated in neutral or mildly acidic solutions of sodium dithionite.[3]



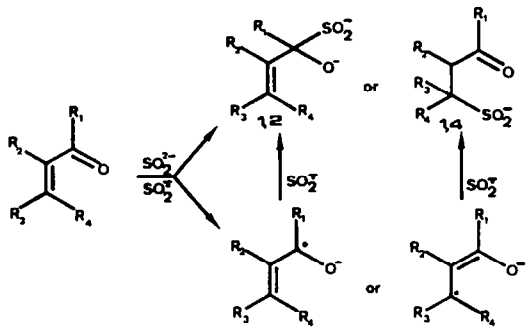
Scheme 1

Plausibly, when the reduction is carried out under phase transfer conditions, the presence of sulfoxylate anion should be favored in the organic layer, whereas in aqueous dimethylformamide the other species should be predominant. In agreement with this assumption, the addition of paraformaldehyde, a reported quencher of sulfoxylate anion,[15] inhibited the reduction of carvone Ia with sodium dithionite under phase transfer conditions (entry 6).

Therefore, reduction of unsaturated ketones by sodium dithionite might be envisaged to take place in the organic layer by nucleophilic attack of the sulfoxylate anion on the carbonyl group followed by hydride transfer to the olefinic bond with concomitant loss of sulfur dioxide, or through direct Michael addition of hydride:



Alternatively, direct 1,4 or 1,2 addition of sulfur dioxide dianion or sulfur dioxide radical anion would lead to water soluble sulfinate derivatives. The involvement of the radical active species may be more important in the reduction of substrates, such as benzalacetone (VIIIa), in which the formation of stabilized radical intermediates is plausible.



In conclusion, the above described procedure for selective double bond reduction of unsaturated conjugated ketones can compete advantageously with other methods reported in the literature;[16,17] such as hydrogenations with heterogeneous or homogenous catalysts, and reductions with dissolving metal or metal hydrides, provided that the lipophilicity of the substrate is high enough to warrant the occurrence of the reaction with sodium dithionite in the organic phase. However, that reduction was unsatisfactory for hydrophilic ketones; in this case, competitive reactions led to the predominant formation of water soluble sulfur derivatives, similar to those obtained in the reaction of unsaturated ketones with sodium dithionite in aqueous dimethylformamide.

EXPERIMENTAL PART

Analytical methods. The ^1H NMR spectra were recorded in a Bruker WP80SY spectrometer operating at 1.88 T (5 mm spinning tubes; $CDCl_3$ with TMS as internal standard; chemical shifts given in ppm downfield, and coupling constants in Hz). Gas chromatographic analyses were carried on Carlo Erba instruments, models 4130 or 4300 using a fused silica capillary column (25 m x 0.32 mm I.D.; SE-54 with H_2 as carrier gas) or glass column (2 m x 1/8 I.D.; 3% OV-101 on Chromosorb W, with N_2 as carrier gas). Adogen 464®(Aldrich) was used as phase transfer catalyst.

General procedure for unsaturated ketone reduction. A mixture of the ketone (3-6 mmole), phase transfer catalyst and sodium bicarbonate in benzene and water was stirred vigorously under nitrogen. Sodium dithionite was added either in one single addition (method A) or in two installments (second half after 15 min, method B) and the mixture heated in an oil bath at 100°C, providing a gentle reflux for 2 h (unless otherwise stated). After cooling, the aqueous layer was separated and extracted twice with diethyl ether. The combined organic extracts were washed with water, dried ($MgSO_4$) and the solvent removed in vacuo to give a residue. This residue was separated by silica gel column chromatography (ratio SiO_2 :crude 30:1) and the fractions containing the reduced compound joined and characterized (GC,NMR).

- 2-Methyl-5-isopropenylcyclohexanone, Ib.
Obtained in 91% yield from Ia (0.60 g/ 14 mmole, in 40 ml of each solvent; CC solvent system hexane: diethyl ether (Hx:DE) 7:3). ^1H NMR ($CDCl_3$): δ 1.05(d, J=6Hz; 3H, CH_3), 1.75(s; 3H, CH_3C=), 1.2-2.5(8H), 4.75(b; 2H, CH_2) (cf. Lit. 16).

- 3,3,5-Trimethylcyclohexanone, IIb.
Obtained in 80% yield from IIa (0.69 g/15 mmole, in 50 ml of each solvent; ethyl acetate (EA) was substituted for diethyl ether as extraction solvent; CC solvent system Hx:EA 7:3). ^1H NMR ($CDCl_3$): δ 0.88(s; 3H, CH_3), 1.02(d, J=6Hz; 3H, CH_3), 1.05(s; 3H, CH_3), 1.26-2.25(7H) (cf. Lit. 18.).
In this reaction, 0.014 g of starting IIa (2% unreacted) was also isolated through the chromatographic separation.

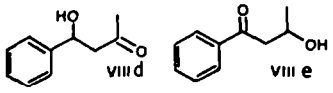
- 3-Methylcyclohexanone, IIIb.
Obtained in 31% yield, from IIIa (0.55 g/15 mmole, in 50 ml of each solvent; CC solvent system Hx:DE 4:1). ^{1}H NMR ($CDCl_3$): δ 1.06(d, J=6Hz; 3H, CH_3), 1.1-2.5(9H) (cf. Lit. 19 and comparison (GC) with an authentic sample).
In this reaction, 0.032 g of the corresponding 3-methylcyclohexanol isomeric mixture (6%) was also obtained.

