An Improved Method for the Use of Acetal-substituted Grignard Reagents in Organic Synthesis

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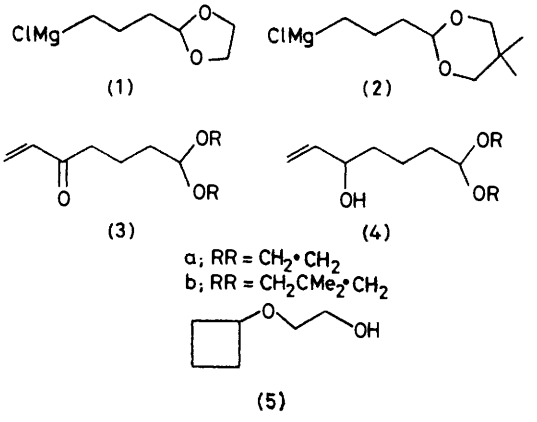
Grignard reagents derived from 2-(3-chloropropyl)-1,3-dioxolan (1) and 2-(3-chloropropyl)-5,5-dimethyl-1,3-dioxan (2) can be prepared in high yield without decomposition. They undergo 1,2-addition to acrylaldehyde to give allylic alcohols (4a and b), which can be oxidized to give monoprotected dicarbonyl compounds.

THE reactions of acetals with Grignard reagents to produce ethers after expulsion of an alkoxy-group have been the subject of considerable investigation.[1] The use of non-terminal acetal-substituted organomagnesium halides in organic synthesis has also been well documented.[1,e,g,l,m,2] However, the synthetic applications of terminal acetal-substituted organomagnesium halides have been limited to only a few examples.[3,4] Johnson [3] has reported the use of the Grignard reagent (1) derived from 2-(3-chloropropyl)-1,3-dioxolan in the synthesis of dienic, trienic, and tetraenic acetals, and Corey [4] used the same reagent in the syntheses of (±)-porantherine. When the Grignard reagent (1) was used in excess (2.0—4.8 mol. equiv.), yields were correspondingly high. The low yield obtained when a molar quantity of (1) was used was attributed to the instability of this reagent, which was partly consumed by ring closure to the salt of 2-cyclobutyloxyethanol (5).[1,e,f] This instability apparently necessitated the use of an excess of reagent in the former two examples.

We have found that both compound (1) and the Grignard reagent (2) derived from 2-(3-chloropropyl)-5,5-dimethyl-1,3-dioxan give high yields of product if the reagent is prepared at a high concentration at room temperature, and the condensation reactions are carried out at −70 °C.

We required the monoprotected oxo-aldehydes (3) for the total synthesis of some alkaloids of the mesembrane series.[5] A simple route would involve the reaction of the



Grignard reagent (1) or (2) with acrylaldehyde to give the allylic alcohol (4), and subsequent oxidation to the ketone (3).

Initial attempts to form the Grignard reagents (1) and (2) in tetrahydrofuran in the concentration range 1—2M,

[1] (*a*) E. Späth, *Monatsh.*, 1914, **35**, 319; (*b*) A. E. Tschitschibabin, *Ber.*, 1914, **47**, 48; (*c*) M. F. Shostakovskii and M. R. Kulibekov, *J. Gen. Chem.* (*U.S.S.R.*), 1958, **28**, 565; (*d*) C. Blomberg and A. D. Vreugdenhil, *Rec. Trav. chim.*, 1962, **81**, 238; (*e*) Cl. Feugeas and H. Normant, *Bull. Soc. chim. France*, 1963, 1441; (*f*) Cl. Feugeas, *ibid.*, pp. 2568, 2579; (*g*) C. Blomberg, A. D. Vreugdenhil, and Tj. Homsma, *Rec. Trav. chim.*, 1963, **82**, 355; (*h*) M. F. Shostakovskii, A. S. Atavin, and B. A. Trofimov, *J. Gen. Chem.* (*U.S.S.R.*), 1964, **34**, 2088; (*i*) R. A. Mallory, S. Rovinski, and I. Scheer, *Proc. Chem. Soc.*, 1964, 416; (*j*) J. Cologne and J. Buendia, *Compt. rend.*, 1965, **261**, 1699; (*k*) R. A. Mallory, S. Rovinski, F. Kohen, and I. Scheer, *J. Org. Chem.*, 1967, **32**, 1417; (*l*) L. Miginiac and J. Blais, *J. Organometallic Chem.*, 1971, **29**, 349; (*m*) H. Normant, *Bull. Soc. chim. France*, 1972, 2161; (*n*) G. Mousset, *ibid.*, p. 1983; (*o*) G. Westera, C. Blomberg, and F. Bickelhaupt, *J. Organometallic Chem.*, 1974, **82**, 291.

