Journal of Organometallic Chemistry, 367 (1989) 11–17
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands
JOM 09757

Reactivity of the secondary benzylic Grignard reagent from 1-phenylethyl chloride with aldehydes and ketones. More evidence for the rearrangement mechanism in benzyl Grignard reactions

Claude Bernardon

Laboratoire de Chimie Organometallique, Université de Paris-Sud, Centre d'Orsay, 91405 (France)

(Received September 26th, 1988)

Abstract

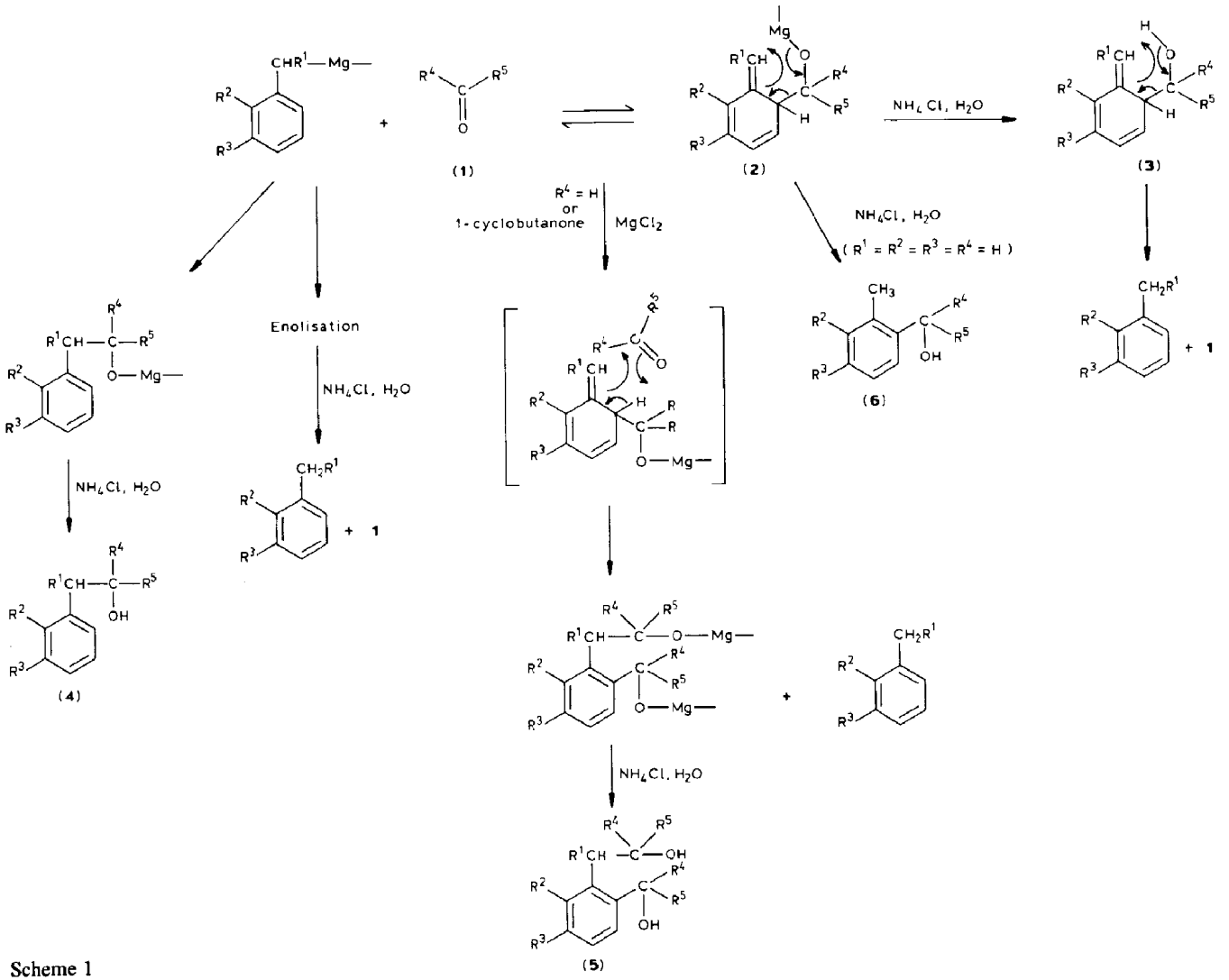
Additional evidence for the mechanism proposed previously to account for diol formation in the reaction of the Grignard reagent from benzyl chloride with aldehydes has been obtained from a study of the interaction of the Grignard reagent from 1-phenylethyl chloride with carbonyl compounds. This Grignard reagent reacts with ketones (except non-enolisable ketones) to give normal alcohols in low yields, and with aldehydes to give diols. However, in contrast to that formed in the reaction of benzylmagnesium chloride, an unstable trienic alcohol formed from the rearrangement of the corresponding alkoxide could be isolated in some case as the major product, providing confirmatory evidence for the existence of an initial reversible rearrangement in the reaction of the benzylic Grignard reagents with carbonyl compounds.

