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ADDITION OF ALKYL-LITHIUM REAGENTS TO 2-ALKENYL-1,3-DIOXANES

M. Kool and G.W. Klumpp*

Scheikundig Laboratorium Vrije Universiteit, De Lairessestraat 174,

Amsterdam, The Netherlands

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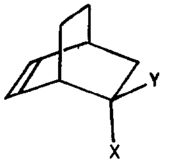
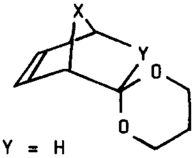
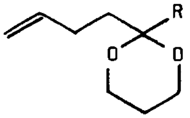
Increasing evidence points to the major influence of intramolecular coordination upon the stability and the reactivity of organolithium compounds.[1-3] Of special interest from a synthetic point of view is the promotion of the addition of alkyl-lithiums to unconjugated carbon-carbon double bonds by a complexing group X, positioned suitably (cf. I) within the olefinic reaction partner.



I: X = OR, NR_2, SR; Y = H
II: X = H; Y = OR, NR_2, SR



III: X = $(CH_2)_2$; Y = nil
IV : X = CH_2 ; Y = CH_2
V : X = $(CH_2)_2$; Y = CH_2
VI : X = $(CH_2)_3$; Y = CH_2



VII: R = H
VIII: R = CH_3

Additions of alkyl-lithiums to alkenes lacking such a group or carrying it in a position pointing away from the double bond (cf. II) take place only in exceptional cases.[4] In earlier communications we reported upon the addition of alkyl-lithiums to the double bonds of alkenyl ethers[5], alkenylamines[6] and an alkenyl sulphide.[6] Crandall and Felkin have observed the addition of alkyl-lithiums to allyl alcohols[7] and Wilkins has observed the addition of n-butyl-lithium to norbornenols.[8] In all cases initial complexation of RLi by X is considered to be the cause of the high stereo- and regioselectivities of these addition reactions and of part of the enormous increase in reactivity, which ensues when X is introduced in the parent alkene. Stabilisation of the addition products by intramolecular chelation is supposed to be another factor contributing to the rate enhancement. Having extended our work on alkenyl ethers to the 1,3-dioxanes III-VIII derived from the corresponding β,γ- and γ,δ-unsaturated carbonyl compounds we now report that these compounds likewise readily add alkyl-lithiums. These results (given in Tables 1 and 2) can be of special synthetic significance: Transformation of a β,γ- or γ,δ-unsaturated carbonyl compound into its dioxane derivative diverts attack of RLi from C=O to C=C. After addition the C=O group can be regenerated by hydrolysis. In a formal sense this recalls the control of regioselectivity which is exerted by Cu(I) salts upon the reactions between RLi and α,β-unsaturated carbonyl compounds.[9]

Table 1. Reactions of 2-alkenyl-1,3-dioxanes III-VI with alkyl-lithiums. Standard conditions: 1 equiv substrate + 2 equiv RLi; ether: pentane or hexane 1:1; 25°C. A: % conversion of starting material into major + minor adduct (by glpc of hydrolysates). B: % d_1 in starting material recovered from D_2O-quench of reaction mixtures.

RLi, R:	III		IV		V		VI	
	A	B	A	B	A	B	A	B
n-Bu	100 + 0	--	0 + 0	5	20 + 0	10	60 + 0	20
i-Pr	100 + 0	--	75 + 7	80	(100 + 0)[a]	--	90 + 5	--
i-Pr[b]			57 + 18	85				
t-Bu[c]	100 + 0	--	16 + 9	75	90 + 0	25	100 + 0	--
t-Bu[b]			20 + 35	85	73 + 7	85	95 + 5	--

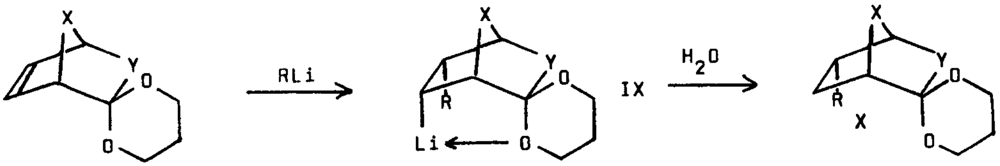
[a] Carried out by Dr. A.H. Veefkind.[11] [b] Hexane, 25°C. [c] At 0°C.

Table 2. Reactions of 2-alkenyl-1,3-dioxanes VII and VIII with alkyl-lithiums. Standard conditions as given in Table 1; % refer to conversion of starting material (by glpc of hydrolysates).

