

REACTION OF 2-ALKOXY-3-CHLOROTETRAHYDROFURANS  
WITH PHENYL LITHIUM\* \*\*

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In the treatment of 2-alkoxy-3-chlorotetrahydrofurans with phenyllithium, the main reaction consists in dealkoxylation to the unstable 3-chloro-4,5-dihydrofuran which is then metallated to the stable 3-chloro-4,5-dihydro-2-furyllithium. The latter compound was isolated in the form of bis(3-chloro-4,5-dihydro-2-furyl) ketone (by reaction with carbon dioxide) and as 3-chloro-4,5-dihydro-2-furyl phenyl ketone (by reaction with lithium benzoate). The dealkoxylation mechanism and probable reasons for the stability of 3-chloro-4,5-dihydro-2-furyllithium are discussed.

As shown by systematic examinations on the reaction of phenyllithium with halo ethers, the ratio substitution/elimination is a function of the halo atom and in the case of  $\beta$ -chloro ethers, vinyl ethers are mainly formed by dehydrochlorination<sup>1</sup>. The reaction of  $\beta$ -halo acetals with organolithium compounds has not been so far reported while with other bases dehydrohalogenations have been again observed<sup>2-4</sup>; to our knowledge, only the reaction of chloroacetaldehyde diethylacetal with sodium amide in liquid ammonia has been reported to result in dealkoxylation with the formation of  $\beta$ -chlorovinyl ethyl ether<sup>5</sup>. Recently, numerous unstable chlorovinyl lithium<sup>6</sup>, 1-chloro- or 1-bromo-2-alkoxyvinyl lithium<sup>7</sup>, and chlorodialkoxyvinyl lithium<sup>8</sup> compounds decomposing at  $-80^\circ\text{C}$  in the course of less than 5 hours have been described. Reactions of 3-chloro- and 3-bromo-2-alkoxytetrahydrofurans with hydroxylic and alkoxide ions<sup>9,10</sup> have been observed to result in dehydrohalogenations with the formation of 2,5- and 4,5-dihydro-2-alkoxyfurans in the ratio of 10 : 1 to 20 : 1. Similar results have been obtained in reactions of 2-alkoxy-3-chlorotetrahydrofurans with sodium amide<sup>11,12</sup>.

In this paper, we wish to report the reaction of 2-alkoxy-3-chlorotetrahydrofurans *Ia*–*Ic* with phenyllithium. Thus, the treatment of 2-ethoxy-3-chlorotetrahydrofuran (*Ia*) with two moles of phenyllithium in diethyl ether at room temperature afforded (after interruption with dry ice) a mixture of products (100%) consisting of polymers (45–50%), ketones *II* and *III* (20% and 15%, resp.), traces of a compound (structure undetermined) exhibiting green fluorescence under ultraviolet light, *trans-Ia* (about 15% after 45 min of the reaction; completely absent after 60–80 min), and biphenyl (8%) which is formed during the preparation of phenyllithium by the Wurtz–Fittig reac-

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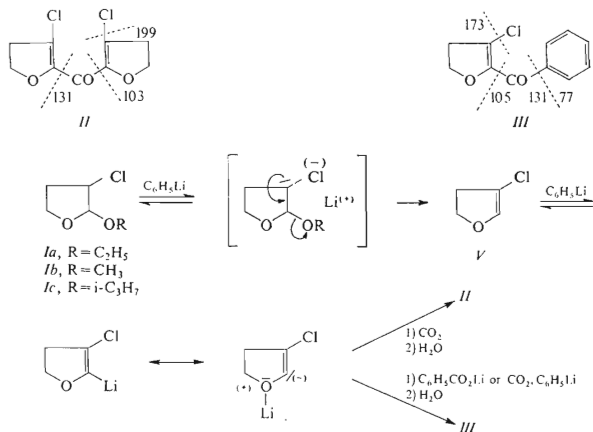
tion<sup>13</sup>. Furthermore, the mixture always contained benzophenone which is formed from the unreacted phenyllithium. The ratio *II/III* and the proportion of polymers increases with the increasing reaction time; after 20 h, the mixture contains only the polymers, the ketone *II*, and biphenyl. The mixture was separated by elution column chromatography and the thus-obtained pure compounds were identified by spectrometry.

