Tetrahedron Letters,Vol.30,No.27,pp 3547-3550 ,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

EXTENDED SCOPE OF THE GRIGNARD REACTION OF β-HALOACETALS. USE OF ACYCLIC ACETALS

A. GREINER

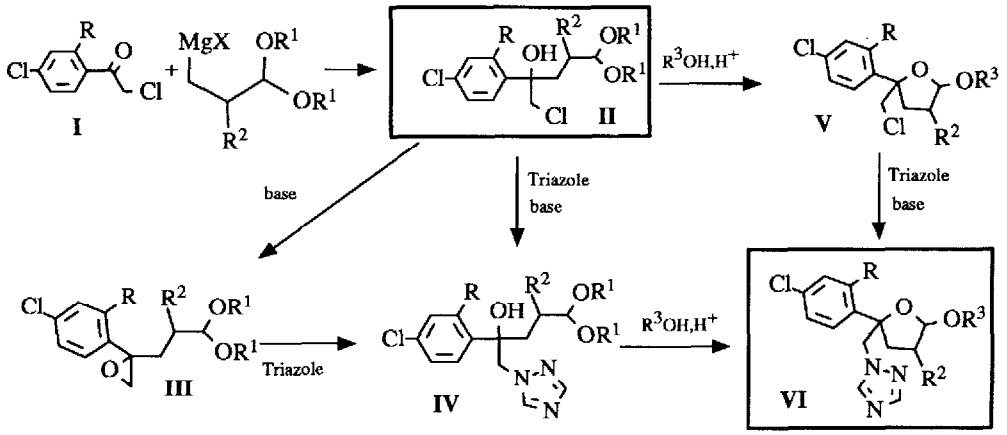
Rhône Poulenc Agrochimie, Centre de Recherches de la Dargoire, BP 9163
69263-LYON CEDEX 09, France

SUMMARY :Careful control of reaction conditions permits the high yield preparation of Grignard reagents from β-halogenoacetals and their condensation with carbonyl compounds, regardless of the halogen (bromine, chlorine) or acetal structure (cyclic, acyclic).

In connection with our research on biologically active compounds, a flexible route to γ-hydroxyaldehydes was needed. A convenient approach to these intermediates, is the coupling of a propionaldehyde homoenolate equivalent with a carbonyl derivative. The simplest of these three-carbon homologating agents[1] is 2-(bromoethyl)1,3-dioxolane, **1a** which has been used extensively since Büchi described the reaction conditions allowing the preparation of this homologating reagent in THF[2]. However side reactions such as Würtz coupling[3] and decomposition during the preparation of the Grignard reagent means that usually two or more molar equivalents of **1a** are required. Another recently proposed explanation for this concluded that a dialkylmagnesium species was formed [4].
An extensive investigation of reaction parameters and reagent structure lead us to a broader application of the Grignard reagents from β-halogenoacetals.

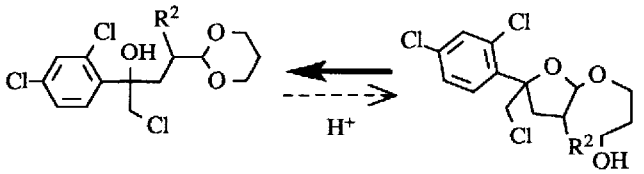
Reactivity of β-bromoalkyldioxolanes and their Grignard reagents:

In our hands, only a slight excess (20 to 30%) of bromide is needed, together with a slight excess of magnesium (1.1 eq.) activated before reaction with a little 1,2-dibromoethane, **provided the temperature is kept below 20°C** during reaction with magnesium[5] and **under vigourous stirring**. If the bromide **1a** is freshly prepared or distilled, the temperature can be lowered to 15°C without decreasing the rate of the reaction[6,7]. Condensation of Büchi's reagent with the poorly reactive and base sensitive α-chloroacetophenones gave high yields of chlorohydrins (table 1, entries 1,2,3), if used quickly after preparation[8]. At this point, the halogenated acetophenones, having a low solubility in THF, were added as a toluene solution. From our experience, toluene has a beneficial effect on yield during condensation of Grignard reagents and aids the redissolution of precipitated organomagnesium species in THF. These chlorohydrins were used to prepare in a few steps the diastereomeric triazole derivatives **VI** bearing an alkoxytetrahydrofurane moiety, which show excellent biological activity against a wide range of fungi[9] .

