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Reduction of DDHQ and TCC Esters by $NaBH_4$-Its Specificity in the Presence of Alkyl/Aryl Esters

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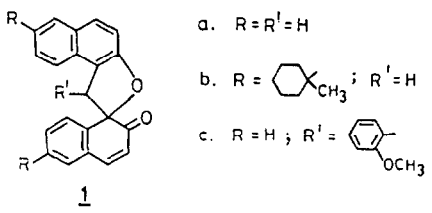
ABSTRACT: DDHQ/TCC esters **3a-f,7a-g** were prepared either by oxidation of spiroketones **1** with DDQ/o-chloranil or by condensation of acid chloride with DDHQ/TCC. $NaBH_4$ reduction of unsaturated DDHQ **3a-b** and TCC **7a-c** esters gave the corresponding allylic alcohols in good yield without any observable 1,4-addition products.Reduction of saturated esters **3e,7d**, gave the corresponding alcohols. Alkyl esters **5** and **6**, methyl benzoate and phenyl benzoate remained unaffected under these reduction conditions. In the reduction of compound **7e** containing both alkyl and TCC esters, TCC ester is selectively reduced. Reduction of TCC mono esters **7f-g** gave the lactones. The observed facile reduction has been rationalised.

It is generally accepted that $NaBH_4$, a powerful reducing agent for aldehydes and ketones, will not reduce carboxylic esters and ortho esters[1]. However, reduction can sometimes be effected by activation of the reagent eg by its conversion in situ into lithium magnesium borohydride or to a more reactive aluminium borohydride etc[2],but these methods have their own limitations. A number of instances wherein reduction of esters by $NaBH_4$ are reported in literature[3] invariably use higher temperatures, longer reaction times and large excess of borohydride. Further, selectivity in ester reductions have not been achieved.

We have recently reported[4] the oxidation of spiroketone **1** with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) to give either tropones **2** and 2,3-dichloro-5,6-dicyanohydroquinone (DDHQ) esters **3** or only DDHQ esters **3** depending on the substituent at β-position in the furan ring.In the course of investigation[4] on the structure of DDHQ ester **3a**, we have noticed that $NaBH_4$(2 mmol)in dry *THF* at room temparature reduces **3a** (1 mmol) to the allylic alcohol **4a** in 80% yield. Even though kinetic studies on the $NaBH_4$ reduction of esters having electron withdrawing alcohol unit have been reported[5], to the best of our knowledge, no systematic study has been made on the synthetic utility of this reduction. In view of the very mild conditions used to bring about the reduction of ester group, we undertook a detailed study of this reduction with a variety of substrates.



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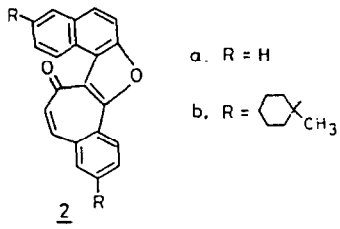

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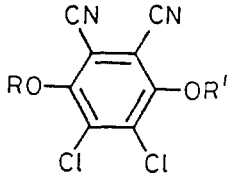

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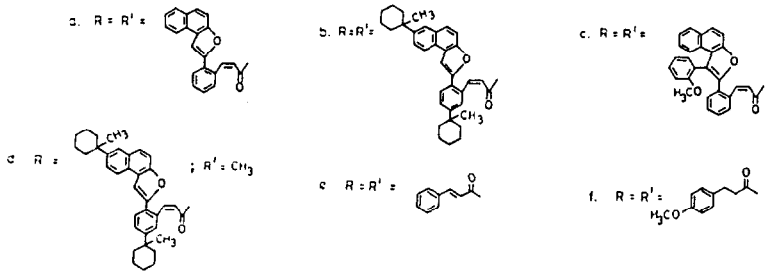

