Kinetic Asymmetric Protonation as a Stereochemistry Determining Step in the Michael Addition of Acetic Acid Derivatives to $\alpha$-Substituted Cinnamic Acid Derivatives

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Summary. The reaction between acetic acid derivatives and $\alpha$-substituted cinnamic acid derivatives has been studied in THF and THF:HMPT (80:20) as an alternative pathway of the Michael addition of phenylacetic and cinnamic acid derivatives. The regioselectivity observed is found to depend on the acceptor functional group and its geometry but not on the solvent used. The diastereoselectivity of the conjugate addition results from kinetic protonation of diastereotopic enolates (1,2-asymmetric induction). It varies from low in the presence of HMPT to considerable or even high in pure THF. The favoured anti or syn configuration in THF depends on the nature of the enolate. The results obtained are rationalized in terms of protonation via transition structures different in type (open vs. chelated) and geometry.

Keywords. Asymmetric induction; Diastereoselective protonation; Michael addition; Regioselectivity.

Introduction

In the course of our investigation of the diastereoselectivity of the Michael reaction in a model system including cinnamic (1) and phenylacetic acid (2) derivatives [1–8]
(Scheme 1, pathway 1), carbanion transformation (3→7) was observed in the particular case of 4c (R² = CN, R³ = N(CH₃)₂), followed by remarkably high diastereoselective protonation of the prochiral intermediate 7. The result was considered to be due to a chelate enforced intramolecular chirality transfer [5, 9].

\[
\begin{align*}
\text{Ph} & \rightarrow \text{CH} = \text{CH} \rightarrow \text{COR}^3 \\
\text{[R}^1\text{CH} - \text{R}^2\text{]} \text{Li}^+ & \quad \xrightarrow{\text{pathway 1}} \quad \text{[Ph} \rightarrow \text{CH} \rightarrow \text{CH} \rightarrow \text{COR}^3 \text{]} \text{Li}^+ \\
\text{Ph} & \rightarrow \text{C(R}^1\text{)} \rightarrow \text{R}^2 \\
\text{[CH}_2\text{COR}^3 \text{]} \text{Li}^+ & \quad \xrightarrow{\text{pathway 2}} \quad \text{[Ph} \rightarrow \text{CH} \rightarrow \text{CH}_2 \rightarrow \text{COR}^3 \text{]} \text{Li}^+
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \rightarrow \text{CH} = \text{CH} \rightarrow \text{COR}^3 \\
\text{[R}^1\text{CH} - \text{R}^2\text{]} & \quad \xrightarrow{\text{pathway 1}} \quad \text{Ph} \rightarrow \text{CH} = \text{C(R}^1\text{)} \rightarrow \text{R}^2 \\
\text{[CH}_2\text{COR}^3 \text{]} & \quad \xrightarrow{\text{pathway 2}} \quad \text{Ph} \rightarrow \text{CH} = \text{C(R}^1\text{)} \rightarrow \text{R}^2 \\
\text{H}_2\text{O}^+ & \quad +
\end{align*}
\]

<table>
<thead>
<tr>
<th>4</th>
<th>R¹</th>
<th>R²</th>
<th>COR³</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Ph</td>
<td>CN</td>
<td>COOCH₃</td>
</tr>
<tr>
<td>4b</td>
<td>Ph</td>
<td>CN</td>
<td>COO'Bu</td>
</tr>
<tr>
<td>4c</td>
<td>Ph</td>
<td>CN</td>
<td>CON(CH₃)₂</td>
</tr>
<tr>
<td>4d</td>
<td>Ph</td>
<td>COOCH₃</td>
<td>COOCH₃</td>
</tr>
<tr>
<td>4e</td>
<td>Ph</td>
<td>COOCH₃</td>
<td>CON(CH₃)₂</td>
</tr>
<tr>
<td>4f</td>
<td>Ph</td>
<td>CON(CH₃)₂</td>
<td>CON(CH₃)₂</td>
</tr>
<tr>
<td>4g</td>
<td>CH₃</td>
<td>CON(CH₃)₂</td>
<td>CON(CH₃)₂</td>
</tr>
</tbody>
</table>