Introduction

In previous studies of the reaction of the 1-napthylmethyl Grignard reagent with formaldehyde [1] and ketones [2], it was shown that the interaction of the carbonyl compounds and benzylic Grignard reagents could be regarded as involving an initial reversible rearrangement step, similar to that observed with allylic and crotylic Grignard reagents [3]. Reactions after this step lead to the observed products. Abnormal formation of diols **5** (Scheme 1), particularly in the case of unhindered aldehydes, could be accounted for in terms of the well known Prins reaction of the rearranged alkoxide **2** in the presence of magnesium salts.

In contrast to that produced in the reaction of 1-naphthylmethylmagnesium chloride, the trienic alcohol **3** formed from the rearranged alkoxide **2** could not be isolated when the Grignard reagent from benzyl chloride was used (Scheme 1,

0022-328X/89/$03.50


(1)
(2)
(3)
(4)
(5)
(6)
Enolisation
NH4Cl, H2O
MgCl2
R4 = H
or
1-cyclobutanone
NH4Cl, H2O
(R1 = R2 = R3 = R4 = H)
+ 1

Scheme 1

$R^1 = R^2 = R^3 = H$). Formation of diols of type **5** in reactions with unhindered aldehydes, or in the case of ketones, with cyclobutanone [2], provided strong support for the existence of the initial reversible rearrangement step.

There are only a few, rather inconclusive, reports on the reaction of secondary benzylic Grignard reagents with carbonyl compounds [4]. We thus decided to reinvestigate the reactions of the secondary benzylic Grignard reagent from 1-phenylethylchloride with aldehydes and ketones.

Results and discussion

All the experimental observations are consistent with the suggested mechanism in Scheme 1. 1-Phenylethylmagnesium chloride reacts with the unhindered aldehydes **1a–1c** and with acetone **1e**, to yield trienic alcohols **3** which are of limited stability. The normal alcohol **4** was obtained in poor yield from aldehydes and ketones other than the non-enolisable benzophenone **1h**. When acetophenone **1g** was used, an increase in the reaction time did not result in an increase in the yield of the normal alcohol **4g**. This result, considered along with the recovery of some of the initial ketone, confirms the existence of the enolisation reaction, such as was observed with the 1-naphthylmethyl Grignard reagent [2]. With acetone **1e**, the disappearance of the rearranged alcohol **3e** is not accompanied by the appearance of the normal alcohol **4e** or a diol when the reaction time is increased and so the enolisation reaction is the only reaction that occurs.

It should be emphasized that the formation of diols **5** at the expense of the trienic alkoxides **2** is always slow. This is consistent with previous observations that Prins or ene reactions that involve tertiary carbenium ions (i.e. tri- or tetra-substituted double bonds) can occur, but more slowly than those with terminal alkenes [5].