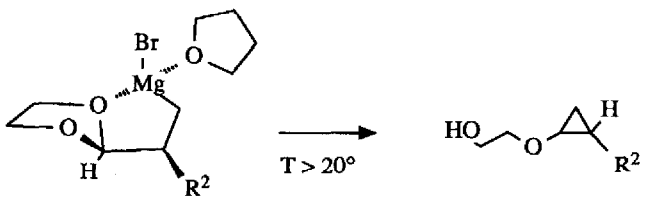


Next, we needed to extend our strategy to analogous structures having an extra alkyl substituant on the tetrahydrofurane ring. Following our previous strategy, the homologous bromide **1b**, was reacted, with efficient stirring and below 20°C, with magnesium actived by 1,2-dibromoethane. However, the condensation with α-chloroacetophenones yielded, in addition to the expected chlorohydrin, a **large amount of the reduction product** of the starting ketone (table 1, entry 4). A larger substituant α to the acetal moiety, **1c**, gave an even more disapointing result with almost exclusive reduction (table 1, entry 5). Hindered Grignard reagents are known to effect reduction instead of condensation with carbonyl compounds[10].

The use of the easier to handle cyclic ketals from 1,3-propanediols[11] was unsatisfactory for our purpose, as the equilibrium for conversion to alkoxytetrahydrofuranes was shifted towards the dioxane ring[12].



In Grignard reagents prepared from β-haloacetals, the magnesium ion is strongly coordinated to the oxygen atoms; this leads to spontaneous exothermic decomposition during preparation at temperatures above 20°C, due to the Lewis acid character of magnesium, although at a slow rate below 35°C as found by Büchi for 5-membered acetals. Thus, an extra substituant in position α to the acetal moiety gives rise to a highly crowded species in the case of acetals derived from ethylene glycol. For these reasons, we decided to investigate the Grignard reaction of the less basic acyclic β-haloacetals, despite the claim that they are unsatisfactory, producing instead alkylcyclopropylethers, even in THF[13].



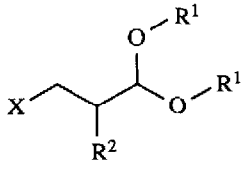
Under our controlled conditions, the produced organo-metallic species reacted satisfactory with the

α-chloroacetophenones, **producing good yields of the expected chlorohydrins II, even with an alkyl substituant α to the acetal moiety**. Their reaction was not quite as clean as for unsubstituted reagents but the reduction product was only present in trace amounts and the crude diastereomeric chlorohydrins (1:1 mixture) could be carried further without purification to give precursors of biologically active compounds in acceptable yields (table 1 entries 6,7).

Nature of the halogen atom:

The iodo analogs of Büchi's acetal react readily with magnesium, even at very low temperature but **should be used with great care**[14]. Another extension was sought by replacing the bromine atom by a less expensive chlorine atom. An advantage of this, is the improved thermal stability of the β-haloacetal during purification by distillation, as the β-bromoacetals decompose exothermically[15] above 120°C, the chloro derivatives being stable until 220°C. This improved thermal stability is obtained at the expense of reactivity towards magnesium[16] but this drawback could be circumvented by using freshly distilled chloroacetals at a 5 M concentration in THF[17]. The temperature in this case had to be kept between 20°and 25° to allow the reaction to proceed. Under these circumstances, the inexpensive 3-chloro-1,1-diethoxypropane could, for the first time, be reacted with magnesium, and the corresponding Grignard reagent condensed with a carbonyl compound (table 1 entries 8,9).

TABLE 1: Condensation of Grignard reagents from β-haloacetals with α-chloroacetophenones **I**



1 X=Br, R^1= -$(CH_2)_2$- **4** X=Cl, R^1= CH_3

2 X=Cl, R^1= -$(CH_2)_2$- **5** X=Cl, R^1= C_2H_5

3 X=Br, R^1= CH_3 **6** X=Br, R^1= -$(CH_2)_3$-

R^2= **a** H; **b** CH_3; **c** nC_3H_7

Entry	Reagent Type/Mol.Excess/Temp.			% Ketone Conv.		Overall isolated Yield/ketone[18]
1	**1a**	1.3 eq.	20-25°C	90	R=Cl	epoxide **III** 74% (*distilled*)
2	**1a**	"	15-20°C	>95	"	chlorohydrin **II** 83% (*recrist.*)
3	**1a**	"	"	>95	R=H	chlorohydrin **II** 80% (*recrist.*)
4	**1b**	"	"	70	R=Cl	reduction 80% (*GLC only*)
5	**1c**	"	"	70	"	reduction >90% (*GLC only*)
6	**3b**	1.2 eq.	"	>95	"	epoxide **III** 68% (*distilled*)
7	**3c**	1.3 eq.	"	80	"	tetrahydrofurane **V** 30% (*dist.*)
8	**4b**	1.2 eq.	20-25°C	90	"	epoxide **III** 50% (*distilled*)
9	**5a**	"	"	85	"	addition >95% (*GLC only*)