*Adducts available by pathway 2

Scheme 1

The observation above prompted us to study an alternative pathway of obtaining compounds 4 in the course of which the intermediate 7 can be directly formed by conjugate addition of α-substituted cinnamic (5) and acetic acid (6) derivatives (Scheme 1, pathway 2); hence, the diastereoselectivity would be determined not in the C–C bond formation but in the protonation reaction step.

This alternative is worth being investigated for two reasons: it provides a new synthetic and stereochemical approach to compounds 4 and allows an investigation of the factors governing the stereoselectivity in the protonation of diastereotopic enolates bearing an adjacent stereogenic centre which is a topic of considerable interest [10–19]. The presence of a second γ-positioned to the carbanionic centre and capable of coordination carbonyl substituent is expected to promote the process of 1,2-asymmetric induction significantly.
Results and Discussion

The reaction was carried out for 60 min at $-78 \, ^\circ C$ in THF (method A) and in a THF:HMPT mixture (80:20 v/v) (method B). The results obtained are listed in Table 1. The data in parentheses concern kinetically controlled ratios obtained by pathway 1 and are given for comparison.

In some of the cases studied, a concurrent 1,2-addition occurs. The attack of the carbonyl group is not of synthetic importance since the initially formed unstable intermediates $\text{Ph-CH=C(R^1)-C(OLi)(R^2)-CH}_2\text{COR}^3$ (8) undergo a second aldol addition to compounds $\text{Ph-CH=C(R^1)-C(OH)-(CH}_2\text{COR}^3)_2$ (10) after elimination to compounds $\text{Ph-CH=C(R^1)-CO-CH}_2\text{COR}^3$ (9). In fact, the products assigned as 1,2-adducts are mixtures of 9 and 10 in different proportions.

The regioselectivity exhibited by the acetic acid esters and amide enolates [20, 21] depends significantly on the functional group in the electrophile and its geometry. The interaction with the available cis-$\chi$-phenylcinnaminitrile ($R^2 = \text{CN}$, entries 1–7) affords the 1,4-adduct, most probably under frontier orbital control [22, 23]. In the case of cis- and trans-$\chi$-phenylmethylcinnamates ($R^2 = \text{COOCH}_3$, entries 8–12), attack of both the carbonyl carbon and the C=C double bond occurs.