It is assumed that in the reaction of benzylmagnesium chloride with aldehydes the trienic alkoxide **2** does not survive hydrolysis or undergoes aromatisation by "a conducted tour process" to give the "*ortho*" alcohol **6**, as postulated by Benkeser [6]. In contrast the trienic carbinol **3** isolated in the reaction of 1-naphthylmethylmagnesium chloride with aldehydes and ketones is stabilized by the aromatic ring, and so the "*ortho*" alcohol **6** is never isolated. Similar results are obtained with the Grignard reagent from 1-phenylethyl chloride, only the rearrangement alcohol being isolated (Table 1, **1a–1c** and **1e**). The mechanism shown in Scheme 1 can account for the unexpected result that in the reaction with benzaldehyde (Table 1, **1d**), after 1 h reaction only benzaldehyde and ethylbenzene were recovered. The slowness of formation of the diol **5d** leads us to conclude that the only species present is the trienic alkoxide **2d**. The equilibrium in Scheme 1 cannot lie significantly towards the initial reagents otherwise the normal alcohol **4d** would also appear, as in the reaction of benzylmagnesium chloride with benzaldehyde (Table 2). The trienic alcohol **3d** from the reaction of 1-phenylethylmagnesium chloride with benzaldehyde, could not be isolated because of its instability. The alkoxide **2d** could not be so unstable since it must be present in large quantities to produce diol **5d** through the slow reaction of the Prins type. In contrast the reaction of 1-naphthylmethyl Grignard reagent with benzaldehyde produces a trienic alcohol sufficiently stable to be isolated (Table 2), and it is evident that the phenyl group is much more effective at stabilizing the rearranged alcohol **3**. The alkyl group in the secondary benzylic Grignard reagent has a much smaller influence. Moreover, an increase in the

Table 1

Reactions of 1-phenylethylmagnesium chloride with aldehydes and ketones $R^4R^5C{=}O$

Carbonyl compound	Substituents		Experimental conditions [a]	Products (% yield)			
	R^4	R^5		**3**	**4**	**5**	Recovered **1**
1a	H	H	A	46	0	40	
1b	CH_3	H	A	52	0	41	
			B	0	0	72	
1c	C_2H_5	H	A	30	7	54	
			B	0	10	78	
1d	C_6H_5	H	A	0	0	0	90
			B	0	0	52	39
1e	CH_3	CH_3	A	30	0	0	
			B [c]	0	0	0	
1f	C_2H_5	CH_3	A	unstable [d]	10	0	
1g	C_6H_5	CH_3	A	0	15	0	78
			B	0	14 [b]	0	82 [b]
1h	C_6H_5	C_6H_5	A	0	55	0	36
1i	cyclobutyl		A	unstable [d]	7	30	
			B	0	8	57	

[a] A, 1 h at 0 °C; B, 4 days at room temperature. Yields after chromatographic separation. [b] Yield from GLC. [c] Unidentified products formed in low yield (^{1}H NMR showed no aromatic signals). [c] The ^{1}H NMR spectrum of the crude products showed signals at ca. 6 ppm characteristic of the alcohols (**3**), the heights of these signals fell rapidly.

reaction time in this reaction results in a higher yield of normal alcohol **5** (Table 2). This shows that the normal alcohol comes not only from the initial reaction of the Grignard reagent with the carbonyl compound, but also from the species regenerated from the reversible rearrangement.

1-Phenylethylmagnesium chloride reacts with cyclobutanone, as does benzylmagnesium [2], to produce the normal alcohol **4i** and a high yield of the diol **5i** (Table 1). The trienic alcohol **3i** was present after hydrolysis as shown by the ^{1}H NMR spectrum of the crude product, but it was too unstable to be isolated pure. Formation of diols from this ketone also confirm the importance of steric factors in the Prins reaction [2]; only aldehydes and cyclobutanone react with the benzylic Grignard reagents to give diols.

In summary, the results shown in Table 1 reveal that the Grignard reagent from 1-phenylethyl chloride reacts like a typical benzylic Grignard reagent with aldehydes

Table 2

Reaction of benzylic Grignard reagents $(R^2R^3C_6H_3)CHR^1MgCl$ with benzaldehyde

Grignard reagent			Experimental conditions [a]	Products (% yield)			
R^1	R^2	R^3		**3**	**4**	**5**	Recovered **1**
H	H	H	A	0	57	8.5	0
H	aromatic ring		A	35	5	10	35
H	aromatic ring		B	0	15	54	23

[a] A, 1 h at 0 °C; B, 4 days at room temperature.

and ketones. However, in some cases the rearranged carbinol can be isolated even though its stability is limited, as in the case of that formed from the Grignard reagent from 1-naphthylmethyl chloride. The reversible formation of the rearranged alkoxide **2** accounts for the formation of all the products from the reaction of benzylic Grignard reagents with carbonyl compounds. The mechanism shown in Scheme 1 applies to the reactions of all benzylic Grignard reagents with carbonyl compounds to give products similar to **3–5**. It should be noted from 1-phenylethylmagnesium chloride, as from other benzylic Grignard reagents that yields of normal alcohols **4** are very low, much better yields are obtained by use of dibenzylcadmium [7] or benzyllithium [8].

