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AN UNEXPECTED RING CLEAVAGE DURING KETALIZATION

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Abstract : 2,2-Disubstituted cyclohexane-1,3-diones 1a-d undergo an unexpected ring cleavage when subjected to ketalization reaction using different diols. The intermediacy of diketal 3a in the formation of cleavage product 4a has been established.

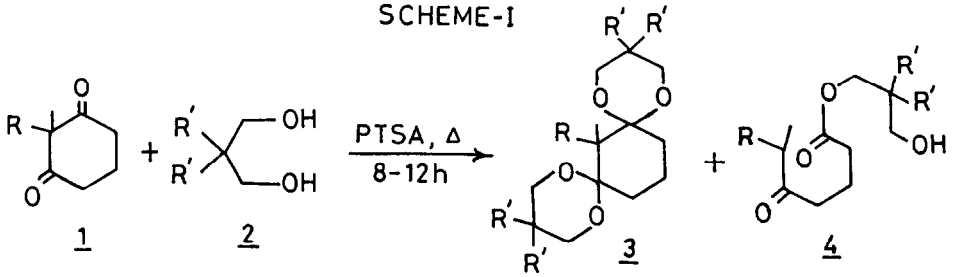
Generally diols have been widely used to protect the carbonyl group in 2,2-disubstituted cycloalkane-1,3-diones[1,2]. In this regard, the efficacy of 2,2-dimethylpropane-1,3-diol 2 to form stable and solid ketals has been well documented[3,4]. Several instances are known wherein the reaction leads to a mixture of mono and diketals, the latter being transformed to the former by mild acid treatment[5]. In our efforts to prepare the diketal of the dione 1a, an unexpected ring cleavage was encountered.

Compound 1a, when refluxed with diol 2 (R'=Me) for 8 h in the presence of a catalytic amount of p-toluenesulphonic acid monohydrate (PTSA) with azeotropic removal of water, gave the diketal 3 and the ring cleaved compound 4 as a mixture in 85% yield. However, the same reaction carried out without removal of water resulted in the ring cleaved compound 4 only (84%) **(SCHEME I)**. The intermediacy of diketal in the formation of ring opened product has been established as follows: when the diketal 3 was treated with PTSA in benzene at room temperature, compound 4 was obtained in 78% yield. Monitoring (HPLC analysis[6]) the ketalization reaction under reflux conditions showed that the diketal 3 and the cleaved compound 4 are formed within 1 h. The monoketal 5 was prepared by reacting compound 1a with the diol 2 at room temperature for 72 h. Treatment of ketal 5 with PTSA under conditions similar to that described for the diketal did not yield compound 4, thus ruling out its intermediacy in the formation of product 4. The structure of ring cleaved product 4a has been confirmed by an unequivocal transformation **(SCHEME II)**.

The generality of this ring-opening was established by reacting the diones 1b-d with the diol 2 (R'=Me) under conditions similar to that adapted for the dione 1a.

The driving force for the facile cleavage observed may be due to three factors:

