Tetrahedron Letters No.45, pp. 3915-3918, 1970. Pergamon Press. Printed in Great Britain.

REACTIONS OF CO-ORDINATED LIGANDS. PART VI.[1] REACTIONS OF NUCLEOPHILIC REAGENTS OF THE TYPE (Nu.M; M = Li or MgX) WITH SATURATED ALKYL HALIDES WHICH HAVE A CO-ORDINATING GROUP IN THE β-POSITION.

By G.W.Cooper and R.P.Houghton.

Department of Chemistry, University College, Cathays Park, Cardiff CF1 3NR.

(Received in UK 14 August 1970; accepted for publication 27 August 1970)

In Part IV of this Series[2] it was reported that the reaction of benzylaminomagnesium iodide with a carboxylic ester proceeds at an enhanced rate if the ester group is adjacent to a substituent which can co-ordinate with magnesium. It is now shown that the rate of reaction between 2-substituted ethyl bromides and certain nucleophilic reagents in which the nucleophilic residue is bonded to magnesium or lithium increases in the same order as the co-ordinating ability of the substituent.

Benzylaminomagnesium iodide (0.0495 M) was prepared from benzylamine and methylmagnesium iodide, and heated under reflux for 1 hr. with 1-bromopentane (1 equiv.) in xylene (100 ml.). 1-Benzylaminopentane (IIa), which was shown to be stable under the conditions of the reaction, was not detected (g.l.c.) in the crude reaction product, although a 10% yield was obtained when the reaction time was increased to 65 hr. In contrast, when the reaction was repeated with a reflux time of 1 hr. and the bromides (I; b-d) were used in place of the 1-bromopentane, the yields of the corresponding amines (II; b-d) were 2, 31 and 55% respectively. Similarly, the yields of the amines (III; a-d) obtained when n-butylaminomagnesium iodide (0.0218 M) was heated under reflux in xylene (100 ml.) for 3 hr. with the bromides (I; a-d, 1 equiv.) were 0, 4, 27 and 44% respectively; the yield of the amine (IIIb) was not increased (2.5%, cf. 4%) when the reaction with the bromide (Ib) was carried out in the presence of one equivalent of the bromide (Id).

$R.CH_2.CH_2.R'$

(I) R' = Br
(II) R' = $NH.CH_2Ph$
(III) R' = NH.n-Bu
(IV) R' = C⋮C.Ph
(V) R' = $S.n\text{-}C_{12}H_{25}$
(VI) R' = $O.n\text{-}C_8H_{17}$

(a) R = n-Pr
(b) R = EtO
(c) R = $MeO.(CH_2)_2.O$
(d) R = $Me.(O.CH_2.CH_2)_2.O$

The same systematic increase in the yields of products arising from nucleophilic substitution was also observed when the four bromides were treated with other nucleophilic reagents in which the nucleophilic residue was attached to magnesium or lithium (see Table 1). The substantial yields of acetylenes obtained when the two bromides (I; c and d) were treated with phenylethynylmagnesium iodide are noteworthy in view of the usual lack of reactivity exhibited by saturated aliphatic bromides towards acetylenic Grignard reagents.[3]

TABLE 1.

Yields of products obtained by treatment of the bromides (I; a-d) with nucleophilic reagents of the type (Nu.M).

Nucleophilic reagents (Nu.M)*	Bromide	Yield (%)	
		Product	Recovered Parent Nucleophile (Nu.H)
Ph.C≡C.MgI (i) (0.0243 M)	1a	0†	92†
	1b	1†	95†
	1c	56‡	
	1d	60‡	
$n\text{-}C_{12}H_{25}S.MgI$ (ii) (0.0123 M)	1a	0‡	76‡
	1b	0‡	84‡
	1c	67‡	
	1d	63‡	
$n\text{-}C_{12}H_{25}S.MgBr$ (ii) (0.0123 M)	1c	56‡	
	1d	47‡	
$n\text{-}C_8H_{17}O.MgI$ (iii) (0.0165 M)	1a	0†	82‡
	1b	0†	87‡
	1c	20‡	
	1d	45‡	
$n\text{-}C_8H_{17}O.Li$ (iv) (0.0140 M)	1a	4†	89‡
	1b	7†	85‡
	1c	44‡	
	1d	71‡	

*Nucleophilic reagent heated under reflux with the bromide (1 equivalent): (i) for 64 hr. in benzene; (ii) for 2 hr. in benzene; (iii) for 44 hr. in xylene; (iv) for 22 hr. in xylene. In all the reactions, 100 ml. of solvent was used. †Yield determined by g.l.c. comparison of the crude reaction product with standard mixtures. ‡Yield of fractionated product.