<table>
<thead>
<tr>
<th>$R^1$</th>
<th>$R^2$</th>
<th>COOR$^3a$</th>
<th>Method and total yield (%)</th>
<th>$1,2/1,4$ (%)</th>
<th>Comp 4 (1.4)</th>
<th>anti/syn (1/4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>CN</td>
<td>COOCH$_3$</td>
<td>A 35$^b$ 0/100 4a</td>
<td>87/13 (46/54)$^e$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>CN</td>
<td>COOCH$_3$</td>
<td>B 40 0/100 4a</td>
<td>60/40 –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>CN</td>
<td>COO'Bu</td>
<td>A 85 0/100 4b</td>
<td>86/14 –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>CN</td>
<td>COO'Bu</td>
<td>B 56 0/100 4b</td>
<td>62/38 –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>CN</td>
<td>CON(CH$_3$)$_2$</td>
<td>A 80 0/100 4c</td>
<td>65/35 –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>CN</td>
<td>CON(CH$_3$)$_2$</td>
<td>A$^d$ 90 0/100 4c</td>
<td>95/5 (95/5)$^e$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>CN</td>
<td>CON(CH$_3$)$_2$</td>
<td>B 65 0/100 4c</td>
<td>62/38 –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>COOCH$_3$</td>
<td>COOCH$_3$</td>
<td>A 52 76/24 4d</td>
<td>22/78 (5/95)$^e$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>COOCH$_3$</td>
<td>COOCH$_3$</td>
<td>A$^f$ 41 40/60 4e</td>
<td>25/75 –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>COOCH$_3$</td>
<td>CON(CH$_3$)$_2$</td>
<td>A 85 40/60 4e</td>
<td>24/76 –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>COOCH$_3$</td>
<td>CON(CH$_3$)$_2$</td>
<td>B 63 38/62 4e</td>
<td>38/62 –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>COOCH$_3$</td>
<td>CON(CH$_3$)$_2$</td>
<td>A$^f$ 58 0/100 4e</td>
<td>23/77 –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_3$</td>
<td>COOCH$_3$</td>
<td>COOCH$_3$</td>
<td>A 44 100/0 –</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_3$</td>
<td>COOCH$_3$</td>
<td>CON(CH$_3$)$_2$</td>
<td>A 63 100/0 –</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>CON(CH$_3$)$_2$</td>
<td>CON(CH$_3$)$_2$</td>
<td>A, B does not react</td>
<td>(38/62)$^g$</td>
<td></td>
<td></td>
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<tr>
<td>Ph</td>
<td>CON(CH$_3$)$_2$</td>
<td>CON(CH$_3$)$_2$</td>
<td>A 86 0/100 4f</td>
<td>41/59 (5/95)$^g$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>CON(CH$_3$)$_2$</td>
<td>CON(CH$_3$)$_2$</td>
<td>B 68 0/100 4f</td>
<td>40/60 –</td>
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<td></td>
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<tr>
<td>CH$_3$</td>
<td>CON(CH$_3$)$_2$</td>
<td>CON(CH$_3$)$_2$</td>
<td>A, B does not react</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_3$</td>
<td>CON(CH$_3$)$_2$</td>
<td>CON(CH$_3$)$_2$</td>
<td>A$^d$ 78 0/100 4g</td>
<td>25/75 –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_3$</td>
<td>CON(CH$_3$)$_2$</td>
<td>CON(CH$_3$)$_2$</td>
<td>B$^d$ 22 0/100 4g</td>
<td>45/55 –</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a cis-configured acceptor, unless otherwise stated; $^{b}$ at $-40 \, ^\circ C$ the yield increases to 84%; $^c$ Ref. [5]; $^d$ reaction is carried out at 22 $^\circ C$; entries 19 and 20: at low temperature, synthesis does not proceed; $^e$ Ref [6]; $^f$ trans-configured acceptor, $^g$ Ref. [2]
the conjugate addition being favoured with the trans-acceptor (compare entries 8 and 9; 11 and 12) because of the steric hindrance of the carbonyl group. The change of the α-substituent from Ph to CH₃ (entries 13 and 14) results in a 1,2-regioselective attack for both steric and electronic reasons.

The 1,4-regiocontrol observed with dimethylamide of cis-configurated α-phenyl- and α-methylcinnamic acids (R² = CON(CH₃)₂, entries 15–20) is in agreement with the general tendency of decrease of 1,2-attack with decreasing electrophility of the carbonyl carbon atom.

In contrast to our expectations [24, 25], the use of HMPT as an additive does not enhance the double bond attack, but causes significant reduction of the total yield as well as complications in the work-up of the reaction mixture.

The fact that no reaction proceeds in the case of entries 15 and 18 where a conjugate addition is expected could be explained by the large stability difference between the donor and the conjugate adduct anions acting as a thermodynamic barrier [26]. This could be overcome by using a proper combination of reagents. Thus, the compound which corresponds to entry 15 is obtained by pathway 1, whereas 4e is accessible in both good yield and diastereoselectivity only by the alternative variant 2.