SCHEME-I



1 2 3 4

R' = H, Me

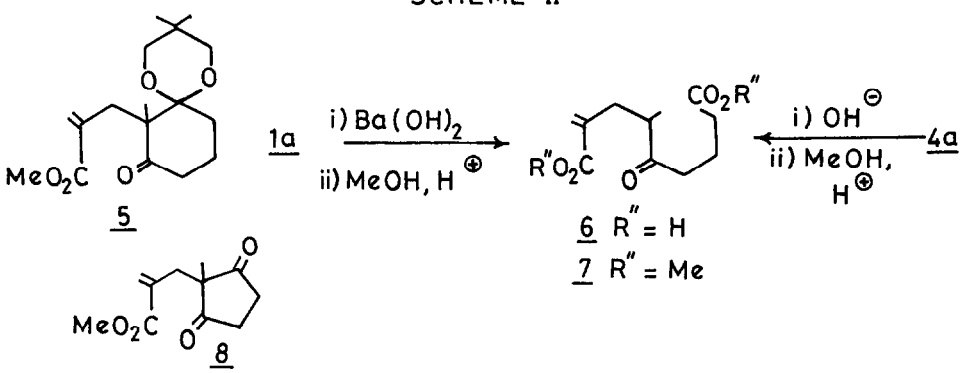
a R = CH_2–C(=CH_2)–CO_2Me

b CH_2–CH(CH_2–SPh)–CO_2Me

c CH_2–CH=CH_2

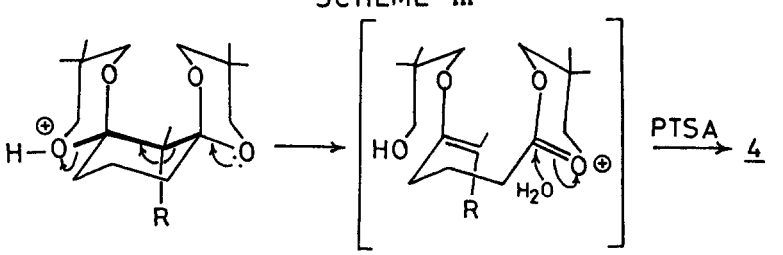
d CH_2–CH_2–SO_2Ph

SCHEME-II



5 6 R'' = H 7 R'' = Me 8

SCHEME-III



i) the nature of the glycol used for the ketalization ii) the acidity of the catalyst iii) the severe syn-axial interaction present in the diketal which is obviated by the cleavage of the ring **(SCHEME III)**.

Varying the glycol portion - viz. using ethane-1,2-diol or propane-1,3-diol - resulted in the corresponding ring-cleaved products being obtained in predominant amounts. Surprisingly the diketal from the above two diols was totally absent in the product mixture, thereby indicating the greater lability of the diketals in these cases. Replacing PTSA with collidinium p-toluenesulphonate as catalyst in the reaction furnished only the starting dione 1a even after 8 h of reflux. With pyridinium p-toluenesulphonate a small amount of monoketal was obtained (^{1}H NMR). In both cases the formation of neither the diketal 3a nor the cleaved product 4a could be detected.

Reaction of the dione 8 with the three diols, provided none of the cleaved product corresponding to 4. Only the monoketal was observed to be formed in major amounts[7]. This can be attributed to the different conformational features in cyclopentane ring.

A prior cleavage of the dione 1a to the acid under the reaction conditions followed by esterification with the diol 2 as an alternative mechanism was ruled out by the extraordinary stability of the dione towards PTSA.

The cleavage reported herein is rather unique and hitherto unreported.

Experimental Section

^{1}H NMR spectra were taken at 90 MHz (Varian EM 390) and ^{13}C NMR at 22.5 MHz (JEOL FX-90Q). Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. IR spectra were recorded on a Perkin Elmer 598 instrument. Mass spectra were recorded on a Varian Mat CH 7 and JEOL DX-303 spectrometers. Chromatographic purifications were carried out using ACME silica gel.

2-Methyl-2-(2-carbomethoxyprop-2-en-1-yl)cyclohexane-1,3-dione 1a: A mixture of 2-methylcyclohexane-1,3-dione (2.2 g, 17.5 mmol), triethylamine (15 mL) and ethyl acetate (50 mL) was refluxed for 30 min. To this a solution of methyl 3-bromo-2-bromomethylpropanoate[8] (4.54 g, 17.5 mmol) in ethyl acetate (5 mL) was added and refluxing continued for 5 h. The crude reaction mixture was washed successively with water, 10% ice-cold HCl, 5% $NaHCO_3$ solution and with water. Removal of solvent followed by chromatography furnished pure material as colourless flakes (hexane-ethyl acetate): 2.97 g, 76%, mp 65-66°C. IR (KBr): 1720, 1690, 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$):δ 1.17 (s, 3H), 1.69-2.93 (m, 8H), 3.56 (s, 3H), 5.29 (s. 1H), 5.96 (s, 1H), MS: m/z 224 (M^+). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.28; H, 7.14. Found: C, 64.42; H, 7.2.

2-Methyl-2-(2-carbomethoxyprop-2-en-1-yl)cyclopentane-1,3-dione 8: This was made as per the above procedure by reacting 2-methylcyclopentane-1,3-dione (2.24 g, 20 mmol), methyl 3-bromo-2-bromomethylpropanoate (5.2 g,20 mmol) in presence of Et_3N (25 mL). Work up followed by chromatography (benzene-ethyl acetate 8:2) furnished colourless crystals (hexane-benzene): 3.36 g, 80%, mp 43-44°C. ^{1}H NMR ($CDCl_3$):δ 1.03 (s, 3H),

2.46 (s, 2H), 2.59 (s, 4H), 3.53 (s, 3H), 5.3 (s, 1H), 5.93 (s, 1H). MS: m/z 210 (M^+).

