725. *The Reaction of Organolithium Compounds with Some Halogeno-acetals.*

By Gurnos Jones and H. D. Law.

Reaction of some organolithium compounds with 3-halogenopropionaldehyde diethyl acetals gives good yields of the acetals $R{\cdot}CH_2{\cdot}CH_2{\cdot}CH(OEt)_2$. The reaction with halogenacetaldehyde diethyl acetals is less uniform, but in one case the acetal $R{\cdot}CH_2{\cdot}CH(OEt)_2$ was obtained in fair yield.

Reaction of bromoacetal with 2-pyridylmethyl-lithium has been shown[1] to give 3-2′-pyridylpropionaldehyde diethyl acetal in 28% yield. As we required 4-2′-pyridylbutyraldehyde for another investigation, we examined the reaction of 2-pyridylmethyl-lithium with 3-chloropropionaldehyde diethyl acetal.

Osuch and Levine[2] have shown that the reaction between 2-pyridylmethyl-lithium and alkyl bromides proceeds in best yield if a 2 : 1 molar ratio of lithium compound to halide is used, and we used this ratio in most of our experiments. The yield of 4-2′-pyridylbutyraldehyde diethyl acetal obtained was 60%, and we were encouraged to test the generality of the reaction. Using 3-bromopropionaldehyde diethyl acetal instead of the chloro-compound gave a lower yield of the acetal (37%), and the chloro-compound was used in subsequent experiments.

Osuch and Levine suggested[2] that 2 mols. of lithium compound are needed because an intermediate complex is formed in which the halide is bonded to the pyridine-nitrogen atom. Since such a complex is not possible with phenyl-lithium we used in our initial reaction between phenyl-lithium and chloropropionaldehyde diethyl acetal a 1 : 1 molar ratio. The yield was disappointingly low (21%) but was increased to 57% by the use of a 2 : 1 molar ratio, and this was used in most of the subsequent experiments. Thus, *n*-butyl-lithium gave with the chloroacetal a 63% yield of *n*-heptaldehyde diethyl acetal.

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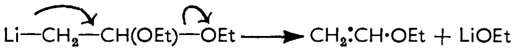
[1] Wibaut and Beets, *Rec. Trav. chim.*, 1940, **59**, 653; 1941, **60**, 905; Spielman, Swadesh, and Mortenson, *J. Org. Chem.*, 1941, **6**, 1780.

[2] Osuch and Levine, *J. Amer. Chem. Soc.*, 1956, **78**, 1723.

These results are assembled in Table 1. All acetals were identified by their infrared absorption, and by hydrolysis and preparation of derivatives of the aldehyde.

Since good yields were obtained with the halogenopropionaldehyde acetals we attempted to extend the scope of the reaction between 2-pyridylmethyl-lithium and bromoacetaldehyde diethyl acetal previously mentioned. By using a molar ratio of 2 : 1 we obtained 3-2′-pyridylpropionaldehyde diethyl acetal in 38% yield from the bromoacetal, but the chloroacetal under similar conditions gave a higher yield (49%). However, attempts to perform similar syntheses with other, more reactive lithium compounds were unsatisfactory. Thus phenyl-lithium and a bromoacetal reacted violently, but the sole product isolated was bromobenzene (76%, based on bromoacetal). If the reaction is a halogen–metal interchange (1*a*) it is to be expected that the intermediate lithium compound (I) would lose lithium ethoxide as shown in (1*b*) to give ethyl vinyl ether. No attempt was made to isolate ethyl vinyl ether from the large volume of diethyl ether used as solvent, but the absence of acetaldehyde diethyl acetal [the product expected when the lithium compound (I) is treated with water] appears to indicate that the lithium compound (I) if formed is unstable.

$$\mathrm{RLi + X{\cdot}CH_2{\cdot}CH(OEt)_2 \longrightarrow R{\cdot}X + Li{\cdot}CH_2{\cdot}CH(OEt)_2\ (I)} \quad . \ . \ . \ . \ . \quad (1a)$$



$$\mathrm{Li{-}CH_2{-}CH(OEt){-}OEt \longrightarrow CH_2{:}CH{\cdot}OEt + LiOEt} \quad . \ . \ . \ . \ . \quad (1b)$$

The reactions of phenyl-lithium or of butyl-lithium with chloroacetal [25] were less informative, much chloroacetal being recovered in both cases, together with uncharacterized low-boiling materials. In neither case was even a trace of the expected acetal found, and so no further experimental modifications were attempted. Summers and Larson have recorded [3] a reaction between phenyl-lithium and 1-bromo-2-ethoxyethane in which ethyl phenethyl ether was obtained: using their conditions (inverse addition; reaction in the cold) we obtained from phenyl-lithium and the bromoacetal some bromobenzene and some unchanged bromoacetal. Attempted reaction of phenylmagnesium bromide with 3-chloropropionaldehyde diethyl acetal in the presence of a trace of ferric chloride [4] gave only 8% of 3-phenylpropionaldehyde diethyl acetal, 90% of the chloroacetal being recovered after 4 hours' boiling of the ethereal solution. After a similar period of reaction in boiling benzene the yield of acetal was the same, but the recovery of chloroacetal was smaller.