The IR spectrum of the ketone *II* exhibited bands of a strongly conjugated carbonyl group ( $1665\text{ cm}^{-1}$ ) and C=C bonds ( $1611$  and  $1600\text{ cm}^{-1}$ ). The PMR spectrum contains only two interacting triplets of the same intensity. Elemental analysis and the molecular weight 234 suggested the formula  $\text{C}_9\text{H}_8\text{Cl}_2\text{O}_3$  and the most probable structure of bis(3-chloro-4,5-dihydro-2-furyl) ketone *II* which was confirmed by the main fragments and their +2 and +4 satellites in the mass spectrum (*m/e*, % of relative intensity): 234 (48), 236 (31), 238 (5), 199 (14), 201 (5), 131 (100), 133 (33), 103 (16), 105 (6), 75 (50), 77 (20), and 39 (70), according to ref.<sup>14</sup> a characteristic fragment of furan derivatives. Both the fragmentation and the relative occurrence of isotopic peaks<sup>15</sup> are in accordance with the structure proposed. So are the analytical data of the 2,4-dinitrophenylhydrazone of ketone *II*. Substitution of the carbonyl oxygen in the ketone *II* by the 2,4-dinitrophenylhydrazone group introduced into the molecule nonequivalency of the two dihydrofuran rings as it may be inferred from the PMR spectrum of the hydrazone; in addition to signals of aromatic protons, this spectrum exhibits two equally intensive interacting pairs of mutually superimposed but non-interacting triplets.

The structure of ketone *II* together with the finding that 2-methoxy-3-chlorotetrahydrofuran (*Ib*) and 2-isopropoxy-3-chlorotetrahydrofuran (*Ic*) gave with phenyllithium the same products as 2-ethoxy-3-chlorotetrahydrofuran (*Ia*) (there were only slight differences in the ratios of the individual products and the reaction rate) led us to suggest the structure of 3-chloro-4,5-dihydro-2-furyl phenyl ketone for the compound *III* as well as the over-all picture of the reaction. The structure *III* was supported by elemental analysis, PMR spectrum (two equally intensive interacting triplets along with an aromatic multiplet), and mass spectrum (particularly the main fragments and their +2 satellites), *m/e* (% of relative intensity): 208 (33), 210 (11), 173 (9), 131 (11), 133 (11), 133 (4), 105 (100), 77 (46), 39 (7), ref.<sup>14</sup>. Similarly to the ketone *II*, also the 2,4-dinitrophenylhydrazone of the ketone *III* analyzed in accordance with the structure proposed. The PMR spectrum of this hydrazone exhibited only two triplets in the region of methylene protons, indicating thus the presence of a single geometrical isomer.

The dependence of the ratio *II/III* on the reaction time might be explained by the decreasing concentration of phenyllithium in the mixture and by the decreasing probability of the reaction among 3-chloro-4,5-dihydro-2-furyllithium, carbon dioxide, and phenyllithium. The disappearance of benzophenone supports the idea that phenyllithium disappears from the mixture as the first compound long before the

conversion of the lithium derivative *IV*. Reaction of a higher excess of phenyllithium and compound *Ia* (6 : 1) leading after interruption with carbon dioxide to a mixture of the ketone *III* and benzophenone containing only traces of the ketone *II* strongly favours the above idea. Interruption of the reaction with lithium benzoate<sup>16</sup> afforded after protolysis as the main product the ketone *III* along with benzophenone and polymers. A direct protolysis of the reaction mixture did not lead to isolation of 3-chloro-4,5-dihydrofuran (*V*); only the proportion of polymers highly increased. This finding does not surprise since the attempted preparation of the hitherto unreported compound *V* in the pure state was in this Laboratory unsuccessful in spite of numerous experiments and different routes<sup>17,18</sup>.