Ketalization of compound 1a: To a solution of diketone (0.9 g, 4 mmol) in benzene (70 mL) was added diol 2 (R'=Me; 1.5 g, 14.4 mmol) and PTSA (0.05 g). The reaction mixture was refluxed for 8 h with azeotropic removal of water. It was then cooled, washed with water and dried (Na_2SO_4). Removal of solvent gave a viscous liquid. Chromatographic purification (benzene - ethyl acetate mixture 9:1) gave 3a as a viscous liquid (1.04 g). IR (CCl_4) 1720, 1630 cm^{-1}. ^1H NMR (C_6D_6)[9]: δ 0.86-1.09 (m, 15H), 1.46-3.13 (m, 8H), 3.36-3.86 (m, 9H), 4.06 (s, 2H), 5.43 (s, 1H), 6.26 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 166.86, 139.18, 126.45, 100.66, 68.86, 68.64, 66.85, 51.58, 35.81, 33.92, 33.1, 32.4, 28.93, 28.55, 22.43, 21.24, 17.99, 12.57. Anal. Calcd for $C_{22}H_{36}O_6$: C, 66.66; H, 9.09. Found: C, 66.86; H, 9.12. Further elution gave 4a as a colourless oil (0.26 g). IR (CCl_4): 3450, 1710, 1620 cm^{-1}. ^1H NMR ($CDCl_3$): δ0.86 (s, 6H), 1.0 (d, 3H), 1.63-2.69 (m, 9H), 3.03 (s, 1H), 3.13 (s, 2H), 3.56 (s, 3H), 3.69 (s, 2H), 5.26 (s, 1H), 5.82 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 212.55, 173.02, 166.9, 137.44, 126.84, 69.1, 67.6, 51.54, 44.26, 39.83, 35.74, 34.83, 32.94, 21.23, 18.37, 15.64. MS: m/z 328 (M^+). Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.19; H, 8.53. Found: C, 62.44; H, 8.48.

Similar conditions were employed for the ketalization of 1b[10], 1c[11] and 1d[12]. 4b: colourless oil; ^1H NMR (C_6D_6): δ 0.8 (s, 6H), 1.0 (d, 3H), 1.65-3.12 (m, 13H), 3.24 (s, 2H), 3.36 (s, 3H), 3.92 (s, 2H), 7.25-7.52 (m, 5H). MS: m/z 436 (M^+). 4c: colourless oil; ^1H NMR (CCl_4-DMSO-d_6) : δ 0.86 (s, 6H), 1.08 (d, 3H), 1.41-2.83 (m, 9H), 3.18 (s, 2H), 3.81 (s, 2H), 4.17 (br s, 1H), 4.87-5.62 (m, 3H).
4d: colourless oil; ^1H NMR (CCl_4-DMSO-d_6) : δ 0.83 (s, 6H), 1.03 (d, 3H), 1.43-2.80 (m, 9H), 3.03-3.33 (m, 5H), 3.78 (s, 2H), 7.56-8.03 (m, 5H).

With ethane-1,2-diol: Ketalization of 1a using ethane-1,2-diol as per the above procedure and chromatography (benzene - ethyl acetate 7:3) furnished monoketal. IR ($CHCl_3$) : 1700, 1620 cm^{-1}. ^1H NMR (C_6D_6) : δ 1.21 (s, 3H), 1.43-3.19 (m, 8H), 3.43 (s, 4H), 3.49 (s, 3H), 5.35 (s, 1H), 6.24 (s, 1H). Further elution with benzene - ethyl acetate (4:6) gave the cleaved product as a colourless oil. ^1H NMR(C_6D_6): δ 0.93 (d, 3H), 1.66-2.93 (m. 10H), 3.46 (s, 3H), 3.60 (t, 2H), 4.10 (t, 2H), 5.33 (s, 1H), 6.13 (s, 1H). MS : m/z 286 (M^+). Total yield : 72%.

Direct conversion of 1 to cleaved compound 4: A mixture of diketone 1a-d (1.8 mmol), diol 2 (R'=Me, 7.2 mmol), benzene (20 mL) and PTSA (50 mg) was refluxed for 1-5 h without azeotropic removal of water. Work up as described above followed by column chromatography furnished the cleaved compound 4a-d (70-90%).

A similar reaction of 1a, 1c and 1d with propane-1,3-diol furnished the corresponding cleaved product.

4a (R'=H) : colourless oil; ^1H NMR ($CDCl_3$): δ 1.09 (d, 3H), 1.73-2.83 (m, 11H), 3.33-4.20 (m, 8H), 5.46 (s, 1H), 6.07 (s, 1H).

4c (R'=H) : colourless oil; ^{1}H NMR ($CDCl_3$) : δ 1.09 (d, 3H), 1.51-2.60 (m, 11H), 3.57 (t, 2H), 4.07 (t, 2H), 4.20 (s, 1H), 4.74-5.80 (m, 3H).

4d (R'=H) : colourless oil; ^{1}H NMR ($CDCl_3$): δ 1.09 (d, 3H), 1.59-2.76 (m, 11H), 3.19 - 4.46 (m, 7H), 7.66 - 8.09 (m, 5H).

When 1a was reacted with ethane-1,2-diol the cleaved product was obtained in 60% yield.

