

Stereoselective Addition of Lithium Amides to Activated Triple Bonds

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The nucleophilic addition of R''_2NLi to alkyl esters of $R'C\equiv CCO_2R$ ($R' = H, CO_2R$; $R = Me, Et$) in apolar solvents, in the presence and in the absence of solvating agents, has been studied. The only or the main reaction product obtained under all experimental conditions was the corresponding (*E*)- $R''_2NCR' = CHCO_2R$. It is suggested that the vinyl-lithium intermediate, which is first formed by an *anti*-type addition of R''_2NLi to the triple bond, undergoes a very fast isomerisation, owing to the highly effective configurationally destabilising R^+ effect of the electron-donating dialkylamino *trans*- β -substituent.

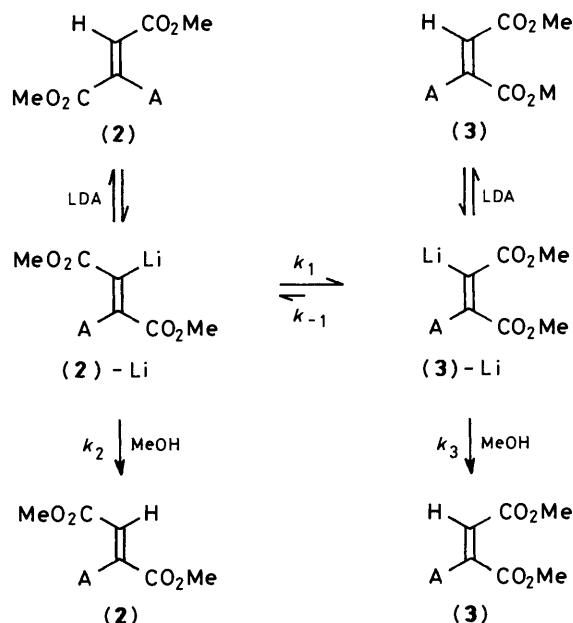
Vinyl-lithium compounds formed by direct lithiation of β -substituted activated olefins are reactive intermediates of great interest. Their multifunctionality and synthetic versatility have been demonstrated by their conversion in stepwise reactions into valuable synthons, which are structural units of many natural products.¹ Such vinyl-lithium compounds are also the intermediates formed in the addition of negatively charged nucleophiles (e.g. lithium compounds) to activated acetylenes of the type $YC\equiv CG$ ($G = CO_2R, CONR, CN, SO_2R, etc.$; $Y = H, G, R, Ar, OR, SR, NR_2, etc.$).² The configurational stability of vinyl-lithium compounds is one of several factors which might affect the stereochemical result of its reaction with an electrophile, and depends, in turn, on several factors such as ion-pairing characteristics, effect of the medium, and substituent effects. The greater the ion-pair contact, the higher is its configurational stability.³⁻⁶ Substituents which stabilise carbanions by delocalisation [$C(O)R$,^{6,7} CO_2R ,⁸⁻¹² CHO ¹²] decrease the configurational stability of the corresponding vinyl-lithium compound. α -Lithiated olefinic nitriles are relatively stable,^{10,13} as the α -substituents stabilising the carbanions by an inductive effect (OR ,¹⁴ SR ,^{15,16} SeR ,¹⁷ NC ,¹⁸ etc.) tend to stabilise the configuration of the corresponding vinyl-lithium compounds. A β -substituent could influence the configurational stability of α -lithiated activated olefins in two ways. The *trans* configuration of an α -lithio derivative of an α,β -disubstituted activated olefin of the type $YCH=CHG$ (**1**) is stabilised owing to internal complexation of the Li counter-ion by the *cis* β -Z-substituent. Compounds (**1a-d**) are some typical examples.



- (1) a; ^{15b} G = CN, Y = SEt
b; ^{15b} G = S(O)R, Y = SR
c; ¹⁹ G = Ph, Y = CO₂R
d; ²⁰ G = CN, Y = NH₂

Another relevant effect of an electron-donating β -substituent has been studied with regard to the influence of a β -substituent A ($A = NR_2, OR, SR$) on the relative configurational stabilities of the dimethyl esters of α -lithiated fumaric acid (**2**)-Li and maleic acid (**3**)-Li (Scheme 1).²¹

Protonation of the reaction mixture obtained from either compound (**2**) or (**3**) with methanol (for which case k_2 and $k_3 \gg k_1$ and k_{-1}), resulted exclusively in compound (**3**). With a relatively weak electrophile such as PhCHO, when the above relationship does not hold, the lactone derived from



Scheme 1.

compound (**2**)-Li resulted, for $A =$ pyrrolidin-1-yl, morpholino, in relatively high yields. These observations confirm (a) the existence of a (**2**)-Li \rightleftharpoons (**3**)-Li equilibrium, by which the two isomeric vinyl-lithium compounds are capable of interconversion, and (b) that $k_1 \gg k_{-1}$. It was concluded²¹ that the configurational stability of a vinyl-lithium compound having a *trans*-substituent of this type is lower than that of the *cis*-isomer.

The purpose of the present work was to verify this conclusion with regard to vinyl-lithium intermediates formed in the addition reaction of lithium amides to activated triple bonds.

