Reactions of Co-ordinated Ligands. Part 8.[1] Reaction of Grignard Reagents with 2-Alkoxy-1,3-dioxolans; an Improved Route to Aldehydes

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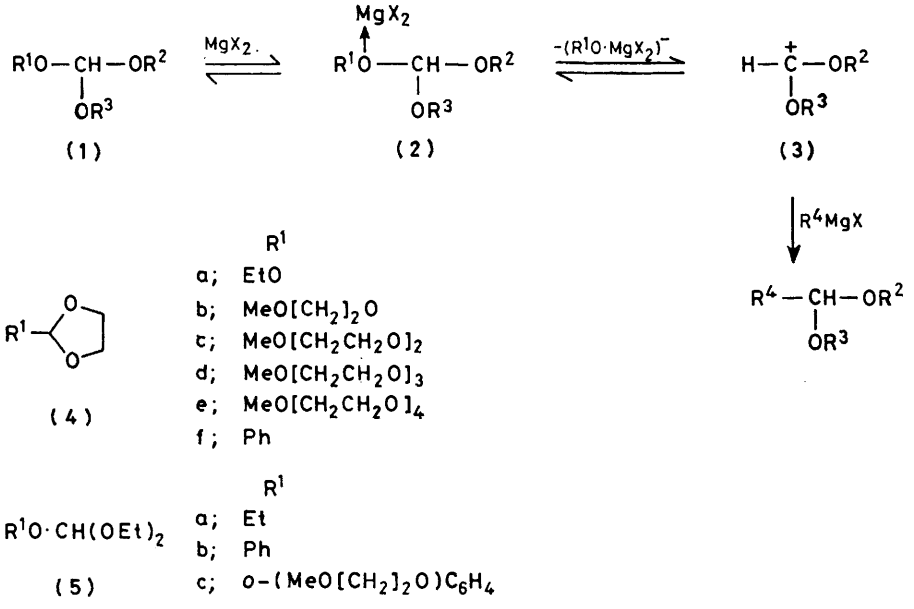
The yields of 2-phenyl-1,3-dioxolan obtained from phenylmagnesium bromide and 2-alkoxy-1,3-dioxolans in which the alkoxy-group is of the type $Me[O{\cdot}CH_2{\cdot}CH_2]_n{-}O$ increase as the value of *n* proceeds along the series 4,3,1,2. Several Grignard reagents (including phenylmagnesium bromide) react with the 2-alkoxy-1,3-dioxolan in which $n = 2$ to give the expected 2-substituted-1,3-dixolans, whose yields are considerably higher than those of the diethyl acetals obtained from the corresponding reaction with ethyl orthoformate.

A STANDARD route to acetals (and hence aldehydes) is the reaction between a Grignard reagent and an orthoformic ester. As a result of a stereochemical investigation in which 2-alkoxy-1,3-dioxans were used, Eliel and Nader [2] suggested that this reaction involves attack by the Grignard reagent on a carbonium ion (3), which is formed in the rate-determining step of the reaction by



loss of a co-ordinated alkoxide group from a magnesium complex (2) of the orthoformic ester. On the basis of this suggestion it can be predicted that the reaction would proceed more readily if the co-ordinated oxygen atom in the magnesium complex (2) was part of a chelating system, since this would increase the affinity of the alkoxy-group for the magnesium atom and hence increase the concentration of the complex (2). In order to confirm this prediction we have examined the reaction of Grignard reagents with the series of 2-alkoxy-1,3-dioxolans (4a—e).