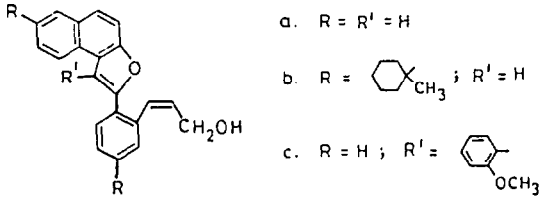

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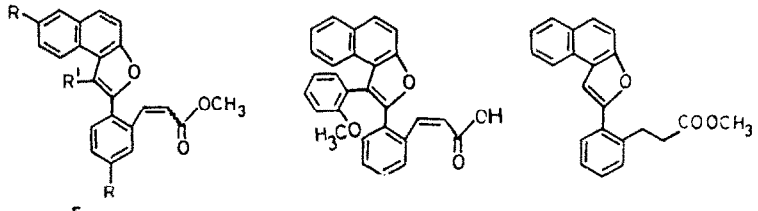
DDHQ diesters **3a-c** required in this study were prepared by oxidation of spiroketones **1a-c** with DDQ in refluxing dry benzene. DDHQ mono ester **3d** was prepared by trans-esterification of the corresponding diester **3b** with dry MeOH. Diesters **3e-f** were prepared by reaction of the corresponding acid chlorides with DDHQ. Structures of these esters are evident from their spectral data (Table 1).

Table 1. Spectroscopic and analytical data of DDHQ and TCC esters

Compound	%Yield	m.p °C	I.R (cm^{-1})	^1H NMR 90 MH_2, $CDCl_3$	Analytical data	Mass m/z,70eV, (% intensity)
3e	70	230	2250, 1750, 1630	6.7(d,J=16.0Hz,1H) 7.4-7.8(m,5H),8.0 (d,J=16.0Hz,1H)	calcd for $C_{26}H_{14}O_4N_2Cl_2$ C,63.8;H,2.9;N,5.7. Found: C,63.4;H,2.87;N,5.6%.	
3f	76	80	2250, 1782	3.1(s,4H),3.8 (s,3H,OCH_3),6.83 (d,J=8.0Hz,2H) 8.18(d with further coupling,J=8.0Hz,2H)	calcd for $C_{28}H_{22}O_6N_2Cl_2$ C,60.75;H,4.0;N,5.1 Found: C,60.4;H,3.9;N,5.0%.	
7c	72	165	1734 1641	6.58(d,J=16.0Hz,1H) 7.3-7.6(m,5H),7.94 (d,J=16.0Hz,1H)	calcd for $C_{24}H_{14}O_4Cl_4$ C,56.7;H,2.75 Found: C,57.2;H,2.96%.	506(M^+,15), 244(30), 131(100), 103(50), 77(37).
7d	82	98	1770	0.70-0.95(m,3H),1.1-1.9(m,30H),2.55(t,2H)	calcd for $C_{42}H_{70}O_4Cl_4$ C,64.6;H8.97 Found: C,64.86;H,9.22%.	534(25), 267(100).
7e	67	low melting	1785, 1740	1.2-2.0(m,4H),2.2-2.75(m,12H),3.7(s,3H)	calcd for $C_{28}H_{38}O_8Cl_4$ C,52.2;H,5.9 Found: C,51.9;H,5.8%.	
7f	75	171	3334, 1788, 1698	4.0(s,3H),7.45-7.80 (m,3H),8.0-8.15(m,1H) 8.6(bs,1H,OH)	calcd for $C_{15}H_8O_5Cl_4$ C,43.9;H,1.95 Found: C,43.93;H,1.92%.	408(M^+,1), 377(50), 244(30), 163(100), 77(25).
7g	90	145	1758 1734	3.90(s,3H),3.93(s,3H) 7.55-7.80(m,3H),8.0-8.15(m,1H)	calcd for $C_{16}H_{10}O_5Cl_4$ C,45.2;H,2.35 Found: C,45.3;H,2.35%.	422(M^+,1), 391(5), 163(100), 77(28).

In a typical experiment, the ester (1 mmol) was treated with $NaBH_4$ (2 mmol) in dry THF for about 3 hrs and the product was isolated in a pure state by extraction with organic solvent followed by column chromatography (silica gel).