EXPERIMENTAL

M. p.s were determined on a Kofler block. 3-Bromopropionaldehyde diethyl acetal [5] and 3-chloropropionaldehyde diethyl acetal [6] were synthesized from acraldehyde. All acetals were dried (K_2CO_3) and distilled immediately before use.

4-2′-Pyridylbutyraldehyde Diethyl Acetal.—A filtered solution of 2-pyridylmethyl-lithium, prepared [7] from bromobenzene (0·2 mole), lithium (0·2 mole), and 2-picoline (0·2 mole) in ether (180 ml.) was stirred under dry nitrogen while 3-chloropropionaldehyde diethyl acetal (0·1 mole) was added. The mixture boiled for 15 min. after the addition without external heating. The mixture was stirred at the b. p. for 4 hr. during which much white solid separated, and was then set aside overnight at room temperature. The cooled mixture was hydrolysed by addition of dilute ammonia and ammonium chloride, the ethereal layer was separated, and the aqueous layer was extracted twice with small portions of ether. The combined ethereal extracts were dried (K_2CO_3) and distilled. The acetal boiled at 143—145°/12 mm. (13·3 g., 60%), and contained traces of diphenyl (<3%). A sample was dissolved in cold dilute hydrochloric acid, and after a few min. diluted and treated with aqueous sodium picrate. The *aldehyde picrate*

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[3] Summers and Larson, *J. Amer. Chem. Soc.*, 1952, **74**, 4498.

[4] Vavon and Mottez, *Compt. rend.*, 1944, **218**, 557.

[5] Nef, *Annalen*, 1904, **335**, 263.

[6] Witzemann, Evans, Hass, and Schroeder, *Org. Synth.*, Coll. Vol. II, p. 137.

[7] Woodward and Kornfeld, *ibid.*, Coll. Vol. III, p. 413.

crystallized from water as yellow prisms, m. p. 131—132° (Found: C, 47·5; H, 3·7. $C_{15}H_{14}O_8N_4$ requires C, 47·6; H, 3·7%).

The above procedure was used in the experiments recorded in Tables 1 and 2.

TABLE 1. *Reactions of* $X·CH_2·CH_2·CH(OEt)_2$.

Lithium compound	X	Product	Yield (%)	B. p./mm.
$2\text{-}C_5H_4N·CH_2–$	Cl	$2\text{-}C_5H_4N·CH_2·CH_2·CH_2·CH(OEt)_2$	60	143—145°/12
,, ...	Br	$2\text{-}C_5H_4N·CH_2·CH_2·CH_2·CH(OEt)_2$	37	143—145°/12
Ph	Cl	$Ph·CH_2·CH_2·CH(OEt)$ [a]	57	106—107°/10
Bu^n	Cl	$CH_3·[CH_2]_5·CH(OEt)_2$ [b]	63	54—57°/9

[a] Aldehyde *p*-nitrophenylhydrazone, m. p. 122—124°; semicarbazone, m. p. 123—125°. [b] Aldehyde *p*-nitrophenylhydrazone, m. p. 108°; semicarbazone, 74°.

TABLE 2. *Reactions with* $X·CH_2·CH(OEt)_2$.

Lithium compound	X	Product	Yield (%)	B. p./mm.
$2\text{-}C_5H_4N·CH_2–$	Cl	$2\text{-}C_5H_4N·CH_2·CH_2·CH(OEt)_2$ [a]	49	131°/12 [b]
,, ...	Br	$2\text{-}C_5H_4N·CH_2·CH_2·CH(OEt)_2$	38	131°/12
Ph	Cl	— [c]	—	—
Ph	Br	PhBr [d]	76	152—153°/758
Bu^n	Cl	Mixture of low b. p. [e]	—	—

[a] Aldehyde, b. p. 118°/13 mm. (lit.,[8] b. p. 106—108°/9 mm.); aldehyde picrate, m. p. 122·5° (yellow prisms) (Found: C, 46·25; H, 3·1. Calc. for $C_{14}H_{12}O_8N_4$: C, 46·1; H, 3·3%). [b] Lit.,[1] b. p. 128°/8 mm. [c] 90% of chloroacetal recovered. [d] In an experiment using PhLi (0·1 mole) and bromoacetal (0·1 mole) with inverse addition, some unchanged bromoacetal was isolated. [e] 30% of chloroacetal recovered.

Reaction of Phenylmagnesium Bromide with 3-*Chloropropionaldehyde Diethyl Acetal*.—(*a*) To the filtered Grignard reagent from bromobenzene (0·1 mole) in ether (150 ml.) was added a trace of ferric chloride,[4] and the mixture was boiled under reflux for 4 hr., then left overnight at room temperature. Working up as described above gave 3-phenylpropionaldehyde diethyl acetal (8%) and unchanged chloroacetal (90%). (*b*) In a similar experiment the ether was replaced by benzene (150 ml.) after addition of the chloroacetal, and boiling under reflux was for 4 hr. The yield of phenylpropionaldehyde diethyl acetal was 8%, and 60% of the chloroacetal was recovered.

DEPARTMENT OF CHEMISTRY, UNIVERSITY COLLEGE OF NORTH STAFFORDSHIRE,
KEELE, STAFFS.
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[8] Miller, *J. Amer. Chem. Soc.*, 1953, **75**, 4849.