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CONJUGATE ADDITION OF ARYLACETONITRILES TO CINNAMIC ACID DERIVATIVES. A CASE OF HIGH DIASTEREOSELECTIVE ASYMMETRIC PROTONATION.

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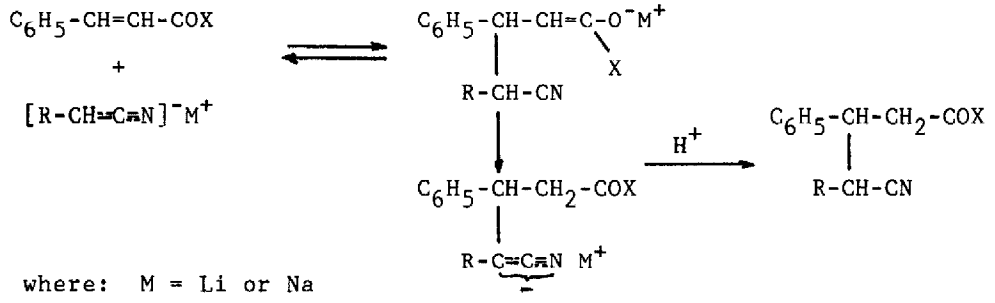
Abstract: A case of the formation of two vicinal asymmetric centers by the Michael addition is studied. The loss of chirality as a result of C_2-C_4 carbanion transformation is followed by asymmetric protonation of the prochiral C_4 centre and high diastereoselective formation of the erythro isomer.

The diastereoselective formation of a C-C bond is one of the most important problems in synthetic organic chemistry. Recently, we demonstrated a high threo preference (E/T=5/95) in the Michael addition of phenylacetic acid dialkyl amides to cinnamic acid derivatives under thermodynamic conditions [1]. The result was explained by a stabilizing chelation in the adduct [2] and a triple ion structure of the chelate was found [3].

The present work deals with the effect of the nitrile group in the donor (as a group with lower complexing ability [4]) on the stereochemical result of the reaction with methyl cinnamate and cinnamic acid dimethyl amide:



where: M = Li or Na

X =	OCH_3	OCH_3	$N(CH_3)_2$	$N(CH_3)_2$
R =	C_6H_5	α-$C_{10}H_7$	C_6H_5	α-$C_{10}H_7$
	1	2	3	4

Most of the reports on the Michael addition of benzyl cyanide are concerned with the regioselectivity of the reaction [5-8]. Stereochemical data have been reported in a few cases but their origin (kinetic or thermodynamic) remains unclear [9-11].

The reaction was carried out in THF at -78° or at ambient temperature. Satisfactory analytical and spectral data were obtained for all new compounds. The

relative configuration of erythro-1 and erythro-3 is assigned after hydrolysis producing erythro-2,3-diphenylglutaric acid [12]. The assignment of the configuration of 2 and 4 is based on the similarity of their ^1H NMR spectra with the spectra of 1 and 3. The differences in the chemical shifts of the C_4-H (cases 1-4) or $COOCH_3$ protons (cases 1 and 2) were used in the determination of the E/T ratios.

Heavy water hydrolysis followed by NMR analysis showed that in the case of the dimethyl amide of cinnamic acid, a C_4 carbanion is formed. This is in accordance with some data given in the literature [13,14]. More unexpected was however the case of methyl cinnamate, where the metal remains at C_2. For this reason these two cases will be considered separately.

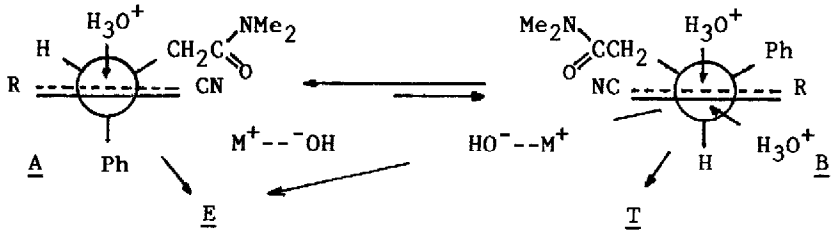
Methyl cinnamate. The stereochemistry of the reaction is represented in Table 1.