[2] (*a*) M. Rosenberger, D. Andrews, F. DiMaria, A. J. Duggan, and G. Saucy, *Helv. Chim. Acta*, 1972, **55**, 249; (*b*) S. Z. Abbas and R. C. Poller, *J.C.S. Dalton*, 1974, 1769; (*c*) J. Ferard and P. F. Casals, *Tetrahedron Letters*, 1974, 2483; (*d*) A. A. Ponaras, *ibid.*, 1976, 3105.

[3] (*a*) A. van der Gen, K. Wiedhaupt, J. J. Swoboda, H. C. Dunathan, and W. S. Johnson, *J. Amer. Chem. Soc.*, 1973, **95**, 2656; (*b*) G. D. Abrams, W. R. Bartlett, V. A. Fung, and W. S. Johnson, *Bio-organic Chem.*, 1971, **1**, 243; (*c*) W. S. Johnson, K. Wiedhaup, S. F. Brady, and G. L. Olsen, *J. Amer. Chem. Soc.*, 1974, **96**, 3979.

[4] E. J. Corey and R. D. Balanson, *J. Amer. Chem. Soc.*, 1974, **96**, 6516.

[5] C. P. Forbes, J. D. Michau, T. van Ree, A. Wiechers, and M. Woudenberg, *Tetrahedron Letters*, 1976, 935.

based on the original method of Feugeas,[1] met with little success. High temperatures (>60 °C) for extended periods (1—3 h) were required before the starting material disappeared, and yields of (4) were low (25—30%). The reaction mixtures contained large proportions of intractable material. All previous attempts[3,4] to prepare compound (1) have also required reflux temperatures. Clearly, in addition to thermally induced decomposition and/or polymerization reactions, one of the major pathways for loss of Grignard reagent is ring closure to the cyclobutyl ether (5) after work-up. We have shown that heating a solution of Grignard reagent (1) to reflux for 2 days results in complete disappearance of the Grignard reagent with the formation of (5) and polymeric material only.

The preparations and reactions of the Grignard reagents (1) and (2) proceeded smoothly and rapidly if the concentration of the chloro-acetal was raised to 5M and the temperature was kept below 30 °C. These results are summarized in the Table. The allylic alcohols (4)

Reactions of Grignard reagents (1) and (2) with acrylaldehyde

Grignard reagent	Product	Yield (%)
(1)	(4a)	85
(2)	(4b)	89

contained only very small amounts of impurities and, although sensitive to low pressure distillation, were readily purified by column chromatography. No trace of ring-closed products was detected.

The allylic alcohols (4) were converted readily into the synthons (3) by oxidation with pyridinium chlorochromate, in methylene chloride.

EXPERIMENTAL

I.r. spectra were obtained with a Unicam SP 200 and n.m.r. spectra with a Varian HA 100 spectrometer. Mass spectral (including accurate mass) measurements were made with a DuPont 21.492 B spectrometer. Qualitative t.l.c. was carried out on silica gel (G254) developed with 40% ethyl acetate in light petroleum (b.p. 40—60 °C). Column chromatography was carried out with silica gel 60 eluted with increasing proportions of diethyl ether in pentane. All Grignard reactions were carried out under dry nitrogen and reagents were transferred by syringe. Solvents were purified and dried by standard procedures.