RESULTS AND DISCUSSION

The ethoxydioxolan (4a) was prepared from 1,2-dihydroxyethane and ethyl orthoformate as described by Baganz and Domaschke,[3] except that toluene-*p*-sulphonic acid was used as the catalyst in place of sulphuric acid. The other members (4b—e) of the series were prepared by heating (4a) with the appropriate alcohol in the presence of toluene-*p*-sulphonic acid until the calculated amount of ethanol had distilled from the reaction mixture. With all five dioxolans the ^1H n.m.r. spectrum showed a singlet at δ 5.8 (H–C-2) and a symmetrical pair of multiplets centred at δ 4.0 (protons on C-4 and C-5) characteristic [4] of 2-alkoxy-1,3-dioxolans, while the mass spectrum (electron impact) showed a base peak at *m/e* 73 corresponding to the ion (3; R^1, $R^2 = -CH_2CH_2-$).[5] The latter spectrum showed no molecular ion M^+, and even under field-desorption conditions only a very weak $(M + 1)^+$ ion was observed; undoubtedly this is due to the ease of fragmentation of the O–C-2 bond.

In order to compare the reactivities of the dioxolans (4a—e) towards a Grignard reagent, each compound was heated under reflux for 2 h with a standard solution of phenylmagnesium bromide in tetrahydrofuran, and the resultant mixture of unchanged dioxolan and 2-phenyl-1,3-dioxolan (4f) was either separated by distillation or examined quantitatively by gas-liquid chromatography. For comparison purposes, ethyl orthoformate (5a) was treated in a similar manner. The results are included in

the Table, and it can be seen that in accordance with the prediction, the dioxolans (4b and c) which have a bi- and tri-dentate alkoxy group, respectively, gave substantially higher yields of the 2-phenyl compound than did the dioxolan (4a). The relatively lower yields obtained from (4d and e) presumably arise because the alkoxy-groups in these dioxolans contain more oxygen atoms than are required to satisfy the remaining co-ordination requirements of the magnesium atom, and hence it is possible

Yields of acetals obtained from the reaction in tetrahydrofuran between Grignard reagents (RMgBr) and orthoesters

R	Ortho-ester	Reaction time/h	Yield of acetal (%)	Yield of unreacted ortho-ester (%)
Ph	(5a)	2	<1 [a]	68 [b]
Ph	(4a)	2	<1 [a]	71 [b]
Ph	(4b)	2	40,[a] 44 [a,c]	40,[a] 41 [a,c]
Ph	(4c)	2	72,[a] 70 [a,c]	10 [a] 15 [b,c]
Ph	(4c)	4	86 [b]	
Ph	(4d)	2	24,[b] 29,[b,c]	63,[b] 67 [a,c]
Ph	(4e)	2	12 [b]	75 [b]
$MeO[CH_2]_3$	(5a)	18	3 [a]	77 [b]
$MeO[CH_2]_3$	(4c)	18	55 [d]	22 [b]
p-$MeOC_6H_4$	(5a)	6	3 [b]	58 [b]
p-$MeOC_6H_4$	(4c)	6	48 [b]	32 [b]
EtCH(Me)	(5a)	7	<1 [a]	81 [b]
EtCH(Me)	(4c)	7	45 [b]	42 [b]
EtCH(Me)	(5b)	0.5	36 [b]	47 [b]
EtCH(Me)	(5c)	0.5	79 [b]	8 [b]

[a] Determined by gas-liquid chromatography. [b] Determined by fractional distillation. [c] Yield from duplicate experiment. [d] Determined by H^1 n.m.r.; acid-catalysed hydrolysis of the reaction product gave a 45% yield (based on RMgBr) of 4-methoxybutyraldehyde.

for the magnesium atom to be fully co-ordinated without being bonded to the oxygen atom directly attached to C-2 of the dioxolan ring; co-ordination of this oxygen is essential, of course, for reaction to occur.

The most reactive of the dioxolans, (4c), was treated with 3-methoxypropylmagnesium bromide and with p-methoxyphenylmagnesium bromide. Both these Grignard reagents have been reported [6,7] to give substantially lower yields of diethyl acetals in their reaction with ethyl orthoformate than obtained with most Grignard reagents. In both cases the yield of 2-substituted dioxolan obtained from (4c) was considerably higher than the yield of diethyl acetal obtained from ethyl orthoformate under identical conditions (see Table).