Ketalization of the dione 8: Diketone 8, diol 2 (R'=Me), benzene and catalytic amount of PTSA were mixed and refluxed without azeotropic removal of water. Work up as above gave an oil. Monoketal : IR (CCl_4): 1740, 1720, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.75 (s, 3H), 0.94 (s, 3H), 1.16 (s, 3H), 2.0-2.79 (m,6H), 3.26-3.72 (m, 7H), 5.49 (s, 1H), 6.13 (s, 1H). Analysis of ^{1}H NMR revealed that the diketal is also present in the reaction product to the extent of 10%.
With propane-1,3-diol: Monoketal ^{1}H NMR ($CDCl_3$) : δ 1.07 (s, 3H), 1.67-2.89 (m, 8H), 3.66-4.09 (m, 7H), 5.56 (s, 1H), 6.17 (s, 1H).
With ethane-1,2-diol: Monoketal ^{1}H NMR ($CDCl_3$) : δ 1.37 (s, 3H), 2.28-3.17 (m, 6H), 3.86 (s, 3H), 4.17 (s, 4H), 5.66 (s, 1H), 6.30 (s, 1H).

Cleavage of diketal 3: To a solution of diketal 3a-d (R'=Me; 0.25 mmol) in benzene (10 mL) was added PTSA (10 mg) and stirred for 4 h. Work up as above gave 4a-d (yield 70-80%).

Preparation of Monoketal 5: To a solution of 1a (2.24 g, 10 mmol) in benzene (100 mL) was added diol 2 (R'=Me; 4.16 g, 40 mmol) and PTSA (100 mg). This was stirred at room temperature for 72 h. Work up followed by chromatography (hexane-benzene 1:1) furnished a colourless oil (2.08 g, 67%). IR (CCl_4): 1710, 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 0.7 (s, 3H), 1.06 (s, 3H), 1.13 (s, 3H), 1.56-3.0 (m, 8H), 3.2-3.86 (m, 7H), 5.46 (s, 1H), 6.06 (s, 1H). MS : m/z 310 (M^+). Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.8; H, 8.39. Found: C, 65.62; H, 8.42. Further elution with benzene-ethyl acetate (9:1) yielded 4a (0.49 g).

Hydrolysis of compound 4a: A mixture of ester 4a (0.23 g, 0.7 mmol), 25% NaOH solution (15 mL) and MeOH (15 mL) was refluxed for 3 h. The reaction mixture was diluted with water and extracted with ether (2 x 25 mL). The aqueous solution was acidified with ice-cold conc. HCl and extracted with ether-ethyl acetate mixture (1:1, 2 x 25 mL). The combined extract was washed with water and dried ($MgSO_4$). Removal of solvent gave a viscous liquid 6 (0.12 g, 75%). IR ($CHCl_3$): 3350 (br), 1720 (br), 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.07 (d, 3H), 1.76-2.83 (m, 9H), 5.56 (s, 1H), 6.23 (s, 1H), 8.4 (br s, 2H).

Esterification of carboxylic acid 6: To a solution of acid 6 (0.1 g, 0.43 mmol) in MeOH (10 mL) was added catalytic amount of conc. H_2SO_4 and refluxed for 6 h. The reaction mixture was diluted with water and extracted with ether (2 x 25 mL). The combined ether extract was washed with $NaHCO_3$ solution and water. Removal

of solvent gave an oil. Chromatographic purification (benzene) gave a colourless liquid 7 (0.09 g, 80%). IR ($CHCl_3$): 1720, 1620 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.03 (d, 3H), 1.69-2.86 (m, 9H), 3.59 (s, 3H), 3.73 (s, 3H), 5.46 (s, 1H), 6.07 (s, 1H).

Cleavage of the diketone 1a: To a saturated solution of $Ba(OH)_2$ (40 mL) was added compound 1a (0.4 g, 1.8 mmol) and stirred overnight at room temperature. The reaction mixture was extracted with ether. Acidification of the aqueous layer followed by extraction with ether-ethyl acetate mixture (1:1) gave a viscous liquid (0.35 g, 80%). Esterification of this liquid with MeOH as above gave 7 which was identical in all respects (HPLC, IR, NMR) with that obtained from 4a.

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References and Notes

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9. The diketal 3a was very sensitive to acid that the signals due to cleaved compound 4 were obtained when the ^1H NMR was taken in $CDCl_3$ (probably due to trace of DCl).
10. Prepared by reacting 1a with $PhSH/Et_3N$ in benzene at room temperature. Yield: 58% mp, 68-69°C. ^1H NMR (CCl_4): δ 1.13 (s, 3H), 1.75-3.23 (m, 11H), 3.46 (s, 3H), 7.06-7.33 (m, 5H). MS: m/z 334 (M^+).
11. This was made by a procedure analogous to that reported for 2-methyl-2-(prop-2-yn-1-yl)cyclohexane-1,3-dione (See reference 2).
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