Experimental

General procedures were as described previously for the reactions of 1-naphthylmethylmagnesium chloride [1,2].

1-Phenylethylmagnesium chloride

Magnesium turnings (6.5 g, 0.4 mol) were placed in a flask fitted with a dropping funnel, a magnetic stirrer and a reflux condenser. A little of a solution of 1-chloro-1-phenylethane (9 g, 0.1 mol) in anhydrous diethyl ether (160 ml) was added to initiate reaction. As soon as the reaction started, the flask was immersed in an ice-bath, the remaining solution added dropwise during 2 h, and the mixture stirred for an addition hour. The yield of Grignard reagent was over 81% (as determined by titration). The solution was kept in a dry-box under pure argon.

*Reaction of 1-phenylethylmagnesium chloride with monomeric formaldehyde (**1a**)*

The procedure was as previously described for the reaction of 1-naphthylmethylmagnesium chloride [1]. The reaction of 0.025 mol of Grignard reagent with 0.175 mol of paraformaldehyde gave 2 g of a pale yellow liquid, a portion of which (0.9 g) was chromatograph with hexane/acetone (20/5 v/v) as eluant. The following products were obtained: ethylbenzene (0.13 g); 1-ethylidene-2-hydroxymethyl-3,5-cyclohexadiene (**3a**) (0.53 g) as a pale yellow oil; ^{1}H NMR (90 MHz, $CDCl_3$); δ 5.95 (m, 5H, =CH), 3.58 (m, 3H, $CHCH_2O$), 2.17 (s, 1H,OH), 1.77 (d, J 7 Hz, 3H, $=CCH_3$); IR: ν 690, 750, 825 (RC=CR), 1580 (=$CHCH_3$), 3340 (OH) cm^{-1}; ^{13}C NMR: δ 13.56 (q, CH_3), 66.36 (t, CH_2OH), 120.91 (d, =CHMe). The ^{1}H NMR spectrum of (**3a**) showed the presence of traces of ethylbenzene; at room temperature, the signals from this slowly increased at the expense of those of the alcohol **3a**, **3d**; decomposition of **3a** was rapid above 50 °C, and gave 2-(2-hydroxymethyl)phenylpropanol (**5a**) as an amorphous residue; ^{1}H NMR: 7.25 (m, 4H, aromatic), 4.7 (m, 2H, CH_2O), 4.18 (s, 1H, OH), 3.3 and 3.6 (m, 3H, $CHCH_2$), 1.2(d, 3H, CH_3). Found: C, 73.12; H, 8.07. $C_{10}H_{14}O_2$ calcd.: C, 72.29; H, 8.43%.

*Reaction of 1-phenylethylmagnesium chloride with aldehydes and ketones **1b** to **1i***

A solution of the carbonyl compound (0.008 mol) in diethyl ether (5 ml) was added dropwise to 25 ml of the solution of the Grignard reagent (0.008 mol) cooled in an ice bath. The mixture was stirred either for 1 hour at 0 °C or allowed to stand for 4 days at room temperature, then treated in an ice bath with 10 ml of saturated aqueous ammonium chloride. The organic product was worked up in the usual way.

Table 3

^{1}H NMR spectral data for rearranged alcohols **3** (see Scheme 1) in $CDCl_3$(ppm downfield from internal $SiMe_4$) [a]

Compound	ethylenic	$CHCR^4R^5$	OH	$=CCH_3$
3a	m, 5H, 5.95	m, 3H, 3.58	s, 2.2	d, 1.77(*J* 7 Hz)
3b	m, 5H, 5.9	m, 2H, 3.52; d, CH_3, 1.18(*J* 6 Hz)	s, 2.25	d, 1.75(*J* 7 Hz)
3c	m, 5H, 5.8	m, 2H, 3.35; m, CH_2, 1.5; t, CH_3, 1.08	s, 2.1	d, 1.75(*J* 7 Hz)
3e	m, 5H, 5.97	d, 1H, 3.38(*J* 6 Hz); s and s, 2×CH_3, 1.2 and 1.1	s, 1.26	d, 1.75(*J* 7 Hz)

[a] All the signals disappeared in time, being slowly replaced by those of ethylbenzene and the corresponding carbonyl compound **1**.