- 4-(2,6,6-Trimethylcyclohex-2-enyl)butan-2-one, Vb.
Obtained in 76% yield from Va (1.15 g /6 mmole in 20 ml of each solvent; CC solvent system Hx:DE 7:3. ^{1}H NMR ($CDCl_3$): δ 0.85(s; 3H, CH_3), 0.95(s; 3H, CH_3), 1.10-2.20(7H), 1.67(s; 3H, CH_3C=), 2.15(s; 3H, CH_3CO), 2.50(t, J=8z; 2H, CH_2CO), 5.38 (br; 1H, H-C=) (cf. Lit. 20).
In this reaction 0.096 g of starting Va (8% unreacted) was also isolated.

- 4-(2,6,6-Trimethylcyclohex-1-enyl)butan-2-one, VIb.
Obtained in 65% yield from VIa (0.58 g/3 mmole in 10 ml of each solvent; CC solvent system Hx:DE 19:1), it was shown by GC analysis to contain up to 3% of starting VIa. ^{1}H NMR ($CDCl_3$): δ 1.00 (s; 6H, CH_3), 1.50 (m; 4H, CH_2), 1.53 (s; 3H, CH_3C=), 2.08 (t, J=6Hz; 2H, CH_2C=), 2.12 (s, 3H, CH_3CO) 2.2-2.5 (4H)(cf. Lit. 20).

- 2,6,6-Trimethylcyclohept-3-en-1-one, VIIb.
Obtained in 63% yield from VIIa (0.60 g/14 mmole in 13 ml of each solvent; CC solvent system Hx:DE 19:1) it was shown by GC analysis to contain up to 3% of starting VIIa. ^{1}H NMR ($CDCl_3$): δ 1.00(s; 3H, CH_3), 1.08(s; 3H, CH_3), 1.15(d, J=8Hz; 3H, CH_3), 2.00(d,ABX; J_{AX}=5.0Hz; 1H, CH_2C=), 2.08(d,ABX; J_{BX}=5.0Hz; 1H, CH_2C=), 2.34 and 2.50(AB system, J=11.0Hz; 2H, CH_2CO), 3.25(complex; 1H, CHCO) 5.55(dd, J=10Hz, J' =4.4Hz; 1H, H-C_3=), 5.80(c, 1H, H-C_4=) (cf. Lit 21).

- 4-Phenylbutan-2-one, VIIIb.
Obtained in 25% yield from VIIIa (1.76 g/12 mmole in 40 ml of each solvent; CC solvent system Hx:DE 4:1). ^{1}H NMR ($CDCl_3$): δ 2.12 (s; 3H, CH_3CO), 2.6-2.9(AA'BB' system; 4H, $ArCH_2CH_2CO$), 7.18 (b; 5H, ArH) (cf. Lit. 20)
In this reaction, 0.127 g of starting VIIIa (7% unreacted) was isolated (elution with Hx:DE 2:1).
A mixture of two byproducts was eluted by Hx:DE 1:1 (0.100 g, 6%), shown to be hydroxyketones VIIId and VIIIe. ^{1}H NMR ($CDCl_3$) VIIId: δ 2.18(s; 3H, CH_3CO), 2.84(2x d, J=4.8Hz and 6.5Hz; 2H, CH_2CO),3.45(b; 1H, OH), 5.15(dd, J=4.8Hz, J'=6.5Hz; 1H, ArCHO), 7.20-7.70(5H, ArH). ^{1}H NMR($CDCl_3$) VIIIe: δ 1.28(d, J=6Hz; 3H, CH_3C-O), 3.10(2x d, J=7.2Hz and 3.6Hz; 2H, CH_2CO), 3.42(b; 1H, OH), 4.42(m; 1H, CH-O), 7.25-8.00(5H, ArH).



- 1-Methylbicyclo(4.4.0)decane-2,8-dione, IXb.
Obtained in 80% from IXa (0.54 g/3 mmole in 10 ml of each solvent; EA as extraction solvent and CC solvent system Hx:EA 3:2), it was shown by GC analysis to contain a cis/trans 61/39 isomer ratio. ^{1}H NMR ($CDCl_3$): δ 1.32(s; 3H, CH_3 trans isomer), 1.35(s; 3H, CH_3 cis isomer), 1.50-2.70(13H) (cf. Lit. 22).
In this reaction, 0.019 g of starting IXa (3.6% unreacted) were eluted with Hx:EA 2:1, and also 0.018 g of hydroxycompounds (3.4% overreduction).

Other reactions under phase transfer conditions (PT)

- Sodium hydroxymethanesulfinate as reagent (PT1)
The mixture of substrate (4 mmole/molar ratio 1), PT catalyst (1.2/0.3), sodium bicarbonate (20/5) and n-alkane as internal standard (molar ratio 0.4-0.5) in benzene/water (3.3 ml/meq substrate) was treated with the reagent (9/2.25) in an oil bath at 100°C.

- Sodium bisulfite as reagent (PT2)
Same treatment as above with the specified reagent (9/2.25).

Other reactions under homogeneous conditions (HR)

- Sodium hydroxymethanesulfinate as reagent (HR1).
The reaction was carried out as in PT1, but no PT catalyst was added, and DMF was substituted for benzene.

- Sodium bisulfite as reagent (HR2).
The reaction was similarly carried out as above in the water/dimethylformamide solvent system, and the reagent was sodium bisulfite.

- Sodium dithionite as reagent (HR3).
  The same treatment as in HR1 with the specified reagent (9/2.25).

- Sodium dithionite in the presence of paraformaldehyde (HR4).
  The reaction was carried out as in HR3, but adding paraformaldehyde to the reaction mixture (18/5).

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REFERENCES AND NOTES

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