Benzylic Substitution of Benzyl Methyl Ether

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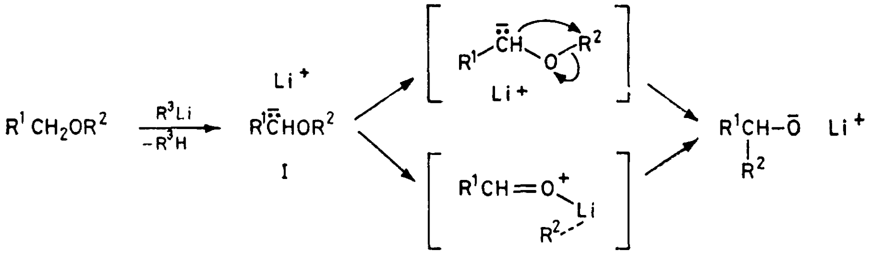
Treatment of benzyl methyl ether with n-butyl-lithium–tetramethylenediamine in hexane gave benzylic-lithiation, without *ortho*-lithiation or a Wittig type rearrangement. The benzylic-lithiated benzyl methyl ether was then allowed to react with benzophenone, 4-methoxybenzophenone, butyl bromide, ethyl phenylacetate, and 4-chlorobenzophenone.

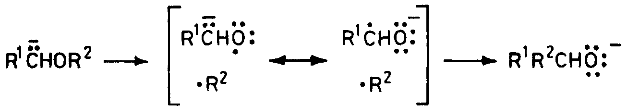
THE Wittig rearrangement is well documented[1,2] and occurs in ethers when in the presence of a strong base (*e.g.* sodamide or organolithium) [see equation (1) where R^1 and R^2 may be alkyl, aryl, or vinyl, and one of the

$$R^1CH_2OR^2 \xrightarrow{R^3Li} R^1R^2CHOLi + R^3H \qquad (1)$$

hydrogens may be replaced by an alkyl or aryl group]. Initially, the mechanism was thought to involve proton abstraction by base from the benzylic carbon, followed by either a concerted or an ion-pair elimination–addition mechanism (Scheme 1).[1] More recent evidence suggests that the radical-pair mechanism[2] shown in Scheme 2 occurs after removal of the proton by the base. One of the radicals in the radical pair is a ketyl radical. There is evidence that, at least in some cases, the radical-pair mechanism accounts for only a portion of the product, and a concerted mechanism may also take place.[3] The radical-pair mechanism has been suggested for cases where R^2 is alkyl or aryl and a [2,3] sigmatropic rearrangement when R^2 is allylic.



SCHEME 1



SCHEME 2

Following reports of *ortho*-lithiation of aromatic compounds such as that observed by Jones and Hauser[4] [see equation (2)], Gschwend and Hamdan,[5] and Meyer

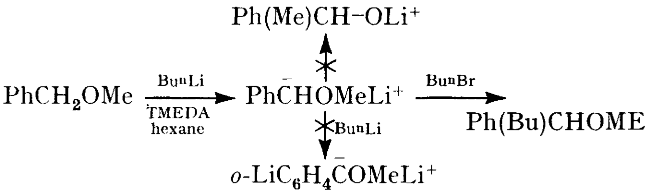
$$PhCH_2NMe_2 \xrightarrow{Bu^nLi} o\text{-}LiC_6H_4CH_2NMe_2 \qquad (2)$$

and Seebach[6] [see equation (3)], a parallel reaction with benzyl methyl ether was attempted in hexane. Tetramethylenediamine (TMEDA) was added to enhance the ability of n-butyl-lithium to extract the *ortho*-proton.

$$PhCH_2OH \xrightarrow{2\ BuLi} o\text{-}LiC_6H_4CH_2O^-Li^+ \xrightarrow{\text{Elecrophile (El)}} o\text{-}ElC_6H_4CH_2O^-Li^+ \qquad (3)$$

Studies showed that, with 1 or 2 equiv. of n-butyl-lithium, neither *ortho*-lithiation nor the usual Wittig rearrangement took place; removal of the benzylic proton resulted in the formation of a hexane-stable anion. Addition of n-butyl bromide to this and work-up gave 1-methoxy-1-phenylpentane in 85% yield. An equimolar proportion of n-butyl-lithium gave a yield of product > 2 mol equiv.