As indicated by reaction products, the treatment of compounds *I* with phenyllithium proceeds *via* an elimination process hitherto unobserved in this field of chemistry. The elimination mechanism which is strongly shifted towards  $\text{E}_{\text{lc}}$ , is highly influenced by the carbanion stability. The carbanion formed by removal of a proton from position 2 of the ring is not stable owing to the electrostatic repulsion between the lone electron pairs on oxygen and the lone pair on the carbon atom; the earlier work<sup>19</sup> is in accordance with this assumption. The chloride anion which is known to be a much more better leaving group than alkoxide anion, is not eliminated in the present case and a dealkoxylation occurs. Furthermore, from the *cis* and *trans* isomers<sup>20</sup> of compounds *I* it is the *cis* isomer which undergoes the preferential reaction.

All these observations favour the Elcb mechanism. By analogy with the cyclopentane ring, other lower monocycles, and some carbobicycles, the E2 reaction of compounds I should mainly obey the *syn*-mechanism, *i.e.*, involve the *trans* isomers of compounds I (ref.<sup>21-25</sup>).

The considerable stability of the organolithium compound IV is surprising, particularly in comparison with data reported in some earlier papers<sup>7,8</sup>. To our opinion, this stability cannot be solely due to the *cis* position of the chloro and lithium atoms which does not favour the elimination. Some other possibility must be therefore taken into consideration, such as the intramolecular<sup>26</sup> or intermolecular<sup>27</sup> stabilisation by solvation of the lithium cation by the basic ethereal oxygen atom.

The formation of a considerable amount of polymers accompanying the present reaction might also be ascribed to a cycloreversal process reported in the reaction of tetrahydrofuran with butyllithium by Bates and coworkers<sup>28</sup> and Tomboulian and coworkers<sup>29</sup>.

## EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block) and were not corrected. The UV spectra were recorded on a Unicam SP 1800 spectrophotometer in ethanol, unless stated otherwise. The IR spectra were taken in potassium bromide discs on Zeiss UR 10 and UR 20 apparatus. The PMR spectra (80 MHz) were measured on a Tesla BS 487 apparatus in deuteriochloroform; chemical shifts are expressed in  $\delta$  (p.p.m.) with respect to tetramethylsilane as internal standard. Elemental analyses were performed on a Carlo Erba Type 1102 apparatus. Mass spectra were measured on a LKB 9000 apparatus. Gas chromatography was performed on Chrom II and Chrom III apparatus, glass or steel columns, 10% of Apiezon L on Chromatom or 4% of poly(ethylene glycol adipate) on the porous plate material (0.1—0.2 mm).

### Materials and Methods

Diethyl ether was dried over sodium wire and, prior to the use, distilled over lithium aluminium hydride. Bromobenzene was dried over phosphorus pentoxide, distilled, and the distillate stored over molecular sieve (4 Å). Lithium was purchased from Lachema, Czechoslovakia, and used in the form of a wire, 0.8 mm in diameter (1 meter, about 0.85 g). Phenyllithium was prepared by a reported procedure<sup>30</sup>; before use, the about 1M solution was filtered through a plug of glass wool. The derivatives Ia—Ic were prepared as reported earlier<sup>20</sup>, redistilled, and stored over activated molecular sieve (4 Å). Their purity was checked by gas chromatography, the ratio *cis/trans* being not changed. Lithium benzoate was prepared by a reported procedure<sup>16</sup>. The glassware was dried at 125°C for at least 1 h. Prior to the reaction, the apparatus was flushed with dry nitrogen for 30 min.