RLi, R:	VII		VIII	
	% addition	% isomerization	% addition	% isomerization
i-Pr	30	20	15	10
i-Pr[a]	95	2	60	3
t-Bu	10	50	-	10

[a] Without solvent, threefold excess of i-PrLi.

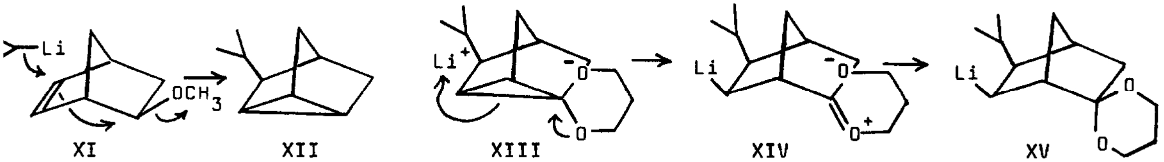
For the addition of i-propyl-lithium to III and to IV and of t-butyl-lithium to IV it was proven that in the major products [in the 16% (20%) product from IV] the alkyl group occupies the position syn to the neighbouring oxygen atom.[10] Maintaining the hypothesis of intramolecular coordination as the driving force of our reactions this result implies cis addition of the alkyl-lithium to III, yielding the intramolecularly coordinated compound IX as the initial adduct and X as its hydrolysis product. The structures of the main products formed (after hydrolysis) from V and VI are assigned by analogy, the alkyl groups R being attached syn to oxygen at the distant carbon atom of the double bond (X). The main products of the additions of i-propyl-lithium and t-butyl-lithium



IX

to IV, V and VI are accompanied by small amounts of an isomer. In the cases of V and VI it is assumed that these by-products are formed by competing radical reactions. Nothing can be said about their structures. In the case of IV it was shown that the 9% (35%) product of the addition of *t*-butyl-lithium carries the *t*-butyl group on the *exo* side.[10] In addition to a radical reaction two alternative possibilities have to be considered in this case:

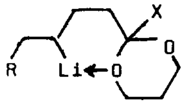
(1) Unassisted slow *exo*-addition of RLi to the strained norbornene double bond can compete successfully with addition of intramolecularly coordinated RLi, which, by its *endo*-nature, is sterically disfavored. This could explain why more *exo*-adduct is formed when the addition reactions are carried out in the absence of ether: Under these conditions sterically more encumbered higher aggregates of RLi may be the reactants. (2) The reaction between *i*-propyl-lithium and *exo*-2-methoxybicyclo[2.2.1]-hept-5-ene (XI) follows a homo-S_N2'-course:[5]



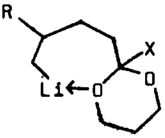
XI XII XIII XIV XV

If a similar reaction course were followed in the case of IV, the cyclopropyl ether XIII formed initially might re-open under the Lewis-acid influence of lithium, thereby causing re-closure of the dioxane ring.

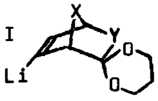
The open-chain compounds VII and VIII did not react with *n*-butyl-lithium. Additions of *i*-propyl-lithium and of *t*-butyl-lithium to VII placed the alkyl groups selectively at the terminal carbon atom, implying the six-membered ring chelate XVI(X=H) as the structure of the single adduct. In the case of VIII addition led to XVI(X=CH_3) and



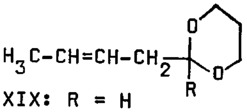
XVI



XVII



XVIII



$H_3C\text{-}CH\text{=}CH\text{-}CH_2\text{-}C(R)(O\ldots O)$

XIX: R = H
XX : R = CH_3

XVII (X=CH_3). At present the interplay of ring strain, non-bonding interactions originating from the methyl group and electronic factors (HCHLi is more favorable than RCHLi) governing the partitioning between XVI and XVII(X=CH_3) cannot be dissected. The addition reactions of IV - VIII are accompanied by competing deprotonations of the starting materials leading to vinyl-lithium derivatives in the case of IV-VI and allyl-lithium derivatives from VII and VIII, neither undergoing addition of RLi. ^1H NMR of IV-d_1 obtained by quenching the reaction mixture with D_2O indicated that lithiation occurred selectively at the =C-H bond nearest to the dioxane grouping (XVIII). Again, initial intramolecular coordination of RLi is held responsible for this type of regioselectivity. V and VI are assumed to behave similarly. D_2O-quench of the reaction mixtures from VII and VIII led to starting material deuterated at the allyl position and to the isomeric olefins XIX and XX deuterated at the terminal allyl position.

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