As 2-substituted-1,3-dioxolans are readily hydrolysed in excellent yield to the parent aldehyde,[8] it is apparent that as far as overall yield is concerned the dioxolan (4c) is superior to ethyl orthoformate for preparing aldehydes from Grignard reagents. In 1970, Stetter and Reske [9] showed that this is also true of diethyl phenyl orthoformate (5b), which recently has become commercially available and is now recommended for preparing aldehydes in preference of ethyl orthoformate.[10] With this orthoester the higher reactivity towards Grignard reagents is the direct result of a co-ordinated phenoxide anion being a better leaving group than a co-ordinated ethoxide anion; the rate-determining step (2)→(3) in the reaction therefore proceeds more rapidly when R = Ph than when R = Et. However, from the results decribed so far it was evident to us that the chelating analogue (5c) should be even more reactive towards Grignard reagents than (5b). The former orthoester, therefore, was prepared by treating equimolar amounts of 1,2-dihydroxybenzene and the toluene-p-sulphonate of 2-methoxyethanol with one equivalent of sodium methoxide, and then heating the resultant o-(2-methoxyethoxy)phenol with ethyl orthoformate in the presence of ethanolic hydrogen chloride. The relative reactivities of ethyl orthoformate, the chelating dioxolan (4c), and the two aromatic orthoesters (5b and c) towards a Grignard reagent were then determined using 1-methylpropylmagnesium bromide in tetrahydrofuran. This reagent was chosen as it also gives unusually low yields (steric hindrance?) in its reactions with ethyl orthoformate.[11] As expected, and as shown in the Table, higher yields of product were obtained when ethyl orthoformate was replaced by the chelating dioxolan (4c), and when the phenoxy-compound (5b) was replaced by the chelating analogue (5c). Indeed, in the latter case the increase in yield was great enough to suggest that (5c) could replace (5b) as a standard reagent for preparing aldehydes from Grignard reagents if a more efficient synthesis of the former compound was available. In this connection it should be noted that an industrial preparation of o-(2-methoxyethoxy)phenol, the immediate precursor of the orthoester, is described in the patent literature.[12]

EXPERIMENTAL

^1H N.m.r. spectra were recorded on $CDCl_3$ solutions (with $SiMe_4$ as an internal standard) with a Perkin-Elmer R14 instrument, and mass spectra with a Varian CH5D instrument. G.l.c. analysis of reaction products were performed on a Varian Aerograph instrument using 10% Carbowax 20M as the stationary phase; in every case a calibration curve was constructed initially using mixtures of known composition, and the figures in the Table are considered to be accurate to ±2%.

The methods described in the literature were used to prepare authentic samples of the diethyl acetals and the diethylene acetals of benzaldehyde,[13,14] 4-methoxybutyraldehyde,[6] 2-methylbutyraldehyde,[11,15] and p-methoxybenzaldehyde.[14,16] In every case the boiling point and refractive index were in agreement with those reported. Tetrahydrofuran was dried by use of powdered potassium hydroxide.[17]

o-(2-*Methoxyethoxy*)*phenol*.—A mixture of 1,2-dihydroxybenzene (61 g), 2-methoxyethyl toluene-p-sulphonate [18] (127 g), and sodium methoxide [from sodium (12.6 g) and methanol (1 200 ml)] was refluxed for 4 h and then kept overnight at room temperature. The methanol was removed under reduced pressure, and the residue was extracted with ether to give a brown oil which was redissolved in methanol (250 ml). The solution was treated with lead(II) acetate (80 g) in methanol (400 ml) and then filtered to remove the lead(II) complex of the unchanged 1,2-

dihydroxybenzene. Hydrogen sulphide was bubbled through the filtrate, and the precipitate of lead(II) sulphide was filtered off. The methanol was removed from the filtrate under reduced pressure, and the residue was dissolved in ether (250 ml). The solution was extracted with 5% aqueous sodium hydroxide (500 ml), and the extract was acidified with 5N-hydrochloric acid and extracted with ether to give the phenol (38.5 g, 42%), b.p. 93—98 °C at 0.7 mmHg (lit.,[12] b.p. 245 °C), n_D^{20} 1.528 2.