As seen from Table 2, the unsaturated ester **3a** was reduced to the corresponding allylic alcohol without any observable 1,4 - addition in about 80% yield [entry 1]. When the corresponding methyl ester 5 was treated with $NaBH_4$ under similar conditions, no reduction occurred and the starting material was recovered quantitatively [entry 2]. Similar reduction of esters **3b-e** gave the corresponding alcohols (**4b**[6],**4c**[7],**4b**, cinnamyl alcohol respectively)in good yields [entries 3-6]. While the saturated DDHQ diester **3f** was reduced to 3-(p-methoxyphenyl)-propanol, the saturated methyl ester **6** failed to undergo reduction [entries 7-8]. Further, phenyl benzoate was not reduced under similar conditions [entry 9]. A 1:1 mixture of 3c and the corresponding methyl ester **5c** on reduction gave the alcohol **4c** and the unreacted methyl ester 5c [entry 10] indicating selectivity.



a. R=R'=H b. R =  ; R'=H

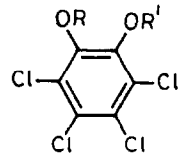
c. R=H ; R' = 

Table 2. Reduction of DDHQ esters with $NaBH_4$

Entry	Ester reduced	% Yield of alcohol	Entry	Ester reduced	% Yield of alcohol
1[4]	3a	80	6	3e	82
2	5a	0	7	3f	80
3	3b	81	8	6	0
4	3c	92	9	phenyl benzoate	0
5	3d	40	10	1:1 mixture of 3c & 5c	80% 4c and 5c

We anticipated that tetrachlorocatechol (TCC) esters **7a-b** should also behave similarly in the $NaBH_4$ reduction. These esters could be prepared by either oxidation of spiroketones **1** with o-chloranil [vide infra] adopting the method developed by us for the preparation of DDHQ esters or condensation of the corresponding acid chloride with TCC.

As expected, refluxing a solution of spiroketones **1a-b** in dry benzene with o-chloranil followed by work up resulted in the formation of tropones **2a-b** along with TCC diesters **7a-b**,as evident from spectral data(vide experimental).



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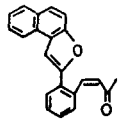
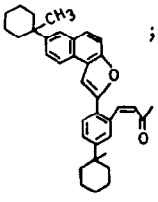
a. R = 

b. R =  ; R' = H

c. R = R' = 

d. R = R' = $CH_3(CH_2)_{16}\overset{O}{\overset{\|}{C}}$

e. R = R' = $MeO\overset{O}{\overset{\|}{C}}(CH_2)_8\overset{O}{\overset{\|}{C}}$-

f. R =  ; R' = H

g. R =  ; R' = CH_3

Diesters **7c-e** were prepared by heating the corresponding acid chloride(2 mmol), prepared from acid and thionyl chloride, with TCC (1 mmol). The ester **7f** was prepared by treating the corresponding acid chloride (1mmol) with TCC (1mmol). Methylation of **7f** with CH_2N_2 gave **7g**. These esters were characterised by spectral and analytical data(Table 1).

Reduction of TCC unsaturated esters **7a-c** with $NaBH_4$ gave the corresponding allylic alcohols [entries 11-13]. TCC diester of stearic acid **7d** gave stearyl alcohol in high yield [entry 14].

As already mentioned, alkyl esters are not reduced under the conditions used [entries 2,7]. This selectivity could be utilised in protecting one of the carboxylic acids in a dicarboxylic acid molecule as alkyl ester, while the other could be transformed to alcohol through the TCC or DDHQ ester. This could be of some synthetic utility. Thus, TCC

diester of sebacic acid monomethyl ester **7e** on reduction with $NaBH_4$ gave hydroxy decanoic acid methyl ester [entry 15].

TCC mono esters **7f-g** on reduction gave lactones[entries 16,17]. The lactones are formed by reduction of TCC ester followed by cyclisation. This was evident from the fact that methyl benzoate remained uneffected under similar reaction conditions [entry 18]. Reduction was comparatively slow in these cases and 5-10% starting material was recovered (Table 3).

