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Chemo- and diastereoselective cyclic ketalization of optically pure 1-aryl-2,2-dimethylpropane-1,3-diols with phenylglyoxal**Hu Xianming and Richard M. Kellogg ****Department of Organic and Inorganic Molecular Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands
(Received March 14, 1996)*

Abstract. Reactions of optically pure 1-aryl-2,2-dimethylpropane-1,3-diols with phenylglyoxal give diastereomerically pure cyclic ketals under acid catalyzed conditions. The structure of one of the products, 2-phenyl-4-(2-chlorophenyl)-5,5-dimethyl-1,3-dioxane-2-carbaldehyde (**7**), has been determined by X-ray crystallography; reaction takes place at the keto group and the aldehyde group is oriented axially.

Introduction

Acetals and ketals are easily prepared by many procedures¹. The most common method is the acid-catalyzed reaction of alcohols with aldehydes or ketones with azeotropic removal of water. In acetalization reactions with chiral 1,2- or 1,3-diols without a C_2 symmetry axis, the formation of one diastereomer is often favoured². The cyclic products may undergo cleavage reactions, or may be used near a prochiral center to control its reactivity and stereoselectivity. On removal of the auxiliary, the newly created chirality centers remain in the final product³.

Phenylglyoxal^a with its two conjugated and highly reactive carbonyl groups is a special case⁴. The reaction of phenylglyoxal and methanol is illustrative; the aldehyde group reacts first but this product is easily isomerized into the ketal⁵. Ebens et al.⁶ have found that optically pure 1-aryl-2,2-dimethylpropane-1,3-diols react with substituted benzaldehydes to give with high diastereoselectivity cyclic acetals. We were interested in combining this chiral auxiliary with phenylglyoxal but unsure whether the rate of cyclization would predominate over that of polymerization, and, if cyclization were to occur, whether the ketone or aldehyde group would react fastest.

We report the reaction of optically pure 1-aryl-2,2-dimethylpropane-1,3-diols with 1- or 2-substituted phenylglyoxals **3-5**, which lead to the trapping of cyclic products. The products were isolated and in each case a single diastereomeric ketalization product was obtained (see Scheme 1). The structures of the condensation products were determined by NMR to be 2-aryl-4-aryl-5,5-dimethyl-1,3-dioxane-2-carbaldehydes. That condensation had occurred at the oxo group, was obvious from observation of the low field aldehydic proton. The reaction is very selective as judged from the aldehyde peak; a small (< 3%) peak perhaps from the other diastereomer was seen adjacent to the major -CHO absorption.

The reactions were not optimized; the yields lie between 40 and 72%. Some polymer was also isolated. The use of the

Lewis acid $BF_3 \cdot O(C_2H_5)_2$ led to lower yields and more polymer.

The absolute configuration of the cyclic acetal of optically pure (*S*)-(-)-**2** with benzaldehyde has been shown to be (2*S*,4*S*) by NOESY-NMR spectroscopy (phenyl equatorial)⁶. Owing to the absence of an anomeric proton, NMR methods unfortunately are not suitable to establish the configuration and conformation of the analogous condensation products with phenylglyoxal. This information is needed for further study of nucleophilic-addition and ring-opening reactions. A determination of the X-ray crystal structure of **7** derived from reaction of *S*-**2** with **4** has been carried out. The postulated structure is confirmed and the configuration is 2*R*,4*S* with the aldehyde group axial (see Figure 1). The configurations of **6** and **8-11** are assumed to be identical.

The speed of cyclization relative to polymerization is probably due to the Thorpe-Ingold (the *gem*-dialkyl) effect⁷. In a wide variety of compounds, ring closure is facilitated when a *gem*-dialkyl substitution pattern is present in the open chain compound. This effect originates from the combined effects of a lower enthalpy of the cyclized product, and an entropy loss in the cyclization step that is smaller for substituted than

Figure 1. The X-ray structure of **7** (the mirror image of the actual product is shown).