Thin-layer chromatography was performed on Silpearl (Kavalier Glassworks, Czechoslovakia) silica gel containing 13% of gypsum as binder (30 × 70 mm layers). Spots were detected by viewing under ultraviolet light. Benzene-cyclohexane (9 : 1) was used as developing agent; the layers were impregnated with fluorescein. The 2,4-dinitrophenylhydrazones of ketones II and III were chromatographed on 90 × 195 mm layers of loose silica gel (particle size, 40—100  $\mu$ ) in the same developing system. The preparative column (270 mm; 32 mm in diameter) was packed with about 150 g of silica gel (particle size, 40—100  $\mu$ ) in 300 ml of tetrachloromethane which was then replaced by cyclohexane. Cyclohexane, benzene, chloroform, and acetone (polymers) were used as eluants.

Reaction of 2-Alkoxy-3-chlorotetrahydrofurans *Ia—Ic* with Phenyllithium

Compound *I* (50 mmol) in diethyl ether (50 ml) was added into a solution of phenyllithium (100 mmol) in diethyl ether (100 ml). In the course of 5 min, the mixture darkened and began to reflux; after about 30 min, the reflux ceased. After 45–60 min, the mixture was poured onto dry ice (about 100 g). When the solid carbon dioxide evaporated, the remaining slurry was diluted with an equal volume of water, filtered if necessary, the aqueous layer of the filtrate was separated, and extracted with three 50 ml portions of diethyl ether. The ethereal layer and extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated under diminished pressure. The residual oil (about 6 g) was chromatographed on a column (see above), 250 ml fractions being taken (the course of chromatography was checked under ultraviolet light). Fractions 1–7 (elution with cyclohexane–benzene 9 : 1 to 1 : 9) contained the *trans* isomer of compounds *I* along with traces of a unidentified substance of a green fluorescence. Elution with benzene afforded biphenyl (fractions 8–10), benzophenone (fractions 11–12), the ketone\* *III* of a blue fluorescence (fractions 13–15), and the fluorescence-extinguishing ketone\* *II* (fractions 16–18). The reaction becomes slower in the order *Ib*, *Ia*, and *Ic* and affords more polymers. Evaporation of the appropriate eluate and repeated crystallisation of the residue from cyclohexane and ethanol afforded 1.1 g of bis(3-chloro-4,5-dihydro-2-furyl) ketone (*II*), yellow crystals, m.p. 87°C,  $R_F$  0.14. UV spectrum:  $\lambda_{\max}$  327 nm ( $\log \epsilon$  3.79). IR spectrum:  $\nu(\text{C}=\text{O})$  1665  $\text{cm}^{-1}$ ,  $\nu(\text{C}=\text{C})$  1600, 1611  $\text{cm}^{-1}$ . PMR spectrum: 3.06 (t, 2 H,  $-\text{OCH}_2-\text{CH}_2-$ ) and 4.50 (t, 2 H,  $\text{OCH}_2$ ),  $J = 10$  Hz (both). For  $\text{C}_9\text{H}_8\text{Cl}_2\text{O}_3$  (235.1) calculated: 45.99% C, 3.43% H, 30.16% Cl; found: 46.12% C, 3.44% H, 26.25% Cl. Ketone *II*, 2,4-dinitrophenylhydrazone. M.p. 149°C (ethanol),  $R_F$  0.36. UV spectrum:  $\lambda_{\max}$  387 nm ( $\log \epsilon$  4.33). PMR spectrum: 2.90 and 2.94 (2 t, each 2 H,  $-\text{OCH}_2-\text{CH}_2-$ ); 4.35 and 4.55 (2 t, each 2 H,  $\text{OCH}_2$ ),  $J = 10$  Hz (both); 7.95 (d, 1 H, 6-H); 8.30 (dd, 1 H, 5-H); 9.05 (d, 1 H, 3-H);  $J_{6-\text{H},5-\text{H}} = 10$  Hz,  $J_{5-\text{H},3-\text{H}} = 2.5$  Hz,  $J_{6-\text{H},3-\text{H}} = 0$ ; 12.15 (s, 1 H, N-H). The N-H proton does not undergo exchange in heavy water even under catalysis of  $\text{CF}_3\text{CO}_2\text{H}$  at 45°C. For  $\text{C}_{15}\text{H}_{12}\text{Cl}_2\text{N}_4\text{O}_6$  (415.2) calculated: 43.39% C, 2.91% H, 13.49% N; found 43.60% C, 3.42% H, 13.45% N.