Other electrophiles gave similar results (see Table 1). The low yield of product from ethyl phenylacetate arises probably as a result of the acidity of the initial product, 1-methoxy-1,3-diphenylacetone, which could undergo further condensation.



$$\begin{tikzcd} & \mathrm{Ph(Me)CH\text{-}\bar{O}Li^+} & \\ \mathrm{PhCH_2OMe} \arrow[r, "\mathrm{Bu^nLi}", "\substack{\mathrm{TMEDA}\\ \mathrm{hexane}}"'] & \mathrm{Ph\bar{C}HOMeLi^+} \arrow[u, "\times"] \arrow[d, "\times\ \mathrm{Bu^nLi}"] \arrow[r, "\mathrm{Bu^nBr}"] & \mathrm{Ph(Bu)CHOME} \\ & o\text{-}\mathrm{LiC_6H_4\bar{C}OMeLi^+} & \end{tikzcd}$$

All the reported[1-6] solvents used for the Wittig rearrangements and related reactions have been moderately polar [*e.g.* hexane–tetrahydrofuran (THF), ether, ether–THF, and THF]. Use of a non-polar solvent, such as hexane with TMEDA either avoids or limits the Wittig rearrangement. It has been recently reported that carbanions derived from benzyl allyl ethers and thio-ethers undergo different rearrangements depending upon the position of metallation.[7] Since the solvent used in these cases was THF–hexane, the above finding indicates that changing the reaction medium should also vary the ratio of different types of rearrangement products.

EXPERIMENTAL

M.p.s were determined on a Mel-Tem apparatus, and were uncorrected. I.r. spectra were measured on a Perkin-Elmer Model 237 or a Beckman Model 4250. ^{1}H N.m.r. spectra were recorded on a JEOL NM-60 HL spectrometer, using tetramethylsilane as the internal standard. Mass spectra were taken on a Hitachi GC-Mass M-52. Elementary analyses were carried out at the Microanalytical Laboratory, Chung-Shan Institute of Science and Technology. Bu^{n}Li in hexane was purchased from Tokyo Kasei Co., Japan, or E. Merck Co., Germany. Hexane was pre-dried over sodium, calcium hydride, or molecular sieve.

TABLE 1

Benzylic substitution of benzyl methyl ether

Electrophile	Product	Yield (%)
Ph_2CO	$PhCH(OMe)C(OH)Ph_2$ (2)	76
BuBr	$PhCH(OMe)Bu$ [a] (3)	85
$PhCO{\cdot}C_6H_4{\cdot}OMe$-*p*	$PhCH(OMe)C(OH)(C_6H_4OMe$-*p*$)Ph$ [a] (4)	65
$PhCO{\cdot}C_6H_4Cl$-*p*	$PhCH(OMe)C(OH)(C_6H_4Cl$-*p*$)Ph$ [a] (5)	40
$EtO{\cdot}CO{\cdot}CH_2Ph$	$PhCH(OMe)C(:O)CH_2Ph$ [a] (6)	22

[a] New compounds, the analytical data for which are given in Table 2.

TABLE 2

Analytical data for reaction products

Product	M.p. (°C) (B.p.)	m/e (M^+)	^{1}H N.m.r.[a] (δ)		$\nu_{max.}$ (cm^{-1})	Elemental analysis Found (Calc.) (%)		
						C	H	Cl
(2)	137—137.5 [b]	304	3.26	(s, 4)	3 500			
			4.99	(s, 1)		82.85	6.45	
			6.90—7.70	(m, 15)	1 070	(82.76)	(6.57)	
(3)	(145—150)	178	0.91	(t, 3)	2 960			
			1.10—2.61	(m, 6)	1 460			
			3.95	(t, 1)	1 100			
			6.54—7.48	(m, 5)				
(4)	141.5—142		3.30	(s, 3)	3 495			
			3.70	(s, 3)	1 090	78.55	6.5	
			5.05	(s, 1)	1 020	(78.45)	(6.53)	
			6.50—7.71	(m, 14)				
(5)	155—155.5		3.20	(s, 3)	3 500			
			3.26	(s, 1)	1 100	73.5	5.55	10.65
			4.90	(s, 1)	1 070	(73.60)	(5.55)	(10.37)
			6.50—7.72	(m, 14)				
(6)			3.26	(s, 3)	2 980			
			3.70	(s, 2)	1 732	80.2	6.55	
			4.71	(s, 1)	1 095	(80.00)	(6.67)	
			6.86—7.50	(m, 10)				

[a] Solvents: CCl_4 for compounds (2) and (4); $DCCl_3$ for compounds (3), (5), and (6). [b] Lit., 139 °C (H. Gross and J. Freiberg, *Chem. Ber.*, 1966, **99**, 3260).

Lithiation of Benzyl Methyl Ether.—To a solution of benzyl methyl ether (2.44 g, 0.02 mol) and TMEDA (2.32 g, 0.02 mol) in dry hexane (100 ml) at −10 °C was added, in drops, Bu^{n}Li (0.02 mol) in hexane *via* a rubber septum. After 3 h the solution gradually turned brownish red and was assumed to contain 0.02 mol of lithiated benzyl methyl ether (1).

General Procedure for the Reaction of (1) *with Electrophiles.*—To the mixture containing (1) (0.02 mol) at −10 °C was added, in drops, a solution of the electrophile (0.02 mol) in hexane (40—80 ml). The mixture was then stirred for 3 h, after which 6N HCl (30 ml) was added. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were dried and evaporated. The residue was then purified by distillation or recrystallization to give the benzylic-substituted benzyl methyl ether. The yields and analytical data for the products are given in Tables 1 and 2, respectively.

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