The diastereoselectivity of the protonation is of kinetic origin since it is not affected by the reaction time or the quenching temperature (control experiments) as well as on the proton source (aqueous NH₄Cl vs. CF₃CO₂H). The only exceptions (see entries 5 and 6) will be discussed later. Intramolecular proton transfer as a stereocontrolling step [27] was excluded by D₂O quenching experiments which demonstrated up to 85% incorporation of deuterium in the carbanion 7.

The analysis of the stereochemical data shows the following general trends:

1. Dependence on the reaction medium polarity (THF:HMPT vs. THF);
2. At low polarity (THF), dependence on the functional group in α-position relative to the carbanionic centre.

Thus, in highly ionizing conditions (excess of HMPT), the diastereoselectivity is uniformly low (anti/syn = 62:38 → 40:60, entries 2, 4, 7, 11, 17, and 20), whereas in THF it varies in a wide range from anti- (in the case of nitrile; anti/syn = 86:14 → 95:5, entries 1, 3, and 6) to syn-preference (in the case of ester and amide enolates, anti/syn = 41:59 → 22:78, entries 8–10, 12, 16, and 19). The influence of HMPT on the stereochemistry suggests that the protonation reaction takes place by different transition structures: open-chain in THF:HMPT (80:20) and chelated in pure THF.

Looking for evidence for chelates as real intermediates in THF, we recorded the IR spectra of some carbanionic species. The examples were selected with regard to 1,4-regioselective addition as well as high chemical yields. The carbonyl and nitrile group IR frequencies in both lithium salts and neutral molecules are shown in Table 2.

Two main tendencies are observed in the IR spectra of the salts compared to those of the neutral molecules: a shift of the absorption band of the R² group (α-positioned to the carbanionic centre) towards lower frequencies and a frequency decrease for the COR³ group (γ-positioned to the carbanionic centre) when it is an amide or no change when it is an ester function. It is noteworthy that in the latter case the absorption band broadens considerably.
Table 2. IR frequencies ($v$, cm$^{-1}$) of carbonyl and nitrile groups in the carbanionic species and the neutral compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>$R^2$</th>
<th>Li salt</th>
<th>neutral molecule</th>
<th>$\Delta v$</th>
<th>Li salt</th>
<th>neutral molecule</th>
<th>$\Delta v$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 4b</td>
<td>CN</td>
<td>2082</td>
<td>2235</td>
<td>153</td>
<td>COO$^-$Bu</td>
<td>1730</td>
<td>0</td>
</tr>
<tr>
<td>2 CH$_3$COO$^-$Bu</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1730</td>
<td>-</td>
</tr>
<tr>
<td>3 CH$_3$COO$^-$Bu + LiBr</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1730</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>4 4c</td>
<td>CN</td>
<td>2080</td>
<td>2239</td>
<td>159</td>
<td>CON(CH$_3$)$_2$</td>
<td>1625</td>
<td>25</td>
</tr>
<tr>
<td>5 4c + cryptand (2,1,1)</td>
<td>CN</td>
<td>2130</td>
<td>2239</td>
<td>109</td>
<td>CON(CH$_3$)$_2$</td>
<td>1650</td>
<td>0</td>
</tr>
<tr>
<td>6 CH$_3$CON(CH$_3$)$_2$</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1650</td>
<td>-</td>
</tr>
<tr>
<td>7 CH$_3$CON(CH$_3$)$_2$ + LiBr</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-1625*</td>
<td>1650</td>
<td>25</td>
</tr>
<tr>
<td>8 4f</td>
<td>CON(CH$_3$)$_2$</td>
<td>1625</td>
<td>1648</td>
<td>23</td>
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<td>23</td>
</tr>
<tr>
<td>9 4g</td>
<td>CON(CH$_3$)$_2$</td>
<td>1630</td>
<td>1650</td>
<td>20</td>
<td>CON(CH$_3$)$_2$</td>
<td>1640</td>
<td>10</td>
</tr>
</tbody>
</table>