Results and Discussion

Nucleophilic addition of lithium amides derived from secondary amines, to alkyl esters of propiolic (**4a**) and acetylenedicarboxylic (**4b**) acids, $R'C\equiv CCO_2R$ [(**4a**; $R' = H$) (**4b**; $R' = CO_2R$)] was carried out in apolar solvents [tetrahydrofuran (THF), diethyl ether (DEE), DEE-hexane, hexane] at $-78^\circ C$ with and without solvating agents (TMEDA, 18-crown-6). The only or the main reaction product obtained on quenching the reaction mixture with water or methanol was the corresponding (*E*)- $R''_2NCR' = CHCO_2R$ (**8**). The nucleophilic

either the methyl ester^{21,25a,b} or the bulky t-butyl ester^{25b} of the intermediate (**5b**)-Li (R' = CO₂R, R = Me, Bu^t; R''N = pyrrolidin-1-yl) obtained by deprotonation of the corresponding olefins. This indicates that the steric interaction which could affect the shifting of the (**5**)-Li⇌(**6**)-Li equilibrium towards (**5**)-Li (decreasing the k'_2/k'_{-2} ratio) is not sufficient to counteract the effect of the *trans*-β-NR''₂ group. It should, however, be mentioned that protonation of the t-butyl esters (in contrast to the methyl esters) of the (**5b**)-Li⇌(**6b**)-Li equilibrium mixture for the case of R''N = morpholino and 4-methylpiperazin-1-yl, resulted in mixtures of the corresponding products (**7b**) and (**8b**), in the ratio 1:4 and 1:3, respectively.^{25b}

It seems reasonable to assume that the reverse order of the configurational stabilities of the vinyl-lithium compounds (**5b**)-Li and (**6b**)-Li observed^{25b} for R''N = morpholino and 4-methylpiperazin-1-yl, as compared to the other R''N substituents used in the present work, is not due solely to the relatively larger steric interaction of the t-butyl ester groups in (**6b**)-Li. This assumption is based on the fact that compound (**8b**) was the main product of the protonation reaction of *both* the methyl (Table, entries 1,2) and the t-butyl^{25b} esters of the (**5b**)-Li⇌(**6b**)-Li equilibrium mixture for R''N = pyrrolidin-1-yl. It might therefore be that an additional factor, which decreases significantly the R⁺ effect of the conjugated amino nitrogen atom (and the related k'_2/k'_{-2} ratio), is effective only in the case of the morpholine and the *N*-methylpiperazine groups, and not in the case of the other R''N-groups involved. This factor is revealed because of the steric interaction of the bulky t-butyl ester groups.

The results of a recent study on the ion-pair basicities of lithium amides in THF²⁶ are fully in line with the above assumption of a relatively smaller R⁺ effect associated with the morpholine and *N*-methylpiperazine substituents. It was reported²⁶ that the pK_a of di-isopropylamine (34.4) is much larger than that of morpholine (28.8). A shift similar to that of the (**5**)-Li⇌(**6**)-Li equilibrium towards (**5**)-Li, presumably for the same reason, was observed for the RO, rather than R''N, derivatives of the corresponding methyl esters, when using phenyl ethers instead of the methyl ether.^{25a}

In summary, the results of the present study favour the conclusion that a *trans* β-NR''₂ group (with the exception of such secondary amino groups as the morpholinyl and *N*-methylpiperazinyl groups) decreases the configurational stability of a vinyl-lithium compound, and that this effect, for the reaction system studied, is by far the dominant factor affecting the k'_2/k'_{-2} ratio.

It seems that the observed effect of a *trans* electron-donating (by I⁺ or R⁺) β-substituent on the configurational stability of α-lithiated olefinic intermediates formed by the addition of lithium nucleophiles to activated acetylenes, or by deprotonation,^{21,25} is probably a general phenomenon. Thus, for example, the addition of RLi (R = Me, Bu) to PhC≡C(O)NMe₂,²⁷ HOCH₂C≡CPh,²⁸ and to PhC≡CPh²⁹ in aprotic solvents, resulted in relatively high yields of the (*E*)-isomers of the corresponding β-substituted olefins.

Experimental

All manipulations and reactions of the acetylenic compounds with the lithium amides were carried out under nitrogen and anhydrous conditions. The required amounts of THF and DEE were directly distilled into the reaction flask from a solution of sodium diphenylketyl in the corresponding ether; hexane was distilled twice over sodium. The lithium amides were prepared

by adding an equimolar amount of BuLi (dissolved in hexane) to a solution of a secondary amine in the apolar solvent.

Reaction of Secondary Lithium Amides with Alkyl Esters of Acetylenecarboxylic Acids.—A solution of BuLi in hexane was added to a cooled (−80 °C) solution of the secondary amine in the apolar solvent (40 ml). The reaction mixture was stirred for 20 min at −80 °C and a solution of the ester of the acetylenic acid in that solvent (10 ml) then added dropwise. The reaction mixture was further stirred for 60 min, and methanol (2 ml) then added. After 10–15 min, ether–water was added, and the mixture then extracted with ether. The composition and yield of product(s) was determined by g.c. of the residue recovered from the organic extract. The residue was then separated by column chromatography (eluant: light petroleum–ethyl acetate). Amounts of reactants, yields, and ¹H n.m.r. data of the products obtained are given in the Table.

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