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Michael Reaction. V. Stereochemistry of the $NaNH_2$ Catalyzed Two-Step Reaction Between Phenylacetic Acid Dialkyl Amides and Methyl Cinnamate or Cinnamic Acid Dialkyl Amides

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The reaction is investigated between sodium-metallated ($NaNH_2$) phenylacetic acid dialkyl amides and methyl cinnamate or cinnamic acid dialkyl amides. The thermodynamic equilibrium between the diastereomeric 2,3-diphenylglutaric acid amidoesters or diamides is 5/95 in favour of the *threo*-isomer. Under kinetic conditions the stereochemistry of the reaction depends on the nature of the donor and the solvent.

(Keywords: 2,3-Diphenylglutaric acid derivatives; Sodium amide catalyzed reaction; Stereochemistry; Thermodynamic and kinetic control over configuration)

Michael Reaktion. V. Stereochemie der durch $NaNH_2$ *katalysierten zweistufigen Reaktion zwischen Dialkylamiden der Phenylessigsäure und Methylestern oder Dialkylamiden der Zimtsäure*

Die Umsetzung zwischen der mit festem $NaNH_2$ gewonnenen Natriumderivaten der Dialkylamiden der Phenylessigsäure und Methylestern oder Dialkylamiden der Zimtsäure wurde untersucht. Das thermodynamische *E*/*T*-Verhältnis zwischen den gewonnenen diastereomeren Amidestern und Diamiden der 2,3-Diphenylglutarsäure beträgt in allen Fällen 5/95. Das stereochemische Ergebnis unter kinetischen Bedingungen hängt von der Natur des Donators und von den Lösungsmitteln ab.

In the previous paper of this series[1] it was found that the stereochemistry of the one-flask reaction between phenylacetic acid dialkyl amides and methyl cinnamate or cinnamic acid dialkyl amides catalyzed by sodium amide depends on the reaction conditions and, in the general case, is probably determined by the formation of neutral reaction products because of the participation of only a catalytic amount of the solid sodium amide used.

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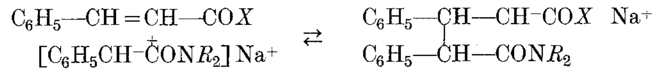
In order to obtain a better understanding of the stereochemistry under definite kinetic and thermodynamic conditions and to eliminate the formation of neutral reaction products we studied the same reaction in two steps: metallation of the starting CH-acid and addition of the corresponding acceptor.

$$C_6H_5CH_2CONR_2 + NaNH_2 \rightarrow [C_6H_5CH^{-}CONR_2]\,Na^+ + NH_3$$



$$\begin{array}{l} C_6H_5-CH=CH-COX \\ [C_6H_5CH^{-}\overset{+}{C}ONR_2]\,Na^+ \end{array} \rightleftarrows \begin{array}{l} C_6H_5-CH-CH^{-}COX\ \ Na^+ \\ C_6H_5-CH-CONR_2 \end{array}$$

I II

	$X =$	$NR_2 =$		$X =$	$NR_2 =$
1	OCH_3	$N(CH_3)_2$	**5**	$N(C_2H_5)_2$	$N(CH_2CH_2)_2O$
2	OCH_3	$N(i\text{-}C_3H_7)_2$	**6**	$N(CH_2CH_2)_2O$	$N(CH_3)_2$
3	OCH_3	$N(C_6H_{11})_2$	**7**	$N(CH_2CH_2)_2O$	$N(C_2H_5)_2$
4	$N(CH_3)_2$	$N(C_6H_{11})_2$	**8**	$N(CH_2CH_2)_2O$	$N(CH_2CH_2)_2O$

For greater convenience in the discussion only the results from the synthesis of **1** and **4** are given in Table 1.