$^*$Frequency ($v$, cm$^{-1}$) in the complex with LiBr

The first observation is connected with the carbanion charge delocalization which is larger in nitrile [28] than in amide and ester moieties [29, 30]. To assign the second carbonyl group shift as well as to rationalize the difference in the behaviour of the amide and ester groups, we recorded the IR spectra of model 1:1 mixtures of LiBr with CH$_3$COO$^-$Bu and CH$_3$CON(CH$_3$)$_2$ in 0.3 M THF solution. The values obtained, just the same as those in the carbanionic species (compare entries 1 and 3, 4 and 7) are indicative of chelation. While the good complexing power of the amide group is well known [20, 21], coordination with the ester group (entry 1) obviously occurs, but not strong enough to cause the band shift. In the presence of an equimolar quantity of cryptand (2,1,1) which is known to act as dechelating agent (entry 5), the absorption of the amide group in the Li-salt of 4e returns to the position in the neutral molecule. This observation is accompanied by a significant decrease of diastereoselectivity ($anti$:$syn = 95:5 \rightarrow 60:40$).

An additional evidence for coordination in the above case is the downfield shift of the amide carbonyl carbon from 170.04 ppm in the neutral $anti$-adduct to 174.60 ppm in the metal form in the $^{13}$C NMR spectra (both spectra recorded in THF-d8).

The stereochemical course of the electrophilic attack on a trigonal carbon having an adjacent chiral centre has been predicted by the theoretical model of Houk [33] (Fig. 1; L, M, and S refer to large, medium and small groups).

![Fig. 1. Houk's model for electrophilic attack on a double bond](image)

Bearing in mind some considerations given in the literature [15], the low diastereoselectivity observed in the presence of HMPT is interpreted in terms of two conformations K and L similar in energy where the substituents on the
stereogenic centre are ranked as follows: CH₂COR³ = L (large group), Ph = M (medium group) and H = S (small group).

When R² is a cyano group, there is no 1,3-allylic strain in conformation L and the phenyl group Ph readily adopts a position partially eclipsed with respect to the double bond. Similar explanations hold for the amide and ester enolates (R² = COOCH₃, CON(CH₃)₂), whose geometry is currently unknown, indicating cis location of the relatively small oxylithium group OLi to the stereogenic centre. Unfortunately, our attempts to trap the lithium enolates with tert-butyldimethylsilylchloride were unsuccessful.

The stereoselectivity in THF and its dependence on the enolate nature is explained by protonation via chelated transition structures different in geometry. Among the possible chelated conformations, those presented in Fig. 3 (conformations M and N) are considered to be the preferred ones for steric reasons (molecular models inspection). When R² = CN, chelation in a conformation analogous to N is not possible. Because of the cation location in the vicinity of the CN nitrogen [28], coordination forces the large group L = CH₂COR³ to adopt the “inside”, e.g. partially eclipsed position in conformation M. Attack anti to the phenyl group results in the predominant formation of the anti isomer. The temperature dependence of the stereochemical result in the case of 4e (entries 5 and 6) has been explained previously [5] by an equilibrium between two chelated conformations. In the case of the amide and ester enolates (R² = COOCH₃, CON(CH₃)₂), protonation via conformation N leads predominantly to the syn isomer. Molecular
models suggest that the decreased selectivity in the case of 4f compared to 4g (entries 16 and 19) is due to enhanced steric hindrance with respect to anti attack, caused by replacing CH$_3$ by Ph.

The present study provides a new synthetic and stereochemical approach to diastereoisomeric 1,3-bifunctionalized propanic systems by means of protonation of diastereotopic enolates. The presence of a carbonyl group in $\gamma$-position to the carbanionic centre is found to be of crucial importance for the observed 1,2-asymmetric induction in THF. The dependence of the stereochemistry on the solvent and on the substitution pattern of the enolate is explained by transition structures different in type and in geometry.