Table 3. Reduction of TCC esters with $NaBH_4$

Entry	Ester reduced	% Yield of alcohol	Entry	Ester reduced	% Yield of alcohol
11	7a	65	15	7e	90
12	7b	70	16	7f	65
13	7c	83	17	7g	66
14	7d	85	18	methyl benzoate	0

The very facile reduction of DDHQ/TCC diesters by $NaBH_4$ could be attributed to the presence of electron withdrawing groups (Cl,CN) in the phenolic moiety. Perhaps, in the case of DDHQ/TCC mono esters (**3d,7a-b, 7f-g**),the electron releasing character of hydroxyl or methoxy group opposes this effect and hence, the reduction is sluggish.

In conclusion, the high yields and selectivity obtained recommend this method for the facile reduction of ester functionality under mild conditions, and particularly for the reduction of TCC or DDHQ esters over alkyl/aryl esters in a synthetic operation.

EXPERIMENTAL SECTION

All melting points are uncorrected.IR(ν_{max} cm^{-1})spectra were recorded on Perkin-Elmer model 781 spectrophotometer.NMR spectra were recorded on FX-90Q FT spectrometer with Me_4Si as internal standard(δ = 0 ppm).MS (70 eV) were recorded on MS-DX 303 spectrometer.Column chromatography was carried out using silica gel.Ether refers to diethyl ether.All organic exctracts were dried over anhydrous Na_2SO_4.

Trans esterification of 3 with dry MeOH

A mixture of compound 3 (600 mg) and dry MeOH (500 ml) was heated to reflux for three days. To the residue in ether (100 ml),obtained after removal of methanol, was added diazomethane in ether (30 ml) at 0°C

After allowing the reaction mixture to stand for five minutes, excess diazomethane was destroyed by adding little HOAc. The ether solution was washed with water and dried. Ether was removed and the residue obtained

was chromatographed . Elution with $CHCl_3$-hexane (1:1) gave 1:1 mixture of cis and trans methyl esters **5b** (200 mg, 38.5%),IR (nujol) 1730 ; ^1H NMR 1.25 (s) and 1.3 (s) (6H), 1.4-2.4 (m,20 H), 3.65 (s) and 3.85 (s) (3H), 6.15 (d,J=10.0 Hz,1H),6.25 (d, J=16.0 Hz)(1H),7.3-8.4 (m,10H). Anal. calcd for $C_{36}H_{40}O_3$ C,82.4; H,8.0 Found:C,81.9; H,7.85%.

Further elution with $CHCl_3$-hexane (2:1) gave **3d** (120 mg, 33%), IR (nujol) 1760 ; ^1H NMR 1.3(s,6H), 1.3-2.4 (m,20H), 4.18 (s,3H), 6.7 (d, J=16.0Hz ,1H) 7.3-8.05 (m,8H) 8.2 (d, J=7.0Hz ,1H), 8.65 (d,J=16.0Hz,1H). Anal.calcd for $C_{44}H_{40}O_4N_2C_{12}$ C,72.2; H,5.5; N,3.8. Found:C,71.8; H,5.3; N,3.6%.

Oxidation of spiroketone 1a-b with o-chloranil

A solution of spiroketone **1a** (298 mg) and o-chloranil (270 mg) in dry benzene (50 ml) was refluxed for 24 hrs. It was concentrated and chromatographed . Elution with $CHCl_3$ gave TCC monoester **7a** (300 mg) m.p 244° C; IR(nujol) 1757 ; ^1H NMR 6.07 (d,J=10.0Hz, 1H), 7.05-7.60 (m,10H), 7.77-7.95 (m,1H), 8.05 (d,J=10.0Hz,1H), MS m/e 542 (M^+, 14), 297 (22), 296 (96), 268 (80), 239 (100), 126 (42). Anal.Calcd for $C_{27}H_{14}O_4Cl_4$ C,59.7; H, 2.58. Found:C, 59.29; H, 2.27%. Further elution with $CHCl_3$-EtOAc (10:1) gave tropone **2a**.