Table 4

^{1}H NMR spectral data for the normal alcohols **4** in $CDCl_3$ (ppm downfield from internal $SiMe_4$)

Compound	aromatic	CR^4R^5OH	ArCHMe	OH	CH_3
4c	m, 5H, 7.2	m, 1H, 4.72; m, CH_3, 1.8; t, CH_3, 1.1	m, 3.5	s, 2.1	d, 1.3(*J* 7 Hz)
4f	m, 5H, 7.2	m, 8H, 1.45 and 1.1	m, 3.8	s, 2.7	d, 1.45(*J* 7 Hz)
4g	m, 10H, 7.2	s, CH_3, 1.55	m, 3.15	s, 1.8	d, 1.25(*J* 7 Hz)
4h	m, 15H, 7.3		q, 3.97	s, 2.45	d, 1.32(*J* 7 Hz)
4i	m, 5H, 7.2	m and m, cyclobutyl(6H), 1.75 and 1.3	q, 3.48	s, 1.6	d, 1.3(*J* 7 Hz)

The products were separated by column chromatography with hexane/acetone as eluant. In the case of carbonyl compounds **1b** to **1i** the proportions of the eluants were: **1b**: 20/5, **1c**: 23/2, **1d–1e**: 27/3, **1f**: 30/7, **1g–1h**: 30/1 and **1i**: 23/2 v/v. The yield of rearranged alcohol **3c** is expressed as a proportion of that of the normal alcohol **4c**, which was isolated by column chromatography after decomposition of **3c** by heating the crude product at 70 °C under vacuum. The ratio of the unstable alcohol **3c** to the normal alcohol **4c** was determined from the ^{1}H NMR spectrum of the mixture after chromatography by comparing the integrals of the aromatic signals from **4c** with those from the ethylenics protons of **3c**. The rearranged alcohols **3f** and **3i** were detected only from the ^{1}H NMR spectra of the crude products which showed the typical multiplet of the ethylenics protons at ca. 6 ppm. The heights of

Table 5

^{1}H NMR spectral data for the diols (**5**) in $CDCl_3$ (ppm downfield from internal $SiMe_4$)

Compound	aromatic	Ar-$COHR^4R^5$	-C-$COHR^4R^5$	2×OH	MeCH	-CH_3
5a	m, 4H, 7.3	m, 2H, 4.7	m, 2H, 3.7	broad s, 4.2	m, 3.3	d, 1.2(*J* 7 Hz)
5b	m, 4H, 7.3	m, 1H, 5.2; m, 1H, 4; m and m, 2×CH_3, 1.3 and 1.1		broad s, 3.3	m, 3.2	m, 1.5
5c	m, 4H, 7.4	m, 1H, 5.3; m, 1H, 4.9; m, 4H, 2×CH_2; m, 6H, 2×CH_3		broad s, 3.5	m, 3.5	m, 1.6
5d	m, 14H, 7.2	s, 1H, 5.9	m, 1H, 4.7	broad s, 3.2	m, 3.5	d, 1.22(*J* 8 Hz)
5i	m, 4H, 7.4	m and m, 12H(2×cyclobutyl), 2.2 and 1.7		broad s, 3.5	m, 3.5	d, 1.52(*J* 8 Hz)

[a] All the diols (**5**) are very viscous colorless oils.

the signals from **3f** and **3i** and were no longer present after 5 h at room temperature. The ^{1}H NMR data for alcohols **3** and **4** and diols **5** are shown in Tables 3, 4 and 5.

