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Stereochemical Differences in the Michael Addition of Phenylacetic Acid Esters and Dialkyl Amides to Methyl Cinnamate or Methyl Crotonate

T. S. Gospodova and **Y. N. Stefanovsky***

Institute of Organic Chemistry with Center of Phytochemistry, Bulgarian Academy of Sciences, Sofia 1113, Bulgaria

Summary. The stereochemistry of the conjugate addition of phenylacetic acid esters and dialkylamides to methyl crotonate is studied. The stereochemical results are compared with these previously obtained for the addition to methyl cinnamate. The differences observed are explained in terms of cyclic transition states with decreasing of the sterical interactions as a result of replacement of a phenyl group by methyl in position 2 of the 1,2-diphenylpropanic skeleton.

Keywords. Cyclic transition state; Mechanism; Michael reaction; Stereochemistry.

Stereochemische Unterschiede bei der Michael Addition von Phenylessig-Estern und -Dialkylamiden an Methylcinnamat oder Methylcrotonat

Zusammenfassung. Es wird die Stereochemie der Addition von Phenylessig-ester und der-dialkylamide an Methylcrotonat untersucht. Die stereochemischen Ergebnisse werden mit den früher publizierten für die Addition an Methylcinnamat verglichen. Die beobachteten Unterschiede werden mit der abnehmenden sterischen Wechselwirkung beim Austausch von Phenyl gegen Methyl am C-2 des 1,2-Diphenylpropan-Skeletts unter der Voraussetzung eines cyclischen Übergangszustandes erklärt.

Introduction

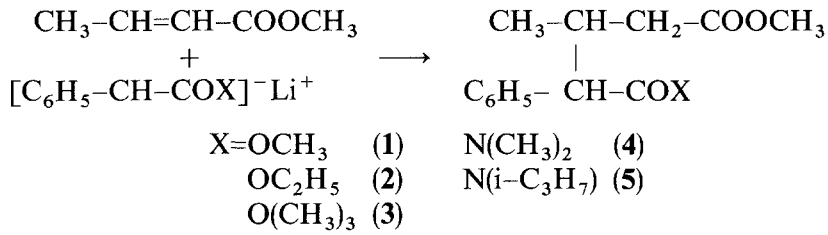
Recently we found that the stereochemistry of the Michael reaction leading to diastereoisomeric 1,3-bifunctionalized-1,2-diphenyl-propanes strongly depends on the functional groups in 1,3-position under kinetic and thermodynamic conditions [1–4].

$$\begin{array}{ll} C_6H_5\text{–}CH\text{–}CH_2\text{–}X & X = CHO, COR, COOR, CONR_2 \\ \quad\quad\quad | & \\ C_6H_5\text{–}CH\text{–}Y & Y = COOR, CONR_2, CN \end{array}$$

Thus, in the case of amide donors definite influence of the bulk of the dialkylamino group on the kinetic selectivity was observed [1]. No electronic, but significant steric *o*-effects of the substitutents in the 1-positioned Ph group was found [5]. The replacement of the dialkylamino with an ester group in the donor used, strongly

increased the kinetic *threo*-preference [3]. Influence of the medium polarity and complexation ability of the metal counterion was registrated as well [2]. When arylacetonitriles were used, the addition to cinnamic dialkylamides occurred with the transition of the metal from 3 to 1 position, formation of a prochiral center at this atom and consequently highly *erythro*-diastereoselective asymmetric protonation at the end of the reaction [4]. The stereochemical data were explained either by cyclic [1, 2] or open [3] transition state hypotheses.

The present work deals with the stereochemistry of the Michael reaction between phenylacetic esters and dialkylamides and methyl crotonate with the aim to check how the change of sterical interactions in the propanic skeleton, e.g. replacement of the 2-positioned Ph with a CH_3 group, will influence the stereochemical course.



Results and Discussion

Configurational Assignment

The relative configuration of the isomeric **1** was determined by the reduction of the isolated product by preparative TLC fractions (five-fold eluation by ether/petroleum ether 1:4 on Kiselgel 60 F_{254}, Merck and a second preparative separation) and study of the intramolecular hydrogen bonding in the isomeric 1,5-diols by IR spectroscopy (Table 1).

According to the regularities found for 1,3-, 1,4- and 1,5-aminoalcohols and diols [6, 7] we assigned *threo*-configuration to the isomer with stronger hydrogen bonding. This correlation allows a conclusion to be made about the configuration of the isomeric **1** (the *LAH* reduction occurs with retention of the configuration).

The ^{1}H NMR spectrum of *threo*-**1** shows a doublet for CH_3 protons located at stronger field than that of the *erythro*-form. We used this observation for the configurational assignment of the other diastereoisomeric pairs.

The experimental data are given in Tables 2 and 3 together with the data for the corresponding diphenylated compounds.