^a Chem. Abstr. name: *a*-oxobenzeneacetaldehyde.

Scheme 1.

for unsubstituted compounds⁸. It is known for several chiral non *C*₂-symmetric 1,3-diols² that the larger substituents on the carbonyl groups tend to arrange themselves equatorially in cyclic acetal products. These results fit in well with the pattern observed here. Although we have not carried out an exhaustive survey on the reactions of all types of diols with phenylglyoxal, we have the impression that **1** and **2** are unique in suppressing polymerization^{5,9}. We have not been able to determine whether the cyclization products are formed under thermodynamic or kinetic control.

In summary, the reactions of optically pure 1-aryl-2,2-dimethylpropane-1,3-diols with phenylglyoxal give diastereomerically pure cyclic ketals under acid catalyzed conditions. Further studies of the products are in progress to determine whether diastereoselective reactions can be carried out on the aldehyde group. Crystal data for **7**: Space group *P*2₁2₁2₁; *a* = 7.867(2) Å; *b* = 8.130(2) Å; *c* = 25.758(3) Å; *V* = 1647.4(7) Å³; *Z* = 4; mol. wt. 329.81; *D*_{calc} = 1.33 g/cm³; diffractometer type: Nonius CAD4F; 293K; Mo K α radiation; 1020 reflections total. The structure was refined to final residuals *R* = 0.075 and *R*_w = 0.079.

Experimental

Materials and measurements

Optically pure 1-aryl-2,2-dimethylpropane-1,3-diols were prepared according to literature methods⁶ as were the phenylglyoxals⁴. ¹H-NMR (200 MHz) and ¹³C-NMR (50.3 MHz) spectra were determined on a Varian Gemini-200 system. CDCl₃ was used as a solvent and Me₄Si as an internal reference. Splitting patterns are designated as: s (singlet); d (doublet); t (triplet); q (quartet); b (broad); m (multiplet). IR spectra were obtained in KBr pellets with a Perkin-Elmer 781 spectrometer. Mass spectra were recorded on an AEI-MS902 mass spectrometer at 70 eV. All melting points were determined on a Mettler FP1 melting-point apparatus and are uncorrected. The X-ray crystallography was carried out on an Enraf-Nonius CAD-4F diffractometer with monochromatized Mo K α radiation (wavelength 0.71073 Å) by Mr. F. van Bolhuis and Mr. C. Kalk.

General procedure for the reaction of 1-aryl-2,2-dimethylpropane-1,3-diols and phenylglyoxals

A mixture of phenylglyoxal **1** (10 mmol), 1,3-diol (10 mmol) and *p*-toluenesulfonic acid (0.2 mol%) dissolved in benzene (140 ml) was put in a 250 ml round-bottomed flask provided with a magnetic bar and attached to a Dean-Stark trap for azeotropic removal of water. The reaction mixture was refluxed for a period of 8 hours and the small amount of water generated was removed. The solvent was removed from the mixture under reduced pressure and the residue was separated by column chromatography on aluminum oxide using dichloromethane as eluant. The condensation product was eluted first. Thick brown materials and polymer were washed out by ethanol. The collected solution was

evaporated on a rotatory evaporator under reduced pressure. The residue was crystallized from dichloromethane by slow evaporation of solvent.

(2*S*,4*R*)-(+)-2-Phenyl-2-formyl-4-phenyl-5,5-dimethyl-1,3-dioxane (**6**). ¹H-NMR (CDCl₃): 0.78 (s, 3H); 0.97 (s, 3H); 3.88 (q, ²*J* 33.0 Hz, 1H); 4.80 (s, 1H); 7.25–7.74 (m, 10H); 9.55 (s, 1H). ¹³C-NMR (CDCl₃): 18.02 (q); 21.79 (q); 34.20 (t); 74.70 (s); 82.99 (d); 116.50 (s); 126.36 (d); 127.54 (d); 127.70 (d); 127.84 (d); 128.59 (d); 129.47 (d); 135.10 (s); 137.20 (s); 198.24 (d). IR (KBr, cm⁻¹): 3062 (m); 3032 (m); 2964 (vs); 2823 (vs); 2873 (vs); 1733 (vs); 1602 (w); 1585 (s); 1544 (s); 1493 (s); 1469 (s); 1450 (s); 1391 (s); 1260 (s); 1260 (vs); 1092 (vs); 1065 (vs); 1028 (vs); 1001 (s); 911 (s); 796 (s); 739 (s); 696 (s). Exact mass for C₁₈H₁₉O₂ requires: *M* - CHO, 267.138, found: *M*⁺ - CHO, 267.138; m.p. 63–64°C; yield 60%.