Table 1. *Two-step formation of* **1** *and* **4**

Solvent	Temp. (°C)	React. time	**1** %	**1** E/T	**4** %	**4** E/T
THF	64	5 s[a]	87	5/95	61	4/96
	22	15 s	93	6/94	53	5/95
	0	15 s	75	31/69	—	—
		60 s	78	9/91	—	—
	—40	60 s	73	38/62	58	6/94
		30 min	76	34/66	56	5/95
	—80	60 s	55	40/60	—	—
Ether	22	15 s	88	7/93	63	6/94
	0	15 s	92	60/40	—	—
		5 min	87	8/92	—	—
	—40	30 min	67	60/40	—	—
Benzene	22	15 s	87	9/91	43	5/95
HMPT	22	15 s	52	69/31	35	48/52
		5 min	38	70/30	55	68/32
	0	15 s	66	22/78	—	—
		15 min	62	67/33	—	—

[a] The prolongation of the reaction time decreases the yield and the E/T ratio becomes 60/40.

Additional experimental data and more extended Tables can be provided on request from the authors.

The metallation is slow. Its completness was controled by methylation with *Me*I or by shifting of the diakyl amide absorbtion band in the IR-spectrum.

In all cases studied the "aldol" stage is very fast. The degree of conversion i.e. the yield of reaction products reflects the general conception for the relative stability of the carbanions I and II, developed by *Ingold*[2] and depends also on the solvent.

The reaction is reversible within a wide range of temperatures. It was proved by concurrent reactions. The *E*/*T* equilibrium ratio is in all cases about 5/95.

Conditions for kinetic control over the configuration of the diamides **4-8** could not be found. The reaction is reversible even at —80° (*THF*). The decrease of the temperature makes the formation of the amidoesters **1-3** irreversible. The conditions for that as well as the observed *E*/*T* ratios are presented in Table 2.

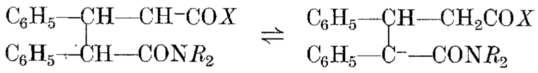
Table 2. *Conditions for kinetic control over the configuration of* **1**, **2** *and* **3**

Solvent	**1**		**2** and **3**	
	Temp. (°C)	*E*/*T*	Temp. (°C)	*E*/*T*
THF	—40	40/60	0	50/50
Ether	—40	60/40	22	65/35
Benzene[a]	—		22	67/33

[a] The reaction was studied only at 22°.

These results seem to be in agreement with the assumption developed in Ref.[3] according to which a transition state with product-like steric interactions corresponds to a more stabilized nucleophile (less reactive organometallic reagent).

The ratios 60/40 in boiling *THF* and 70/30 in *HMPT* are the same as observed in the one-flask reaction. This is probably due to the following isomerization as postulated in the previous work.



$$\begin{array}{l} \mathrm{C_6H_5{-}CH{-}CH\text{-}CO}X \\ \mathrm{C_6H_5{-}CH{-}CON}R_2 \end{array} \rightleftharpoons \begin{array}{l} \mathrm{C_6H_5{-}CH{-}CH_2CO}X \\ \mathrm{C_6H_5{-}C^{-}{-}CON}R_2 \end{array}$$

More detailed investigations on the origin of the different equilibrium *E*/*T* ratios observed during the reaction performed under the two procedures are in progress.

Experimental

Metallation of Phenylacetic Acid Dialkyl Amides

Two equivalents of freshly ground $NaNH_2$ were added to the solution of the starting dialkyl amide (1.25 mmol) in the corresponding dry solvent (2 ml *THF*, ether and benzene or 1.5 ml *HMPT*) under dry nitrogen (traces of oxygen lead to formation of 1,2-diphenylsuccinic acid dialkyl amides). The optimal conditions for complete metallation were 120 min at 80° in benzene, 180 min at 34° in ether, 45 min at 64° in *THF* and 15 min at 22° in *HMPT*.

Synthesis of the Amidoesters (**1**-**3**) *and Diamides* (**4**-**8**) *of 2,3-Diphenylglutaric Acid*

To the appropriately cooled solution of the metallated donor the solution of an equimolar amount of the acceptor in the same solvent was added. The reaction was stopped by adding water and the mixture worked up as described in[1]. The diastereomeric ratios were determined as in the previous cases[1,4] on the basis of the C_6H_6—, —$COOCH_3$ and —$CON(CH_3)_2$ chemical shifts differences in the PMR-spectra.

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