Diethyl o-(2-*Methoxyethoxy*)*phenyl Orthoformate* (5c).—A mixture of the preceding phenol (27 g), ethyl orthoformate (24 g), and a saturated solution of hydrogen chloride in dry ethanol (1 ml) was heated at 130 °C until the calculated volume of ethanol had distilled off, and was then dissolved in ether (400 ml). The solution was extracted with 2N-aqueous sodium hydroxide (200 ml), dried ($CaCO_3$), and fractionated to give the *orthoester* (9 g, 21%), b.p. 128—130 °C at 1 mmHg, n_D^{18} 1.488 2; δ 1.23 (6 H, t, OCH_2CH_3), 3.42 (3 H, s, OMe), 3.82 (6 H, m, OCH_2CH_2OMe and OCH_2Me), 4.14 (2 H, t, OCH_2CH_2OMe), 5.74 (H, s, ArOCH), and 7.02 (4 H, m, C_6H_4); *m/e* 225 (M^+ — OEt) and 103 [$\overset{+}{C}H(OEt)_2$] (Found: C, 62.2; H, 8.1. $C_{14}H_{22}O_5$ requires C, 62.2; H, 8.2%).

2-(2-*Methoxyethoxy*)-1,3-*dioxolan* (4b).—2-Methoxyethanol (40 g) was added dropwise with stirring to 2-ethoxy-1,3-dioxolan [3] (59 g) and toluene-*p*-sulphonic acid (0.80 g), and then ethanol (26 g) was removed by distillation through a 25-cm Dufton column. Fractionation of the residue gave the *dioxolan* (43 g, 58%), b.p. 95 °C at 18 mmHg, n_D^{22} 1.426 0; δ 3.35 (3 H, s, OMe) and 3.59 (4 H, m, OCH_2CH_2O) (Found: C, 48.4; H, 8.5. $C_6H_{12}O_4$ requires C, 48.6; H, 8.2%).

The following compounds were prepared similarly: 2-[2-(2-*methoxyethoxy*)*ethoxy*-1,3-*dioxolan* (4c) 44%, b.p. 96 °C at 0.3 mmHg, n_D^{19} 1.437 6 (Found: C, 49.7; H, 8.6. $C_8H_{16}O_5$ requires C, 50.0; H, 8.4%); 2-{2-[2-(2-*methoxyethoxy*)*ethoxy*]*ethoxy*}-1,3-*dioxolan* (4d) 41%, b.p. 139 °C at 0.2 mmHg, n_D^{22} 1.445 0 (Found: C, 50.6; H, 8.7. $C_{10}H_{20}O_6$requires C, 50.8; H, 8.5%); 2-(2-{2-[2-(2-*methoxyethoxy*)*ethoxy*]*ethoxy*}*ethoxy*)-1,3-*dioxolan* (4e) 43%, b.p. 159 °C at 0.2 mmHg, n_D^{23} 1.447 7 (Found: C, 50.7; H, 8.5. C_{12}-$H_{24}O_7$ requires C, 51.4; H, 8.6%).

General Procedure for the Reaction of Grignard Reagents with Orthoesters.—The Grignard reagent was prepared (under N_2) in the usual manner from magnesium (0.041 g atom), the organic halide (0.043 mol), and dry tetrahydrofuran (20 ml). The orthoester (0.035 mol) in dry tetrahydrofuran (80 ml) was then added dropwise with stirring at room temperature, and the resultant solution was refluxed under nitrogen for the period shown in the Table. The solution was cooled in ice, and ice-cold saturated aqueous potassium carbonate (10 ml) was added dropwise with stirring. The precipitate was filtered off and washed with ether (5 × 15 ml), and the filtrate and washings were combined and dried (K_2CO_3). The solvent was carefully removed by fractionation through a 25-cm Dufton column, and the components of the residual liquid were either determined by gas-liquid chromatography or separated by fractional distillation.

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