T a b l e 1

Addition to methyl cinnamate.

R		M	T°C	Time	Yield, %	E/T
C_6H_5	(1)	Li	-78	60 sec	69	46/54
			22	180 min	42	65/35
		Na	-78	60 sec	60	66/34
			22	60 min	45	63/37
α-$C_{10}H_7$	(2)	Na	-78	60 sec	61	72/28
			22	60 sec	72	77/23

The ratio 46/54 is kinetically controlled and can be explained by a cyclic transition state (see [1]) which still can be realized with Li as the counterion. When sodium is used, an open transition state is consistent with the observed erythro diastereoselectivity and its increase in the case of 2.



The coincidence of the stereochemistry under kinetic and thermodynamic conditions was proved by concurrent reactions. Such a coincidence is described in the literature [15] and explained by similar steric interactions in the transition state and the reaction adduct. The predominance of the erythro isomer under thermodynamic conditions in contrast to previous results [1] is, in our opinion, due to a change of the preferred chelated to non-chelated conformation indicated

by a low $J_{3,4}$-value (about 5 Hz against 12 Hz in previously studied cases).

Dimethyl amide of cinnamic acid. When the Li reagent of phenylacetonitrile is reacted at -78°, a secondary, kinetically controlled addition of the 1,4-adduct to the acceptor occurs. The resulting product has a threo configuration around the C_3-C_4 bond, which proves the reversibility of the conjugated addition at this low temperature. At 22° the side reaction becomes reversible and the equilibrium is shifted to the 1,4-reaction product with the metal at C_4. Hydrolysis of this product leads to the pure erythro isomer. When the Na reagent is used, no side product is obtained (see Table 2) and the formation of the C_4 carbanion is faster.

T a b l e 2

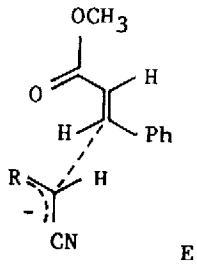
Addition to cinnamic acid dimethyl amide.

R		M	T°C	Time	Yield,% 1,4-	side prod.	E/T
C_6H_5	(3)	Li	-78	60 sec	14	20	75/25
				240 min	20	40	50/50*
			22	120 min	87	--	100/0
		Na	-78	60 sec	60	--	65/35
				60 min	90	--	100/0
α-$C_{10}H_7$	(4)	Na	22	120 min	87	--	100/0

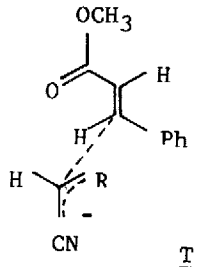
*/ The metal is 100% at C_4 in E and 60% in T.

There are reasons to assume that the C_2-C_4 carbanion transformation occurs intramolecularly in both diastereomeric adducts like the case described by **S.Berrada** and **P.Metzner** [16].

Two prochiral intermediate conformations are under consideration, in which intramolecular coordination of the metal is possible. The stereochemical course of protonation will depend on the environment of the C_4 centre. The molecular models show that **A** can be considered as more stable and its protonation seems to be allowed only from the side of the methine proton which will give diastereoselectively the erythro isomer. The C_4 centre of **B** is accessible from both sides and will deliver a mixture of isomers. Obviously this is the cause for the



E



T

result 50/50 obtained at low temperature. When the equilibrium is shifted to **A** the result of protonation is about 100% erythro isomer. The addition of 20% HMPT or 12-crown-4 to the reaction mixture, which leads to the ratio 27/83 is an evidence for participation of the metal in the stabilization of A.

The above study presents an interesting case of the formation of two vicinal asymmetric centers by means of the Michael addition. The loss of chirality as a result of intramolecular metal transfer is restored with complete erythro diastereoselectivity as a result of asymmetric protonation of the prochiral intermediate.

The results obtained contribute to the understanding of the factors governing the diastereoselective formation of C-C bonds.

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