Evaporation of the appropriate eluate and crystallisation of the residue from diethyl ether afforded 0.75 g of 3-chloro-4,5-dihydro-2-furyl phenyl ketone (*III*), m.p. 36–38°C,  $R_F$  0.30. UV spectrum:  $\lambda_{\max}$  257 ( $\log \epsilon$  3.73) and 324 nm ( $\log \epsilon$  3.42). PMR spectrum: 2.98 (t, 2 H,  $-\text{OCH}_2-\text{CH}_2-$ ); 4.47 (t, 2 H,  $\text{OCH}_2$ ),  $J = 10$  Hz (both); 7.0–8.20 (m, 5 H,  $\text{C}_6\text{H}_5$ ). For  $\text{C}_{11}\text{H}_9\text{ClO}_2$  (208.6) calculated: 63.32% C, 4.35% H, 17.02% Cl; found: 63.19% C, 4.52% H, 16.23% Cl. Ketone *III*, 2,4-dinitrophenylhydrazone. M.p. 203°C (ethanol),  $R_F$  0.60. UV spectrum (dioxane):  $\lambda_{\max}$  383 nm ( $\log \epsilon$  4.39). PMR spectrum: 3.22 (t, 2 H,  $-\text{OCH}_2-\text{CH}_2-$ ) and 4.83 (t, 2 H,  $-\text{OCH}_2$ ),  $J = 10$  Hz (both); 7.35–8.0 (m, 5 H,  $\text{C}_6\text{H}_5$ ); 8.15 (d, 1 H, 6-H); 8.40 (dd, 1 H, 5-H); 9.20 (d, 1 H, 3-H);  $J_{6-\text{H},5-\text{H}} = 10$  Hz;  $J_{5-\text{H},3-\text{H}} = 2.0$  Hz;  $J_{6-\text{H},3-\text{H}} = 0$  Hz; 12.1 (s, 1 H, NH).

The following additional compounds were obtained by column chromatography of the reaction mixture (6 g): biphenyl (about 0.42 g; identified by UV spectrum), *trans-I* (0.8 g; the isomeric purity was determined by gas chromatography and PMR spectrum according to the signal of the anomeric proton<sup>20</sup>, a substance of a green fluorescence under UV light (traces dissolved in *I*), and polymers (about 2.5 g).

\* Ketones *II* and *III* are unstable on light and at room temperature; they undergo a rapid autocatalytic decomposition with the formation of hydrogen chloride and furan derivatives as the primary products; they may be stored at  $-20^\circ\text{C}$  in the dark for at least two months. The ketone *II* is a strong skin irritant.

## Reaction of 3-Chloro-4,5-dihydro-2-furyllithium (IV) with Lithium Benzoate

To a mixture of phenyllithium (60 mmol), compound *Ia* (25 mmol), and diethyl ether (90 ml) there was added after 1 h lithium benzoate (10 g; 78 mmol). The reaction mixture was stirred at room temperature for 3 h, decomposed with water (50 ml), and processed as usual to afford an oil which was shown by thin-layer chromatography to contain the ketone *III*, traces of the ketone *II*, benzophenone, and polymers. Column chromatography afforded pure ketone *III*, identical with an authentic specimen. PMR spectrum of its 2,4-dinitrophenylhydrazone was also identical with that of an authentic specimen.

Reaction of Excess Phenyllithium with 2-Ethoxy-3-chlorotetrahydrofuran (*Ia*)

A solution of phenyllithium (120 mmol) in diethyl ether (120 ml) was allowed to react at room temperature for 100 min with compound *Ia* (20 mmol) in diethyl ether (20 ml). The mixture was then poured onto Dry Ice and processed as usual to show the presence of the ketone *III* along with traces of the ketone *II*.