From the data given the conclusion can be drawn that the high thermodynamic *threo*-diastereoselectivity is determined by the stabilizing chelation in the reaction adduct as observed before [1]. This is supported by the fact that in the presence of *HMPT* the diastereoselectivity decreases. In contrast to the diphenyl analogs chelation is also observed in the case of diesters. Probably the replacement of the

Table 1. IR data for hydrogen bonding in the isomeric 3-methyl-2-phenyl-1,5-pentandiols (CCl_4, 3×10^{-3} mol/l)

TLC-fraction	$\nu_{OH\ free}$	$\nu_{OH\ assoc.}$	ν_{OH-Ph}	$\Delta\nu\ cm^{-1}$
a (higher R_f)	3637	3528	3600	109
b (lower R_f)	3637	3494	3600	143

Table 2. Addition of alkyl phenylacetate enolates to methyl crotonate

R	T °C	Time	Me/Ph			Ph/Ph* [3]		
			E/T (*THF*)	Yield %	*E/T* (*HMPT*)[a]	Yield %	*E/T* (*THF*)	*E/T* (*HMPT*)[a]
CH_3	−78	60 s	20/80	32	20/80	38	6/94	
		60 m	20/80	40	20/80	60	5/95	40/60
	22	60 s	44/56	31			6/94	
		60 m	54/46	54			45/55	
C_2H_5	−78	60 s	24/76	37			7/93	40/60
		60 m	20/80	42	20/80	64		
	22	60 s	16/84	29			6/94	
		60 m	0/100	42			40/60	
t-C_4H_9	−78	60 s	10/90	53	23/77	48	7/93	30/70
		60 m	5/95	66	26/74	61		
	22	60 s	12/88	47			8/92	
		60 m	2/98	67	42/58	38	63/37	
	64	5 m	20/80	44				

[a] *THF* + 23% *HMPT*

Table 3. Addition of N,N-dialkylphenylacetamide enolates to methyl crotonate

R	T °C	Time	Me/Ph			Ph/Ph*[1]		
			E/T (*THF*)	Yield %	*E/T* (*HMPT*)[a]	Yield %	*E/T* (*THF*)	*E/T* (*HMPT*)
CH_3	−78	60 s	22/78	32	15/85	38	47/53	
		60 m	17/83	38	15/85	60		
	22	60 s	32/68	60	29/71	65		70/30
		60 m	2/98	67	45/55	69		
i-C_3H_7	−78	60 s	44/56	42	0/100	24		
		60 m	44/56	43	0/100	40		
	22	60 s	46/54	57	48/52	11	65/35	
		60 m	41/59	61	33/67	49		
		18 h	0/100	60				

[a] *THF* + 23% *HMPT*

phenyl group with methyl increases the ionic character of the O–Li bond. Another possible explanation is the general decrease of the steric interactions due to the skeleton transformation.

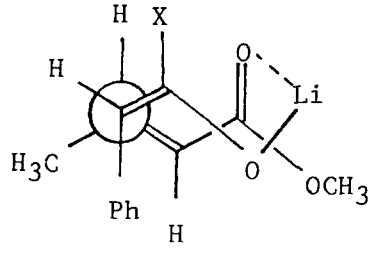
Threo-diastereoselectivity under thermodynamic conditions is also observed in the case of amidoesters. The reaction with dimethyl amide is better reversible (the ratio $E/T = 2/98$ is reached for 60 minutes at 22 °C).

It is worth noting that going from methyl to *tert*-butyl ester (Table 2) the equilibrium *E*/*T* ratio changes from 1:1 to 2/98. This fact is difficult to explain.

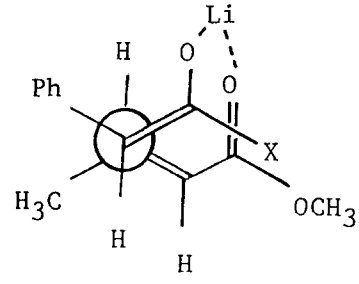
The kinetically controlled stereochemistry differs from the case of diphenyl analogs studied before in the decreasing *threo*-diastereoselectivity (from *E*/*T*= 5/95 to 20/80) when diesters were synthesized. Addition of *HMPT* does not change the stereochemistry.

In the case of amidoesters the same stereochemical result is observed. In comparison to the diphenyl analog the *threo*-diastereoselectivity increases when dimethyl amide was used whereas the *E*/*T* ratio for diisopropyl amide is 44/56. The addition of *HMPT* does not change the stereochemistry of the addition of diethyl amide while diisopropyl amide leads to practically pure *threo*-isomer.

To explain the observed stereochemical results we assume cyclic transition states E-1/T-1.



