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The Reaction of Dilithium Carboxylates with Acyclic α.β-Enones- a Continuous Transition from 1.2- to 1.4-Addition.

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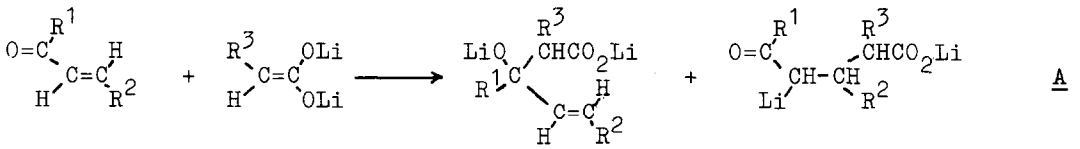
The addition of resonance stabilized organolithium derivatives to α.β-enones has been investigated intensively during the past few years[1]. From the experimental data which have thus been accumulated one may draw the following conclusions. a. Under kinetic control each one of the various types of organolithium compounds shows a characteristic preference for either 1.2- or 1.4-addition. Substituent effects can only modify but not totally change this intrinsic reactivity. b. Under thermodynamic control generally the 1.4-adduct is predominantly formed[2].

We studied the reaction of the α.β-unsaturated ketones 1 with the dilithium carboxylates 2[3] under kinetically controlled conditions (THF, -50°, 1 hr) (equation A) and found that by an appropriate choice of the substituents R^1, R^2 and R^3 the whole range from pure 3 to pure 4 may be covered (Table 1). To our knowledge 2 is the first organolithium species with which such a continuous transition from clean 1.2- to clean 1.4-addition can be accomplished under kinetic control.



1 2 3 4 A

The primary adducts 3 and 4 were hydrolyzed with 2N H_2SO_4 to give the 4.5-unsaturated 3-hydroxycarboxylic acids 5 and the 5-ketocarboxylic acids 6 respectively.

The irreversibility of reaction A was proved by converting 5f into 3f with 2 mole equivalents of lithium diisopropylamide in THF and heating the reaction mixture to 50° for 2 hrs. After hydrolytic workup 5f without any trace of 6f was isolated in quantitative yield. An analogous experiment was performed with pure 6f and again the starting material was recovered unchanged. These results are in a striking contrast to those obtained from 7 and 8 which despite their similarity to 2 react with enones irreversibly at -78°

and reversibly at room temperature[4].

$C_6H_5CH=C=NLi$ (7) $CH_3\overset{X}{C}H=\overset{OLi}{C}(OCH_3)$ (8) (X = OC_6H_5, OCH_3, SC_6H_5, SCH_3, CH_3)

The ratio of 3:4 in reaction A is determined by two factors: 1. the intrinsic preference of 2 for either 1.2- or 1.4-attack. 2. the steric and electronic effects exerted by R^1,R^2 and R^3. To get some insight into the first factor we performed A with a minimum number of substituents and reacted methyl vinyl ketone with dilithium acetate (run a, Table 1). From the fact that 3a was obtained exclusively we concluded that 2 has a natural favor for 1.2-addition. In order to see to what extent this intrinsic reactivity can be modified by substituent effects we kept R^2= C_6H_5 constant and varied only R^1 and R^3 (runs b-o). From Table 1 it can be realized that the tendency towards 1.2-addition is maintained as long as an alkyl group occupies the R^1-position and the steric repulsion between R^1 and R^3 which arises during the attack of 2 at the carbonyl carbon of 1 is only moderate. This is illustrated by runs b-e which furnish 3 as the sole product. If, however, R^1= $C(CH_3)_3$ (runs f-j), the attack at the carbonyl carbon is drastically retarded by the steric congestion between R^1 and R^3 and, consequently, 1.4-addition gains in importance. This trend is substantially enhanced by increasing the size of R^3; so the ratio of 3:4 switches from 69:31 for R^3= H (run f) to 0:100 for R^3= CH_3, C_2H_5, $CH(CH_3)_2$ and $C(CH_3)_3$ (runs g-j).

Turning to the systems with R^1= C_6H_5 we have to take into account that a phenyl group in this position influences the reactivity of 1 not only by a steric but also by a resonance effect which deactivates the carbonyl group towards nucleophilic attacks. This explains the decrease in the ratio of 3:4 which is observed on comparing runs d and k; in both cases the steric interactions for the 1.2-addition pathway are alike; however, k is influenced by the resonance effect of the R^1-phenyl group and d not. As a consequence of this it may be expected that a combinantion of this phenyl substituent with bulky R^3s should lead to a substantial preference for 1.4-addition. Indeed, the ratio of 3:4 goes down from 71:29 to 0:100 in the sequence k,l,m,n,o. Finally the influence of R^2 was examined (runs p,q,r). Again steric factors play a dominant role. 2-Thienyl (run p) and 2-furyl (run q) both have one ortho-H less than a phenyl group (run k); this reduces the steric repulsion for the attack at the β-carbon of 1, and, hence, the ratio of 3:4 changes from 71:29 (run k) to about 60:40 in runs p and q. On the other hand, the bulky 1-naphthyl group in run r blocks the β-position, and 3r is predominantly formed in this case.

In summary we may say that although reaction A has an intrinsic preference to proceed via 1.2-addition both steric and mesomeric effects of the substituents R^1,R^2 and R^3 may be efficiently combined to accomplish clean 1.4-ad-

Table 1. Ratios of 5:6 (= 3:4) and total yields of 5+6 resulting from reaction A.

Run	R^1	R^2	R^3	ratio of 5:6 (=3:4)[a]	mp[b] (°C)	yield %
a	CH_3	H	H	100:0	oil[c]	68
b	"	C_6H_5	H	100:0	"	72
c	C_2H_5	"	H	100:0	86-87	80
d	$CH(CH_3)_2$	"	H	100:0	125-126	73
e	C_2H_5	"	C_2H_5	100:0	80-85	85
f	$C(CH_3)_3$	"	H	69:31	106-118	45
g	"	"	CH_3	0:100	80-105	76
h	"	"	C_2H_5	0:100	104-124	83
i	"	"	$CH(CH_3)_2$	0:100	166-172	67
j	"	"	$C(CH_3)_3$	0:100	116-117	79
k	C_6H_5	"	H	71:29	137-138	67
l	"	"	CH_3	68:32	126-134	85
m	"	"	C_2H_5	62:38	135-136	65
n	"	"	$CH(CH_3)_2$	50:50	131-141	77
o	"	"	$C(CH_3)_3$	0:100	137-138	88
p	"	2-thienyl	H	65:35	104-108	73
q	"	2-furyl	H	60:40	122-126	57
r	"	1-naphthyl	H	85:15	175-176	85

a) This ratio was determined by means of the relative intensities of the ^{1}H-NMR-signals of the vinyl protons of 5 and of the protons at C-2,C-3 and C-4 of 6.

b) With the exception of c and d, which furnish pure 5c and 5d respectively, the melting points refer to the mixtures of isomers and diastereomers obtained from A without further purification.

c) bp. 135-140°C/0.001 torr.

dition as well.

5 and 6 are valuable synthetic intermediates. So in the following letter a new synthesis of substituted 1.3-butadienes making use of 5 will be described[5]. On the other hand, the preparative utility of 5-ketocarboxylic acids like 6 has been discussed extensively by STETTER who developed a method for preparing simply substituted compounds of this class in three steps starting from resorcine[6]. In case of bulky R^1- or R^3- groups reaction A represents a one-step alternative to STETTER's procedure. A has the additional advantage of making even complicated substitution patterns of 6 readily available (e.g. in runs g,h,i,j,o).

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