General Procedure for the Preparation of the Acetals.—4-Chlorobutan-1-ol was oxidized with pyridinium chlorochromate in methylene chloride according to a standard procedure.[6] The crude 4-chlorobutanal was acetalized according to the procedure of Pleshakov [7] to give 2-(3-chloropropyl)-1,3-dioxolan,[7] b.p. 55° at 0.2 mmHg (lit.,[7] 69—70° at 0.6 mmHg), $\nu_{max.}$ (neat) 1 055, 1 160, 2 930, and 3 010 cm^{-1}, n_D^{27} 1.4469 (lit.,[7] n_D^{20} 1.4548), $\delta(CCl_4)$ 1.66—2.10 (m, $CH_2{\cdot}CH_2$), 3.58 (t, *J* 6 Hz, CH_2Cl), 3.72—4.06 (m, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$), and 4.85 [t, *J* 4 Hz, $CH(OR)_2$], in 67% overall yield, or 2-(3-*chloropropyl*)-5,5-*dimethyl*-1,3-*dioxan*, b.p. 78° at 0.2 mmHg, $\nu_{max.}$ (neat) 1 150, 2 920, and 3 020 cm^{-1}, n_D^{27} 1.4487, $\delta(CCl_4)$ 0.73 (s, Me), 1.20 (s, Me), 1.62—2.16 (m, $CH_2{\cdot}CH_2$), 3.58 (t, *J* 6 Hz, CH_2Cl), 3.53 (ABq, *J* 11 Hz, $CH_2{\cdot}CMe_2{\cdot}CH_2$), and 4.5 [t, *J* 4 Hz, $CH(OR)_2$] in 73% overall yield (Found: C, 56.0; H, 8.95; Cl, 18.4%; $M^+ - 1$, 191.0838. $C_9H_{17}ClO_2$ requires C, 56.10; H, 8.9; Cl, 18.4%; $M - 1$, 191.0838).

General Procedure for Grignard Reactions.—The chloroacetal (20.7 mmol, 1 equiv.) mixed with dibromoethane (1.6 mmol, 0.16 equiv.), in dry tetrahydrofuran (4 ml) was added to magnesium (59.2 mmol, 2.8 equiv.). The reaction was initiated on slight warming and the mixture was maintained below 30 °C by periodic cooling with a water-bath. After 1 h no starting material remained (t.l.c.). The mixture was diluted with tetrahydrofuran (12 ml) and cooled to —70 °C. Acrylaldehyde (62.1 mmol, 3 equiv.) in tetrahydrofuran (5 ml) was added dropwise over 20 min, and the mixture was stirred for a further 30 min and then quenched by dropwise addition of aqueous ammonium chloride. The mixture was permitted to warm to room temperature, diluted with water (150 ml), neutralized with glacial acetic acid (to pH 6), and extracted with ether. The combined ether layers were dried ($MgSO_4$) and concentrated to produce the allylic alcohols * (4), which were purified by column chromatography to produce homogeneous oils. In this way, the Grignard reagent (1) produced 6-(1,3-*dioxolan*-2-*yl*)*hex*-1-*en*-3-*ol* (4a) (17.6 mmol, 85%), $\nu_{max.}$ (neat) 1 030, 1 130, 2 860, and 3 400 cm^{-1}, $\delta(CCl_4)$ 1.4—1.78 (m, $CH_2{\cdot}CH_2{\cdot}CH_2$), 2.10br (s, OH, D_2O-exchangeable), 3.74—3.96 (m, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$), 3.90—4.18 (m, RC*H*OHR), 4.77 [t, *J* 4 Hz, $CH(OR)_2$], 4.95—5.30 (m, CH_2=C), and 5.65—6.03 (m, −C=CH−) (Found: $M^+ - 1$, 171.1021. $C_9H_{16}O_3$ requires $M - 1$, 171.1025); and the Grignard reagent (2) produced 6-(5,5-*dimethyl*-1,3-*dioxan*-2-*yl*)*hex*-1-*en*-3-*ol* (4b) (18.4 mmol, 89%), $\nu_{max.}$ (neat) 915, 1 009, 1 117, 2 828, 2 940, and 3 410 cm^{-1}, $\delta(CCl_4)$ 0.70 (s, Me), 1.15 (s, Me), 1.26—1.70 (m, $CH_2{\cdot}CH_2{\cdot}CH_2$), 2.25br (s, OH, D_2O-exchangeable), 3.43 (ABq, *J* 11 Hz, $OCH_2{\cdot}CMe_2{\cdot}CH_2O$), 3.52—3.80 [m, RCH(OH)R], 4.46 [t, *J* 4.5 Hz, $RCH(OR)_2$], 4.95—5.28 (m, CH_2=C), and 5.64—6.00 (m, −C=CH−) (Found: M^+, 214.1555; $M^+ - 1$, 213.1485. $C_{12}H_{22}O_3$ requires *M*, 214.1568; $M - 1$, 213.1490).