(2*R*,4*S*)-(–)-2-Phenyl-2-formyl-4-(2-chlorophenyl)-5,5-dimethyl-1,3-dioxane (**7**). ¹H-NMR (CDCl₃): 0.83 (s, 3H); 1.18 (s, 3H); 3.92 (q, ²*J* 43.7 Hz, 1H); 5.42 (s, 1H); 7.25–7.69 (m, 9H); 9.57 (s, 1H). ¹³C-NMR (CDCl₃): 18.68 (q); 21.73 (q); 35.73 (s); 75.05 (t); 78.14 (d); 116.80 (s); 126.30 (d); 126.37 (d); 128.59 (d); 129.09 (d); 129.30 (d); 129.50 (d); 130.29 (d); 136.50 (s); 137.40 (s); 137.65 (s); 198.13 (d). IR (KBr, cm⁻¹): 3072 (m); 3060 (w); 2972 (vs); 2823 (vs); 2883 (s); 1742 (vs); 1600 (m); 1550 (s); 1508 (s); 1483 (s); 1395 (s); 1372 (s); 1275 (vs); 1120 (vs); 1075 (s); 1060 (s); 1040 (s); 755 (s); 718 (s). Exact mass for C₁₈H₁₈ClO₂ requires: *M* - CHO, 301.099, found: *M*⁺ - CHO, 301.099; m.p. 91–92°C; yield 72%.

(2*S*,4*R*)-(+)-2-(2-Chlorophenyl)-4-(2-chlorophenyl)-5,5-dimethyl-1,3-dioxane-2-carbaldehyde (**8**). ¹H-NMR (CDCl₃): 0.83 (s, 3H); 1.07 (s, 3H); 4.01 (q, ²*J* = 43.0 Hz, 1H); 5.23 (s, 1H); 7.20–7.76 (m, 8H); 9.83 (s, 1H). ¹³C-NMR (CDCl₃): 18.79 (q); 21.64 (q); 35.57 (t); 79.18 (s); 82.76 (d); 100.88 (s); 126.37 (d); 126.97 (d); 127.70 (d); 128.17 (d); 128.55 (d); 128.97 (d); 129.10 (d); 129.22 (s); 130.33 (d); 130.36 (s); 132.74 (s); 135.98 (s); 196.47 (d). IR (KBr, cm⁻¹): 3082 (m); 2972 (vs); 240 (s); 2842 (s); 1735 (vs); 1600 (m); 1571 (w); 1474 (s); 1438 (s); 197 (s); 1372 (m); 1280 (s); 1270 (s); 1120 (vs); 1056 (vs); 1006 (s); 941 (m); 760 (s); 731 (m); 704 (m). Exact mass for C₁₈H₁₇Cl₂O₂ requires: *M* - CHO, 335.061 found: *M*⁺ - CHO, 335.061; m.p. 101–103°C; yield 40%.