General procedure for Grignard reaction of β-haloacetals:

β-Bromoacetals: All Grignard reagents are prepared at 15 to 20°C, by dropwise addition of a 1 to 1.5 M THF solution of the acetal to 1,2-dibromoethane activated magnesium turnings[5]. After all magnesium has reacted, a toluene solution of the corresponding α-chloroacetophenone is added at -30°C[8].

β-Chloroacetals: The Grignard reagents are obtained on up to a 1 M scale by adding at once a 5 M THF solution

of the **freshly distilled acetal** to the activated magnesium turnings and controlling the temperature between 20°C and 25°C by using a dry ice/acetone bath. After completion, the medium is diluted to a 1.5 M concentration with dry toluene and used as above.

During this investigation, we have shown **the versatile synthetic utility of a wide range of** (chlorinated or brominated, cyclic or acyclic, α-substituted or unsubstituted) **β-haloacetals**[19], by using carefully adapted reaction conditions.

References and notes.

1. J.C.STOWELL, Chem.Rev. (1984) **84**, 409 and references cited therein.
2. G.BUCHI, H.WUEST J.Org.Chem. (1969) **34**, 1122.
3. S.A.BAL, A.MARFAT, P.HELQUIST J.Org.Chem. (1982) **47**, 5045.
4. M.SWORIN, W.L.NEUMANN Tetrahedron Lett. (1987) **28**, 3217.
5. Commercial magnesium turnings fom FLUKA, ref. 63035 were used.
6. On a large scale temperatures as low as 12°C have been used successfully in our lab for this reaction.
7. Several authors prepared this type of reagent at 25°C, but needed an excess of magnesium or the activated powder to succeed. See for exemple: A.A.PONARAS Tetrahedron Letters (1976), 3105 ; A.MARFAT, P.HELQUIST Tetrahedron Lett. (1987) **28**, 4217. From our experience, a temperature of 25°C, although being satisfactory on small scale, lowers already the yield on a large scale.
8. Addition temperature should be maintained below 0°C. At higher temperatures, a significant amount of epoxide is formed. The reaction medium is always quenched with anhydrous acetic acid at low temperature 15 minutes after completed addition of carbonyl compounds. Yield was not improved by longer reaction times.
9. RHONE-POULENC AGROCHIMIE European Patent 151084; C.A. (1985) **103**, 196107.
10. F.C.WHITMORE, R.S.GEORGE J.Am.Chem.Soc (1942) **64**, 1239.
11. J.C.STOWELL J.Org.Chem. (1976) **41**, 560.
12. For a convenient deprotection procedure of dioxanes see for exemple:T.SATO, K.NARUSE, T.FUJISAWA Tetrahedron Lett. (1982) **23**, 3587.
13. J.P.GALY Bull.Chem.Soc.Fr. (1971), 4582.
14. CAUTION!!! the corresponding iodo derivative may explode violently on distillation: J.C.STOWELL, B.T.KING, H.F.HAUCK Jr. J.Org.Chem. (1983) **48**, 5381.