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## REFERENCES

1. Summers L., Larson M. L.: *J. Am. Chem. Soc.* **74**, 4498 (1952).
2. McElvain S. M., Kundiger D.: *Org. Syn.* **23**, 45 (1945).
3. McElvain S. M., Morris L. R.: *J. Am. Chem. Soc.* **73**, 206 (1951).
4. Bedoukian P. Z.: *J. Am. Chem. Soc.* **79**, 889 (1957).
5. Eglinton G., Jones R. H., Shaw B. L., Whiting M. C.: *J. Chem. Soc.* **1954**, 1860.
6. Köbrich G., Flory K.: *Chem. Ber.* **99**, 1773 (1966).
7. Ficini J., Depezay J. C.: *Tetrahedron Letters* **1968**, 937.
8. O'Connor R. B.: *J. Org. Chem.* **33**, 1991 (1968).
9. Zezula V.: *Thesis*. Institute of Chemical Technology, Prague 1973.
10. Zezula V., Kratochvíl M.: *This Journal* **36**, 2720 (1971).
11. Quenchen F., Normant H.: *Compt. Rend.* **228**, 1301 (1949).
12. Bolotina L. M., Kučenko N. I., Moškin P. A.: *Dokl. Akad. Nauk SSSR* **174**, 601 (1967).
13. Wittig G., Merkle W.: *Ber.* **75**, 1491 (1942).
14. Benyon J. H., Saunders R. A., Williams A. E.: *The Mass Spectra of Organic Molecules*, p. 463. Elsevier, Amsterdam 1968.
15. McLafferty F. W.: *Interpretation of Mass Spectra*, p. 22. Benjamin, New York 1967.
16. Talalajeva T. V., Kočeškov K. A.: *Metody Elementoorganičeskoj Chímii, Li, Na, K, Rb, Cs*, p. 840. Nauka, Moscow 1971.
17. Zapletal V.: *Thesis*. Purkyně University, Brno 1968.
18. Kratochvíl M., Bulenkova L., Zezula V.: Unpublished results.
19. Berlin K. D., Rathore B. S., Peterson M.: *J. Org. Chem.* **30**, 226 (1965).
20. Zezula V., Kratochvíl M.: *This Journal* **35**, 1745 (1970).
21. Cristol S. J., Hoegger E. F.: *J. Am. Chem. Soc.* **79**, 3438 (1957).
22. DePuy C. H., Thurn R. D., Morris G. F.: *J. Am. Chem. Soc.* **84**, 1314 (1962).

23. DePuy C. H., Morris G. F., Smith J. S., Smat R. J.: J. Am. Chem. Soc. 87, 2421 (1965).
24. Kwart H., Takeshita T., Nyce J. L.: J. Am. Chem. Soc. 86, 2606 (1964).
25. Sicher J.: Angew. Chem. 84, 186 (1972).
26. Taylor K. G., Hobbs W. E., Saquet M. J.: J. Org. Chem. 36, 369 (1971).
27. Köbrich G., Flory K., Fischer R. H.: Chem. Ber. 99, 1901 (1966).
28. Bates R. B., Kroposki L. M., Potter D. E.: J. Org. Chem. 37, 560 (1972).
29. Tombouliau P., Amick D., Beare S., Dumke K., Hart D., Hites R., Metzger A., Nowak R.: J. Org. Chem. 38, 322 (1972).
30. Evans J. C. W., Allen C. F. H.: Org. Syntheses Coll., Vol. II, p. 517. Wiley, New York 1946.

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*Note added in proof:* In a paper, submitted for publication the same day as the ours (Schlosser M., Schaub B., Spahic B., Sleiter G.: Helv. Chim. Acta 56, 2166 (1973)), compound *V* and its metallation to *IV* with butyllithium at  $-78^{\circ}\text{C}$  has been described. The data of Schlosser and co-workers concerning the stability and reactivity of compound *IV* and our findings are mutually supportive.