**Experimental**

All experiments were carried out under an argon atmosphere in a dry flask equipped with a rubber septum for introduction of the reagents by syringe. THF was freshly distilled prior to use. HMPT was dried and distilled from CaH$_2$ and kept on molecular sieves (4 Å). Staring materials were commercially available or prepared from the corresponding acids. n-BuLi (1.6 M in hexan) was used as purchased (Aldrich).

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker WM-250 spectrometer operating at 250.13 MHz for $^1$H and 62.89 MHz for $^{13}$C. CDCl$_3$ was used as the solvent and TMS as an internal standard. IR spectra were taken on a Specord 75 IR spectrometer in CaF$_2$ cells. Melting points were measured on a Kofler apparatus and are uncorrected. Analytical TLC was performed on Kieselgel Merk 60 F$_{254}$ plates. The products were isolated by recrystallization or by column chromatography on silica gel 40 (partical size 0.015–0.035 mm). The analyses of the diastereoisomeric mixtures were performed using the difference in location of appropriate protons in the $^1$H NMR spectra.

**Structures**

The diastereoisomeric pairs 4a, 4c [5, 34], 4d [6], 4e [35] (anti and syn) have been described and their relative configuration have been assigned as cited. The relative configurations of anti and syn t-butyl-4-cyano-3,4-diphenyl-butoanotes (4b) were elucidated using the correlation between $^1$H NMR chemical shifts and the steric structure of 4-cyano-3,4-disubstituted butyric acid derivatives [34]. Thus, anti configuration was assigned to the isomer with the H-4 proton located downfield.

The diastereoisomeric 2-methyl-3-phenyl-glutaric acid dimethylamides 4g were correlated with the anti acid obtained by stereospecific hydrolysis of the corresponding diethyl glutarate, prepared as reported by Yamagushi [36].

**General procedure for enolization and 1,2/1,4-addition**

The starting lithium enolates were generated by applying LDA at $-78°C$ for 30 min. In the case of dimethylacetamide, the metallation was carried out for 30 min at 0°C as reported [20]. Thus, to 1.1 mmols of LDA in 1 ml THF, 1 mmol of the corresponding nucleophile in 1 ml of the same solvent was added dropwise at the appropriate temperature. The reaction mixture was kept stirring for the time required; then, 1 mmol of the unsaturated compound in 1 ml THF was added at the temperature wanted. The reaction was quenched after 60 min by the addition of saturated aqueous NH$_4$Cl solution or CF$_3$CO$_2$H. THF was then removed under reduced pressure, and the residue was extracted with methylene chloride. After drying and evaporation of the solvent, the reaction products were isolated by recrystallization or by column chromatography on silica gel. The experiments in the presence of HMPT (method B) were carried out by adding HMPT (0.6 ml; 20 vol. %) to the metal enolate prior to electrophile addition.

Compounds 9 and 10, resulting from 1,2-addition, gave satisfactory elemental analyses and spectral data (available upon request from the authors).
**tert-Butyl-4-cyano-3,4-diphenyl-butanoates (4b (anti) and 4b (syn))**

Compound 4b (anti) was isolated from the reaction mixture obtained after method A by recrystallization from ethanol. M.p.: 100–102 °C; Rf = 0.4 ether:petroleum ether = 1:3); IR (CHCl₃, ν (cm⁻¹)): 1730 (COO'Bu), 2235 (CN); ¹H NMR (CDCl₃, δ (ppm)): 1.31 (s, 9H, COOtBu), 2.66, 2.69, 2.72, 2.75 (dd, 1H, H-2), 2.80, 2.83, 2.86, 2.89 (dd, 1H, H-2), 3.46–3.55 (m, 1H, H-3), 4.26, 4.29 (d, 1H, C-4, J = 6.2 Hz); found: C, 78.55; H, 7.30; C₂₁H₂₃O₂N requires C, 78.47; H, 7.21.