15. Stability of haloacetals was checked by thermal differential analysis and gave the following decomposition thresholds: **1a**: 120°C (145 cal./g); **2a**: 210°C; **5a**: 170°C; **6a**: 215°C.
16. D.N.BRATTESANI, C.H.HEATHCOCK J.Org.Chem. (1975) **40**, 2165.
17. C.P. FORBES, G.L. WENTELER, A. WIECHERS, J.Chem.Soc. Perkin I (1977), 2353.
18. Physical data of isolated products: **epoxide III** (entry 1) R=Cl, R^1=$(CH_2)_2$, R^2=H; $Bp_{0.02}$= 147-150°C; NMR: ^{1}H ($CDCl_3$): CH_2-CH_2: 1.55,1.71,1.71,2.21 (4H,m); CH_2O: 2.73,2.99 (2H,m); $O(CH_2)_2O$: 3.76,3.86 (4H,m); OCHO: 4.78 (1H,m); Ph-H: 7.16 (1H,m) 7.29 (1H,d) 7.30 (1H,d). **chlorohydrin II** (entry 2) R=Cl, R^1=$(CH_2)_2$, R^2=H; Mp= 87°C(heptane); NMR: ^{1}H ($CDCl_3$):CH_2-CH_2: 1.55,1.55,2.05,2.62 (4H,m); CH_2Cl: 4.01,4.26 (2H,m); $O(CH_2)_2O$: 3.85,3.96 (4H,m); OCHO: 4.83 (1H,m); Ph-H: 7.28 (1H,m) 7.37 (1H,d) 7.79 (1H,d). **chlorohydrin II** (entry 3) R=H, R^1=$(CH_2)_2$, R^2=H; Mp= 99°C(cyclohexane); NMR: ^{1}H ($CDCl_3$):CH_2-CH_2: 1.62,2.01 (4H,m); CH_2Cl: 3.75 (2H,s); $O(CH_2)_2O$: 3.87 (4H,m); OCHO: 4.84 (1H,m); Ph-H: 7.38 (4H,s). **epoxide III** (entries 6,8) R=Cl, R^1=CH_3, R^2=CH_3 $Bp_{0.07}$= 125-138°C; NMR: ^{1}H ($CDCl_3$): **diast.A**: CH_3-CH: 1.00 (3H,d); CH_2O: 2.72,2.96 (2H,m); OCH_3: 3.20,3.22 (6H,s); OCHO: 3.92 (1H,m); Ph-H: 7.24 (1H,m) 7.36 (1H,d) 7.44 (1H,d). **diast.B**: CH_3-CH: 0.80 (3H,d); CH_2O: 2.76,3.00 (2H,m); OCH_3: 3.25,3.30 (6H,s); OCHO: 4.00 (1H,m); Ph-H: 7.24 (1H,m) 7.36 (1H,d) 7.44 (1H,d). **tetrahydrofurane V** (entry 7) R=Cl, R^2=nC_3H_7, R^3=CH_3 $Bp_{0.5}$= 140-145°C; mixture of **4 diast.** NMR: ^{1}H ($CDCl_3$): OCH_3: 3.40,3.47,3.49,3.54.
19. β-haloacetals used in this study were commercial products or prepared in 35-65% yield by addition of dry halohydric acids to a CH_2Cl_2 solution of the α,β-unsaturated aldehyde, followed by acetal formation in the corresponding alcohol or diol and distillation over K_2CO_3 in vacuum.
1b Bp_4= 71°C; NMR: ^{1}H ($CDCl_3$): CH_3-CH: 1.08 (3H,d); CH_3-CH: 2.05 (1H,m); CH_2Br: 3.45 (2H,m); $O(CH_2)_2O$: 3.90 (4H,m); OCHO: 4.82 (1H,d). **1c** Bp_{10}= 88°C; NMR: ^{1}H ($CDCl_3$): CH_3-CH_2: 0.93 (3H,d); CH_3-$(CH_2)_2$: 1.40 (4H,m); CH-CH_2Br: 1.90 (1H,m); CH_2Br: 3.52 (2H,d); $O(CH_2)_2O$: 3.91 (4H,m); OCHO: 4.87 (1H,d). **3b** Bp_{12}= 70-74°C; NMR: ^{1}H ($CDCl_3$): CH_3-CH: 1.01 (3H,d); CH_3-CH: 2.08 (1H,m); CH_2Br: 3.42 (2H,m); OCH_3: 3.36, 3.34 (2x3H,s); OCHO: 4.21 (1H,d). **3c** Bp_{12}= 92-94°C; NMR: ^{1}H ($CDCl_3$): CH_3-CH_2: 0.93 (3H,d); CH_3-$(CH_2)_2$: 1.40 (4H,m); CH-CH_2Br: 1.87 (1H,m); CH_2Br: 3.54 (2H,d); OCH_3: 3.38, 3.41 (2x3H,s); OCHO: 4.32 (1H,d). **4b** Bp_{12}= 54-55°C; NMR: ^{1}H ($CDCl_3$): CH_3-CH: 1.00 (3H,d); CH_3-CH: 2.08 (1H,m); CH_2Cl: 3.56 (2H,m); OCH_3: 3.28, 3.32 (2x3H,s); OCHO: 4.24 (1H,d).

(Received in France 29 April 1989)