E-1

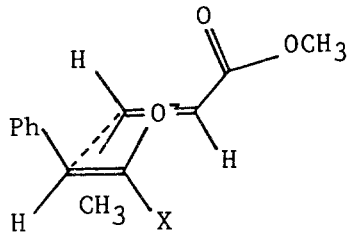


T-1

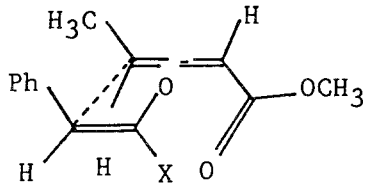
One can make the conclusion that the replacement of one of the phenyl groups with methyl leads to a decrease of the general sterical interactions. The same stereochemistry could be a result of an increased electrophility of the acceptor leading to an earlier transition state. This general diminishing of the interactions explains the relative decreasing of the amount of the *threo* isomer in the case of diesters (E-1 is favoured). In the more hindered amidoesters where in the diphenyl compounds the *E*/*T* ratio is about 1:1 because of the significant NR_2/OCH_3 interaction in T-1, the diminishing of the skeleton interactions will favor T-1 (increasing of the *threo*-isomer is really observed). In the same transition state, going from dimethyl to diisopropyl amide a decrease of the *threo*-diastereoselectivity is observed.

Addition of 23% *HMPT* does not change the stereochemistry of the reaction of ester enolates and of N,N-dimethylphenylacetamide enolate. In the case of the bulkier diisopropylamide the reaction leads to pure *threo*-isomer. Such a high *threo* selectivity has been observed by us before [8], but only when the reaction was carried out in *HMPT*. This selectivity was explained by the necessity of correspondence between the polarity of the medium and the polarity of the transition state; postulate of Heublein [9]. According to this the transition states T-2/E-2 are possible. One can see that in such a synclinal position of the functional groups an increase of the bulk of the amido group will favour the transition state T-2. It is not clear, however, why only addition of *HMPT* makes the polarity of the medium high enough (for the Ph/Ph analog under these conditions the *E*/*T* ratio is 40/60).

The data given in this paper show that the stereochemistry of the obtained diesters and amidoesters with substituted propane skeleton strongly depends on the



T-2



E-2

skeleton interactions, on the bulk of the functional groups, and the polarity of the medium. This allows a control of the stereochemical results for such a type of reaction.

Experimental

M.p.s. were taken on a Kofler apparatus and are uncorrected. ^{1}H-NMR spectra were measured on Tesla BS 487C and Brucker WM 250 spectrometers in $CDCl_3$ with Me_4Si as an internal standard. *THF* was dried and freshly distilled over *LAH*. Syntheses were carried out under argon atmosphere. TLC was performed on Kieselgel Merck 60 PF_{254}.

Enolization

The Li enolates of the esters were prepared according to [3]. The Li enolates of the dialkyl amides were obtained using *LDA* for N,N-dimethylphenylacetamide at 0 °C and for N,N-diisopropyl-phenylacetamide at 22 °C. In both cases enolization occurs practically in 5 min.

Synthesis and General Procedure

To a solution of 1 mmol Li enolate in 1 ml *THF* was added 1 mmol of the electrophile dissolved in 1 ml of *THF* at the corresponding temperature. At the end of the reaction time the process was stopped by addition of a few drops of dilute hydrochloric acid. After extraction with $CHCl_3$, drying the solution over sodium sulphate, and evaporation of the solvent the yields were determined by preparative TLC. The experiments in the presence of *HMPT* were carried out by adding *HMPT* (0.9 ml; 23 vol%) to the enolate reaction mixture.

For the analysis of the mixtures of the isomeric **1–5** the differences in the location of the CH_3, $COOCH_3$ and CH_2(**5**) protons were used.

The m.p.s. of the pure compounds, the solvents used for the recrystallization, the liquid phases for TLC and ^{1}H-NMR data are given in Table 4.

Table 4. Physical constants and ^{1}H-NMR data of the diastereoisomeric **1–5**

Compound and configuration	M.p.°C (solvent)	R_f (Et_2O:LP ratio)[b]	δ
erythro-**1**	oil	0.3 (1:4)	1.07 (d, 3H, CH_3), 1.90 (dd, 1H, H-4), 2.17 (dd, 1H, H-4), 2.71 (m, 1H, H-3), 3.38 (d, 1H, $J_{2,3} = 10.78$ Hz, H-2), 3.58 (s, 3H, $COOCH_3$), 3.66 (s, 3H, $COOCH_3$), 7.26–7.34 (m, 5H, C_6H_5)

Table 4. (Continued)