Fractional recrystallization of the reaction mixture obtained in the presence of HMPT from ethanol (method B), followed by preparative TLC of the mother liquor (ether:petroleum ether = 1:4, fourfold eluation) gave access to the isomer 4b (syn) as a viscous oil. Rf = 0.4 (ether:petroleum ether = 1:3); IR (CHCl₃, ν (cm⁻¹)): 1730 (COO'Bu), 2235 (CN); ¹H NMR (CDCl₃, δ (ppm)): 1.23 (s, 9H, COOtBu), 2.73–2.89 (m, 2H, H-2), 3.53–3.62 (m, 1H, H-3), 4.06, 4.09 (d, 1H, H-4, J = 6.2 Hz); found: C, 78.64; H, 7.40; C₂₁H₂₃O₂N requires C, 78.47; H, 7.21.

**2-methyl-3-phenyl-glutaric acid dimethylamides (4g (anti) and 4g (syn))**

The crude product from the synthesis in THF (method A) afforded the isomer 4g (syn) after recrystallization from ethanol. M.p.: 130–132 °C; Rf = 0.29 (ether:methanol = 20:1); IR (CHCl₃, ν (cm⁻¹)): 1648 (CO amide); ¹H NMR (CDCl₃, δ (ppm)): 0.90, 0.93 (d, 3H, CH₃, J = 6.87 Hz), 2.52, 2.55, 2.58, 2.61 (dd, 1H, H-4), 2.77, 2.83 (d, 6H, N(CH₃)₂), 2.77, 2.83, 2.86 (dd, 1H, H-4), 2.96, 3.02 (d, 6H, N(CH₃)₂), 3.18–3.30 (m, 1H, H-2), 3.41–3.50 (m, 1H, H-3), 7.16–7.34 (m, 5H, C₆H₅); found: C, 69.30; H, 8.63; C₁₆H₂₄O₂N₂ requires C, 69.53; H, 8.75.

Attempts to isolate pure 4g (anti) by the techniques used failed. The product was synthesized as follows:

To 1 mmol (278 mg) of anti diethyl-2-methyl-3-phenyl glutarate, obtained as reported by Yamagushi [36], 2.5 ml of conc. acetic and 1.5 ml of conc. hydrochloric acid were added and the homogenous reaction mixture was heated at 100 °C for 4 h. After cooling to room temperature, it was neutralized (pH = 7) using solid Na₂CO₃, followed by extraction with methylene chloride and washing with water. Drying over Na₂SO₄ and evaporation of the solvent afforded 190 mg (85%) of anti 2-methyl-3-phenyl-glutaric acid as a pale yellow oil. The stereospecifity of the hydrolysis under the conditions used was proved by ¹H NMR analysis of the crude product. The acid was dissolved in 3 ml of dry benzene and heated at boiling temperature for 15 min with 2.2 mmol (220 mg) of thionyl chloride. The reaction mixture was treated with an excess of aqueous dimethylamine at 0 °C and then left at room temperature for 1 h. The organic layer was washed with water, dried over Na₂SO₄, and the solvent was evaporated. Purification by column chromatography (eluent ether:methanol = 20:1) afforded 200 mg (84%) of 4g (anti) as colourless oil. Rf = 0.29 (ether:methanol = 20:1); IR (CHCl₃, ν (cm⁻¹)): 1648 (CO amide); ¹H NMR (CDCl₃, δ (ppm)): 1.15, 1.18 (d, 3H, CH₃, J = 6.77 Hz), 2.68–3.04 (m, 2H, H-4), 2.77, 2.80 (d, 6H, N(CH₃)₂), 2.88, 2.93 (d, 6H, N(CH₃)₂), 3.11–3.21 (m, 1H, H-2), 3.41–3.50 (m, 1H, H-3), 7.16–7.34 (m, 5H, C₆H₅); found: C, 69.60; H, 8.50; C₁₆H₂₄O₂N₂ requires C, 69.53; H, 8.75.

**References**


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