2-*Cyclobutyloxyethanol* (5).—The Grignard reagent (1), prepared as before, was diluted to 1.5M with tetrahydrofuran and refluxed under nitrogen for 48 h. Quenching with aqueous ammonium chloride and work-up produced a thick oil which, upon distillation, afforded the homogeneous alcohol † (5), b.p. 70° at 1 mmHg, $\nu_{max.}$ (neat) 1 110, 1 138, 2 850, and 3 350 cm^{-1}, $\delta_H(CCl_4)$ 1.24—2.38 (6 H, m, cyclobutyl), 3.22—3.72 (m, A_2B_2, $ROCH_2CH_2O$), 3.78 (s, OH, D_2O-exchangeable), and 3.78—4.12 (quintet, R_2CHOR), $\delta_C(CDCl_3)$ 12.59 (1 C, t, $CH_2[CH_2]_2$), 30.45 (2 C, t, $CH_2{\cdot}CH_2{\cdot}CHO$), 61.88 (1 C, t, OCH_2CH_2OH), 69.08 (1 C, t, $O{\cdot}CH_2{\cdot}CH_2{\cdot}OH$), and 73.76 (1 C, d, $[CH_2]_2CHO$), in 32% yield. This alcohol, on treatment with acetic anhydride–pyridine, afforded the acetate quantitatively, $\delta(CCl_4)$ 1.2—2.3 (9 H, m, cyclobutyl, OAc), 3.35—3.50 (2 H, t, CH_2OCO), 3.70—4.05 (1 H, quintet, R_2CHOR), and 4.05—4.20 (2 H, t, $ROCH_2R$). The residue was an intractable tar.

General Oxidation Procedure.—The oxidations were carried out with pyridinium chlorochromate according to a general method for acid-labile compounds.[6] Compound (4a)

* Both the allylic alcohols (4) and the unsaturated ketones (3) were unstable at room temperature (t.l.c.) and so were characterized by high resolution mass spectrometry and not by elemental analysis.

† Despite repeated distillation this alcohol gave analytical results slightly outside the expected limits. Accordingly, the ^{13}C and ^1H n.m.r. spectra of the acetate were also obtained.

[6] E. J. Corey and K. W. Suggs, *Tetrahedron Letters*, 1975, 2647.

[7] M. G. Pleshakov, A. E. Vasil'ev, I. K. Sarycheva, and N. A. Preobrazhenskii, *J. Gen. Chem.* (*U.S.S.R.*), 1961, **31**, 1433.

yielded, after distillation (120° and 0.3 mmHg), the homogeneous 6-(1,3-*dioxolan*-2-*yl*)*hex*-1-*en*-3-*one* (3a), $\nu_{max.}$ (neat) 1 135, 1 456, 1 679, and 2 890 cm^{-1}, $\delta(CCl_4)$ 1.48—1.88 (m, CH_2CH_2), 2.50—2.70 (m, RCH_2CO), 3.67—4.00 (m, OCH_2-CH_2O), 4.77 [t, *J* 4 Hz, $RCH(OR)_2$], and 5.60—6.50 (ABX, CH_2=CH–COR) (Found: $M^+ - 1$, 169.0853. $C_9H_{14}O$ requires $M - 1$, 169.0864), in 66% yield; and compound (4b) after distillation (160° and 0.3 mmHg), yielded the homogeneous 6-(5,5-*dimethyl*-1,3-*dioxan*-2-*yl*)*hex*-1-*en*-3-*one* (3b), $\nu_{max.}$ (neat) 1 133, 1 405, 1 679, 2 800, and 2 920 cm^{-1}, $\delta(CCl_4)$ 0.67 (s, Me), 1.15 (s, Me), 1.41—1.86 (m, CH_2·CH_2), 2.46—2.64 (m, RCH_2CO), 3.42 (ABq, *J* 11 Hz, CH_2·CMe_2·CH_2), 4.34 [t, *J* 4.5 Hz, $RCH(OR)_2$], and 5.62—6.48 (ABX, CH_2=CH–COR) (Found: M^+, 212.1427. $C_{12}H_{20}O_3$ requires *M*, 212.1412), in 46% yield.

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