Compound and configuration	M.p.°C (solvent)	R_f (Et_2O:LP ratio)[b]	δ
threo-**1**	oil	0.3 (1:4)	0.77 (d, 3H, CH_3), 2.25 (dd, 1H, H-4), 2.49 (dd, 1H, H-4), 2.71 (m, 1H, H-3), 3.41 (d, 1H, $J_{2,3} = 10.14$ Hz, H-2) 3.65 (s, 3H, $COOCH_3$), 3.68 (s, 3H, $COOCH_3$), 7.26–7.32 (m, 5H, C_6H_5)
erythro-**2**[a]	oil	0.28 (1:4)	1.08 (d, 3H, CH_3), 1.23 (m, 3H, $COOCH_2CH_3$), 1.91 (dd, 1H, H-4), 2.16 (dd, 1H, H-4), 2.62 (m, 1H, H-3), 3.36 (d, 1H, $J_{2,3} = 10.76$ Hz, H-2), 3.57 (s, 3H, $COOCH_3$), 4.12 (m, 2H, $COOCH_2CH_3$), 7.22–7.40 (m, 5H, C_6H_5)
threo-**2**[a]	oil	0.28 (1:4)	0.77 (d, 3H, CH_3), 1.23 (m, 3H, $COOCH_2CH_3$), 2.25 (dd, 1H, H-4), 2.50 (dd, 1H, H-4), 2.62 (m, 1H, H-3), 3.38 (d, 1H, $J_{2,3} = 10$ Hz, H-2), 3.68 (s, 3H, $COOCH_3$), 4.12 (m, 2H, $COOCH_2CH_3$), 7.22–7.40 (m, 5H, C_6H_5)
erythro-**3**[a]	oil	0.36 (1:4)	1.10 (d, 3H, CH_3), 1.32 (s, 9H, $COOBu^t$), 1.89 (dd, 1H, H-4). 2.15 (dd, 1H, H-4), 2.63 (m, 1H, H-3), 3.24 (d, 1H, $J_{2,3} = 10.14$ Hz, H-2), 7.20–7.35 (m, 5H, C_6H_5)
threo-**3**[a]	oil	0.36 (1:4)	0.77 (d, 3H, CH_3), 1.38 (s, 9H, $COOBu^t$), 2.23 (dd, 1H, H-4), 2.53 (dd, 1H, H-4), 2.63 (m, 1H, H-3), 3.26 (d, 1H, $J_{2,3} = 10.79$ Hz, H-2), 3.67 (s, 3H, $COOCH_3$), 7.20–7.35 (m, 5H, C_6H_5)
erythro-**4**[a]	oil	0.15 (3:2)	1.06 (d, 3H, CH_3), 1.89 (dd, 1H, H-4), 2.17 (dd, 1H, H-4), 2.77 (m, 1H, H-3), 2.92 (d, 6H, $CON(CH_3)_2$), 3.57 (s, 3H, $COOCH_3$), 3.68 (d, 1H, $J_{2,3} = 12$, 2Hz, H-2), 7.22–7.40 (m, 5H, C_6H_5)
threo-**4**	79–81 benzene/hexan	0.15 (3:2)	0.73 (d, 3H, CH_3), 2.32 (dd, 1H, H-4), 2.54 (dd, 1H, H-4), 2.74 (m, 1H, H-3), 2.94 (d, 6H, $CON(CH_3)_2$), 7.20–7.42 (m, 5H, C_6H_5)
erythro-**5**	68–71 benzene/hexan	0.43 (3:2)	0.7 (d, 3H, $CH(CH_3)_2$), 1.07 (d, 3H, CH_3), 1.17 (d, 3H, $CH(CH_3)_2$), 1.30 (d, 3H, $CH(CH_3)_2$), 1.43 (d, 3H, $CH(CH_3)_2$), 1.88 (dd, 1H, H-4), 2.19 (dd, 1H, H-4), 2.80 (m, 1H, H-3), 3.29 (m, 1H, $CH(CH_3)_2$), 3.56 (s, 3H, $COOCH_3$), 3.59 (d, 1H, $J_{2,3} = 18.4$ Hz, H-2), 4.16 (m, 1H, $CH(CH_3)_2$), 7.19–7.30 (m, 5H, C_6H_5)
threo-**5**	40–43 benzene/hexan	0.43 (3:2)	0.63 (d, 3H, $CH(CH_3)_2$), 0.74 (d, 3H, CH_3), 1.16 (d, 3H, $CH(CH_3)_2$) 1.30 (d, 3H, $CH(CH_3)_2$), 1.42 (d, 3H, $CH(CH_3)_2$), 2.32 (dd, 1H, H-4), 2.60 (dd, 1H, H-4), 2.73 (m, 1H, H-3), 3.25 (m, 1H, $CH(CH_3)_2$), 3.57 (d, 1H, $J_{2,3} =$ 9.5 Hz, H-2), 3.66 (s, 3H, $COOCH_3$), 4.14 (m, 1H, $CH(CH_3)_2$), 7.19–7.38 (m, 5H, C_6H_5)

[a] In these cases the chemical shifts are taken from mixtures of diastereoisomeric products

[b] LP = light petroleum (b.p. 40–70 °C)

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