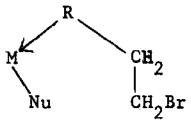
TABLE 2.

New compounds* obtained from the bromides (I; b, c, and d).

Compound.	B.p./mm.	n_D	Found (%)				Formula	Required (%)			
			C	H	N	S		C	H	N	S
11c	124-26°/0.9	1.5058(24°)	68.6	9.0	6.6		$C_{12}H_{19}NO_2$	68.9	9.15	6.7	
11d	138-140/0.2	1.4927(23°)	66.6	9.1	5.4		$C_{14}H_{23}NO_3$	66.4	9.15	5.5	
111b	64-66/30	1.4175(24°)	66.4	13.3	9.8		$C_8H_{19}NO$	66.15	13.2	9.6	
111c	82-84/0.2	1.4308(25°)	61.4	11.7	7.7		$C_9H_{21}NO_2$	61.7	12.1	8.0	
111d	88-90/0.2	1.4180(25°)	60.0	11.2	6.2		$C_{11}H_{25}NO_3$	60.2	11.5	6.4	
1Vb	130-132/20	1.5328(25°)	82.4	8.3			$C_{12}H_{14}O$	82.7	8.1		
1Vc	114-116/0.3	1.5317(25°)	76.8	7.9			$C_{13}H_{16}O_2$	76.4	7.9		
1Vd	135-138/0.3	1.5240(25°)	72.15	7.7			$C_{15}H_{20}O_3$	72.55	8.1		
Vc	164-168/0.4	1.4600(25°)	67.0	11.9		10.1	$C_{17}H_{36}O_2S$	67.1	11.9		10.5
Vd	162-164/0.1	1.4632(25°)	65.5	11.7		9.0	$C_{19}H_{40}O_3S$	65.5	11.6		9.2
V1b	118-119/30	1.4230(20°)	71.55	13.1			$C_{12}H_{26}O_2$	71.2	12.95		
V1c	98-100/0.4	1.4418(25°)	67.3	11.7			$C_{13}H_{28}O_3$	67.2	12.1		
V1d	114-118/0.25	1.4508(25°)	65.45	11.8			$C_{15}H_{32}O_4$	65.2	11.7		

*All compounds had i.r. and n.m.r. spectra in accord with the assigned structures.

These observations are understandable if it is assumed that the presence of the ether groups in the bromides (I; b-d) enable the reactions concerned to proceed by a comparatively fast intramolecular route which involves complexes of the type (VII) in which the nucleophilic residue (Nu) is held close to the saturated carbon atom which undergoes nucleophilic substitution.



(VII)

As the ether groups of the three bromides (Ib), (Ic), and (Id) may function as mono-, di-, and tri-dentate ligands respectively, the observed order of reactivity of the three bromides, i.e. (Id)>(Ic)>(Ib), is in accord with their ability to enter into complex formation. The slightly lower yields of products obtained when n-dodecylthiomagnesium bromide was used in place of the corresponding iodide in the reactions with the bromides (I; c and d) suggests that nucleophilic displacement of bromide by iodide preceeds displacement by the thiol anion to a small extent with the latter reagent. The similarity of the yields ofsulphides isolated from these two bromides in the experiment with the thiomagnesium halides contrasts with the differences observed in the experiments with the other nucleophilic reagents. If this is not an experimental artifact, it could arise because the large sulphide anion sterically hinders the co-ordination of the three oxygen atoms of the bromide (Id) with the magnesium, and only allows the bromide to function as a bidentate ligand.

The increase in reactivity which arises from the presence of the chelating groups in the bromides (I; c and d) suggests the use in organic synthesis of other chelating groups which could be introduced into an organic molecule in order to activate an adjacent functional group towards attack by an inorganic or organometallic reagent, and then be removed at the end of the reaction sequence. We are at present investigating this possibility.

We thank the S.R.C. for a postgraduate studentship (to G.W.C.).

REFERENCES:

1. Part V, P.H.Chapman, R.P.Houghton and C.S.Williams, J.Chem.Soc.(C), 1970, 1183.
2. K.Blaževič, R.P.Houghton and C.S.Williams, J.Chem.Soc.(C), 1968, 1704.
3. R.A.Raphael, "Acetylenic Compounds in Organic Synthesis" Butterworths Scientific Publications, London, 1965, p.17.