Similar oxidation of spiroketone **1b** (500 mg) with o-chloranil (270 mg) in dry benzene gave **7b** (400 mg); m.p 117°C;IR(nujol) 1760 ; ^1H NMR 1.2(s,6H), 1.0-2.2(m,20H), 6.5(d,J=16.0 Hz,1H), 6.75(s,1H), 6.95(d, J=8.0 Hz,1H), 7.15(s,1H), 7.3-8.0(m,7H),8.5(d,J=16.0 Hz,1H).Analysis calcd.for $C_{41}H_{38}O_4Cl_4$ C,77.36;H,6.0.Found:C,77.12;H,5.92 and **2b**.

Preparation of 5c:

Compound **3c** (500 mg) and 10% NaOH (100 ml) were refluxed until the yellow colour of the solid disappeared (48 hr).The white solid was filtered off and dried at 0°C.The dried solid was stirred with 10% HCl (50 ml) for 1hr.The solid was exctracted with EtOAc (100 ml), washed with water (25 mlx3) and dried. Removal of EtOAc gave the acid **5d** (450 mg), m.p 110°C ($CHCl_3$),IR(nujol) 1689 ; ^1H NMR 3.6(s,3H,OCH_3),5.63(d, J=12.0 Hz,1H), 6.85-7.05 (m,7H), 7.1-7.2 (m,2H), 7.25-7.65 (m,7H), 7.7-8.0 (m,3H); MS m/e (relative intensity) 420(M^+,100), 374(56), 343(44), 313(30),269(24). HRMS calcd.for $C_{28}H_{20}O_4$ 420.1362.Found, 420.1365.

Esterification of this acid **5d** (420 mg) with $MeOH/H_2SO_4$ gave methyl ester **5c** (400 mg),m.p 80°C ($CHCl_3$-pet.ether); IR(thin film) 1728; ^1H NMR 3.4(s,3H),3.45(s,3H),5.45(d,J=12.0 Hz,1H),6.7-7.8(m,15H). HRMS calcd. for $C_{29}H_{22}O_4$ 434.1518.Found,434.1555.

General Procedure for the preparation of DDHQ or TCC esters from acid chloride and DDHQ/TCC.

A mixture of acid (2 mmols) and thionyl chloride (2.5 mmols) was heated at 100° C for one hour. After addition of DDHQ Or TCC (1 mmol) the mixture was again heated for 2 hrs. Water was added after cooling and the solid separated was extracted with EtOAc. The EtOAc extract was washed with water and dried . The residue obtained after removal of EtOAc was chromatographed . Elution with $CHCl_3$-hexane (3:1) gave the ester, which was crystallised from $CHCl_3$-hexane. Spectral and analytical data of these esters are given in Table.1.

General procedure for reduction of esters.

To a solution of ester (1 mmol) in dry THF (20 ml), $NaBH_4$ (2 mmol) was added at 0° C.The mixture was stirred at the same temperature for 2 hrs. and further at room temperature for 2 hrs. THF was removed in vacuo,

excess $NaBH_4$ was quenched with saturated NH_4Cl solution, and the organic compound extracted with ether. The ether layer was washed with water and dried. Removal of ether gave alcohol which was purified by column chromatography.

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6. Spectroscopic data of **4b** : semi solid, IR(neat) 3334 ; ^1H NMR 1.25(s,3H),1.3(s,1H),1.3-2.4(m,20H),4.4(d with allilic coupling ,J=6.0 Hz,2H),6.1(doublet of triplet,J=12.0 and 6.0Hz,1H),6.9(m,10H).Analysis calcd. for $C_{35}H_{40}O_2$ C,85.4;H,8.1. Found: C,85.2;H,8.0.
7. Spectroscopic data of **4c**: m.p 70°C;IR(thin film) 3412 ; ^1H NMR 3.65(s,3H),3.95-4.2(m,2H),5.5(doublet of triplet,J=12.0 and 6.0 Hz,1H),6.4(d with allylic coupling,J=12.0 Hz,1H),6.9-8.1(m,14H).MS m/e 406(M^+,100),388(25),269(35).HRMS calcd. for $C_{28}H_{22}O_3$,406.1569. Found, 406.1564.