(2*R*,4*S*)-(–)-2-(2-Chlorophenyl)-4-phenyl-5,5-dimethyl-1,3-dioxane-2-carbaldehyde (**9**). ¹H-NMR (CDCl₃): 0.80 (s, 3H); 0.98 (s, 3H); 3.98 (q, ²*J* = 37.2 Hz, 1H); 4.92 (s, 1H); 7.27–8.13 (m, 9H); 9.77 (s, 1H). ¹³C-NMR (CDCl₃): 18.15 (q); 21.80 (q); 34.53 (t); 74.48 (s); 87.62 (d); 100.92 (s); 126.3 (d); 127.00 (d); 127.28 (d); 127.92 (d); 128.65 (s); 129.98 (d); 130.87 (d); 132.05 (d); 132.17 (s); 196.37 (d). IR (KBr, cm⁻¹): 3074 (m); 3041 (m); 2974 (vs); 2887 (s); 1745 (vs); 1600 (m); 1582 (w); 1504 (m); 1475 (s); 1454 (s); 1447 (s); 1397 (s); 1270 (s); 1292 (s); 1275 (s); 1245 (s); 1125 (vs); 1055 (vs); 1029 (vs); 951 (m); 801 (w); 745 (s); 705 (s). Exact mass for C₁₈H₁₈ClO₂ requires: *M* - CHO, 301.100, found: *M*⁺ - CHO, 301.100; m.p. 85–87°C; yield 51%.

(2*S*,4*R*)-(+)-2-(4-Methylphenyl)-4-phenyl-5,5-dimethyl-1,3-dioxane-2-carbaldehyde (**10**). ¹H-NMR (CDCl₃): 0.77 (s, 3H); 0.95 (s, 3H); 2.39 (s, 3H); 3.85 (q, ²*J* = 28.1 Hz, 1H); 4.79 (s, 1H); 7.24–7.60 (m, 9H); 9.52 (s, 1H). ¹³C-NMR (CDCl₃): 17.99 (q); 21.77 (q); 34.37 (t); 34.40 (q); 74.64 (s); 82.92 (d); 114.35 (s); 126.27 (d); 127.38 (d); 127.54 (d); 127.67 (d); 127.85 (s); 128.14 (s); 129.32 (d); 129.35 (s); 198.24 (d). IR (KBr, cm⁻¹): 3078 (m); 3042 (m); 2981 (vs); 2938 (s); 2880 (s); 1740 (vs); 1605 (m); 1510 (m); 1500 (m); 1471 (s); 1455 (s); 1400 (s); 1371

(s); 1270 (vs); 1120 (vs); 1060 (vs); 1028 (vs); 1002 (s); 915 (m); 817 (s); 800 (m); 742 (s); 706 (s); 626 (m), Exact mass for $C_{19}H_{21}O_2$ requires: M - CHO, 281.154, found: M^+ - CHO, 281.154; m.p. 64-66°C; yield, 56%.

(2R,4S)-(+)-2-(4-Methylphenyl)-4-(2-chlorophenyl)-5,5-dimethyl-1,3-dioxane-2-carbaldehyde (**11**). 1H -NMR ($CDCl_3$): 1.04 (s, 3H); 1.09 (s, 3H); 2.43 (s, 3H); 4.32 (q, $^2J = 85.3$ Hz, 1H); 5.35 (s, 1H); 7.17-7.96 (m, 8H); 9.52 (s, 1H). ^{13}C -NMR ($CDCl_3$): 19.07 (q); 21.42 (q); 40.68 (t); 70.80 (s); 72.23 (q); 78.07 (d); 114.05 (s); 126.21 (d); 128.46 (d); 128.52 (d); 129.13 (d); 129.25 (d); 129.63 (d); 129.79 (s); 129.86 (s); 143.69 (s); 166.88 (s); 198.15 (d). IR (KBr, cm^{-1}): 3074 (m); 3041 (m); 2971 (vs); 2942 (s); 2881 (s); 1721 (vs); 1610 (m); 1575 (w); 1510 (w); 1473 (s); 1441 (s); 1395 (s); 1372 (s); 1278 (vs); 1180 (s); 1110 (vs); 1045 (s); 1028 (s); 1000 (m); 914 (w); 845 (m); 818 (m); 755 (s); 715 (m). Exact mass for $C_{20}H_{21}ClO_3$ requires: M - CHO, 315.115, found: M^+ - CHO, 315.115; m.p. 93-95°C; yield, 48%.

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