Reaction of benzylmagnesium chloride with benzaldehyde

A solution of benzaldehyde (0.0155 mol) in 10 ml of diethyl ether, was added at 0 °C during 5 min to a solution containing the Grignard reagents (0.0155 mol) in 30 ml of diethyl ether, the mixture was stirred for 1 h at 0 °C, then hydrolysed and worked up as usual. The crude product was chromatographed on silica gel with $CHCl_3$ as eluant to give: 1,2-diphenylethanol. ^{1}H NMR ($CDCl_3$): δ 7.27 and 7.17(s and m, 10H, aromatic), 4.8(t, 1H, CHO), 2.97(d, 2H, CH_2), 2.1(s, 1H, OH); lit m.p. 67 °C, found 67 °C and 1-phenyl-2-(2-phenylhydroxymethyl)phenylethanol as an amorphous residue. ^{1}H NMR ($CDCl_3$): δ 7.2(m, 14H, aromatic), 6.05 and 5.8(s and s, 1H, ArCHAr), 4.8(m, 1H, CCH), 2.9(m, 2H, CH_2), 3.8(s, 2H, 2-OH). Found: C, 82.74; H, 6.11. $C_{21}H_{20}O_2$ calcd.: C, 82.89; H, 6.58%.

Reaction of 1-naphthylmethylmagnesium chloride with benzaldehyde

The procedure was as described for the reaction of 1-naphthylmethylmagnesium chloride with ketones [1,2]. The crude product was chromatographed on silica gel with hexane/acetone (22.5/2.5 v/v) as eluant. The yield of rearranged alcohol **3** is expressed as a proportion of that of the normal alcohol **4**, as described previously [2], which was separated after decomposition of the rearranged alcohol **3** present in the crude product. Column chromatography on silica gel afforded rearranged alcohol 1-methylene-2-phenylhydroxymethyl-1,2-dihydronaphthalene (**3**) as a pale yellow oil. ^{1}H NMR($CDCl_3$): δ 7.3 (m, 9H, aromatic), 6.3(d, *J* 10 Hz, 1H, =CH), 5.57(s, 1H, methylene), 5.35(q, *J* 6 Hz, 1H, CHO), 3.18(m, 1H, CHCO), 1.98(s, 1H, OH), this alcohol was, as usual, of limited stability, the NMR spectra showed signals from 1-methylnaphthalene and benzaldehyde, complete decomposition occurred rapidly above 50 °C; the normal alcohol 2-naphthyl-1-phenylethanol (**4**) as a white solid; m.p. 68 °C; ^{1}H NMR($CDCl_3$): δ 7.3(m, 12H, aromatic), 4.92(t, 1H, CHOH), 3.37(d, *J* 7 Hz, 2H, CH_2), 2.0(s, 1H, OH) and the diol 2-(2-phenylhydroxymethyl)naphthyl-1-phenylethanol (**5**) as an amorphous residue. Found: C, 84.56; H, 5.98. $C_{25}H_{22}O_2$ calcd.: C, 84.74; H, 6.21%. ^{1}H NMR($CDCl_3$): δ 7.35(m, 16H, aromatic), 5.73 and 6.32(s and s, 1H, ArCHOHAr), 4.75(m, 1H, CHOH), 4.0(s, 2H, 2-OH) and 3.3 (m, 2H, CH_2).

References

1 C. Bernardon and A. Deberly, J. Chem. Soc., Perkin Trans. 1, (1980) 2631.
2 C. Bernardon and A. Deberly, J. Org. Chem., 47 (1982) 463.
3 R.A. Benkeser, M.P. Siklosi and E.C. Mozden, J. Am. Chem. Soc., 100 (1978) 2134.
4 M.S. Kharasch and O. Reinmuth, Grignard reactions of nonmetallic substances, New York, Prentice–Hall, 1954.
5 (a) B.B. Snider and D.J. Rodini, Tetrahedron Lett., 21 (1980) 1815; (b) B.B. Snider, D.J. Rodini, Th.C. Kirk and R. Cordova, J. Am. Chem. Soc., 104 (1982) 555; (c) B.B. Snider, R. Cordova and R.T. Price, J. Org. Chem., 47 (1982) 3643.
6 R.A. Benkeser and D.C. Snyder, J. Org. Chem., 47 (1982) 1243.
7 C. Bernardon, Tetrahedron Lett., 18 (1979) 1581.
8 M. Clarembeau and A. Krief, Tetrahedron Lett., (1985) 1093.