Diastereoselectivity in the Synthesis of Unnatural α-Amino Acid Esters by Phase Transfer Catalysis

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Two unnatural α-amino acid esters were prepared in good yields *via* phase transfer catalyzed Michael addition of ethyl N-acetylaminocyanoacetate to chalcone and benzalketone. For both α-enones, a progressive increase in product diastereomeric excess (d.e.) was observed during the course of reaction, even in the absence of quaternary ammonium salt. However, for a fixed reaction time, higher d.e. values were obtained under phase transfer catalytic condition. Analogous reactions were performed using S-aryl thiocinnamates as Michael acceptors, affording a 2-pyrrolidinone in good yield but low d.e. These results were interpreted on the basis of the reversibility of the Michael reaction.

Key words: Phase Transfer Catalysis, Unnatural α-Amino Acid, Diastereoselectivity

Introduction

α-Amino acids have been the focus of great interest in all areas of both the physical and life sciences for over 150 years. It is well known that α-amino acids are vital to life itself as the "building blocks" of peptides, proteins, and many other natural products. Beyond this fundamental role, amino acids are used extensively as food additives, agrochemicals, as enzyme inhibitors, antibacterial agents, neuroactive compounds, pharmaceutical starting materials and fungicides [1 – 4]. Amino acids have also been used in organic synthesis as synthetic targets, as a source of chiral raw materials, and as constituents for reagents and/or catalysts in asymmetric synthesis. The importance of amino acids has prompted the development of methods for their racemic and asymmetric synthesis [1].

With a surge of interest focused on small peptides and peptidomimetics, new methods are needed to prepare an array of unnatural amino acids designed to improve binding potency, chemical and biological stability, and pharmacokinetic characteristics when substituted into peptide-based compounds [5]. The incorporation into peptides results in significant influence on the conformational preferences, which eventually provides useful information for the elucidation of enzymatic mechanism [5 – 6].

The Michael addition is one the most valuable methods for carbon-carbon and carbon-heteroatom bond formation [7]. Stereochemical and mechanistic aspects of these classical reactions have been object of intense investigation, mainly focused on the direct addition of enolates or stabilized carbanions [8]. Regio-, enantio- and diastereoselectivity of the phase transfer catalyzed version of this type of reaction is well documented [9], as well as its applicability to the synthesis of unnatural α-amino acids [10].

Results and Discussion

Herein, we wish to report on the Michael addition of ethyl N-acetylaminocyanoacetate to α-enones and to S-aryl thiocinnamates, promoted by quaternary ammonium salts, as a valuable method for the synthesis of three novel unnatural α-amino acid esters (**3a**, **3b** and **5**, Scheme).

The present report will be divided into two parts: the first one deals with variation of several reaction parameters, aiming at optimization of product yield; the second one is dedicated to a study on the diastereoselectivity of the above mentioned addition reactions.

Part one: optimization of reaction conditions

*1,4-Addition of **1** to chalcone **2a***: In order to verify the influence of the addition of a quaternary

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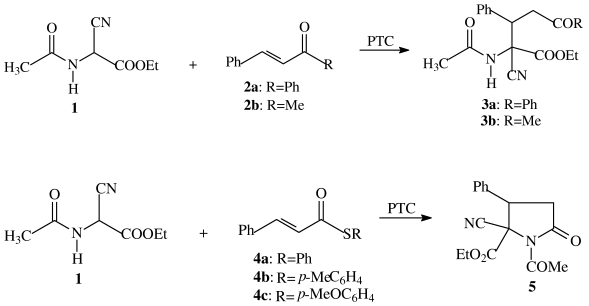
Table 1. Michael addition of **1** with enone **2a**, influence of phase transfer catalyst.

Entry	Time (h)	Catalyst	Yield of **3a**[*] (%)
1	2	none	26
2	2	TEBAC	67
3	4	none	48
4	4	TEBAC	65
5	6	none	71
6	6	TEBAC	73

[*] Isolated product, column chromatography on silica using dichloromethane/acetone (9:1 v/v).



ammonium salt on the rate of reaction, ethyl N-acetylaminocyanoacetate **1** was allowed to react with chalcone **2a** in toluene at 60 °C, in presence or absence of triethylbenzylammonium chloride (TEBAC) and using, as base, a catalytic amount of KOH (Table 1).

The analysis of data of Table 1 shows that equilibrium product concentration could be reached after 2 hours under the influence of TEBAC (Table 1, entries 2, 4 and 6), as compared to 6 hours for the biphasic uncatalyzed process (Table 1, entry 5). A more detailed monitoring of the catalyzed reaction (Table 2) demonstrated that no more than 15 min. were necessary to afford **3a** in 70% yield (Table 2, entry 2).

It is worth noting that the same reaction performed at room temperature yielded, after 15 min., 43% of **3a**. Moreover, at 60 °C, but in the absence of solvent, 63% of **3a** was formed for the same reaction time. Using this environmentally friendly system, the performance of several ammonium salts was compared (Table 3). Slightly better results were obtained for TBAH as compared to the other three catalysts (Table 3, entries 1 – 4), whereas Aliquat 336® showed to be less efficient.

*1,4-Addition of **1** to benzalketone **3b**:* Likewise, after examination of various parameters, adduct **3b** could be prepared in 80% yield, as follows: The mixture was stirred vigorously by a mechanical stirrer, at 60 °C for 2 hours, using triethylbenzylammonium chloride (TEBAC) as phase catalyst and a catalytic amount of KOH as base. In this case, the mixture could not be stirred in the absence of solvent (toluene).

Table 2. TEBAC catalyzed addition of malonate **1** to chalcone **2a** at different reaction times.

Entry	Time (min)	Yield of **3a** (%)	d. e. (%)
1	5	49	35
2	15	70	46
3	30	69	72
4	60	71	81
5	120	67	85

Table 3. Michael addition of **1** with chalcone **2a**, during 15 min, in absence of solvent, using different tetraalkylammonium salts as catalysts.

Entry	Catalyst	Yield of **3a** (%)
1	TEBAC	63
2	TBAH[a]	70
3	cetrimide[b]	61
4	CBTA[c]	61
5	aliquat[d]	51

[a] tetrabutylammonium hydrogen sulfate; [b] hexadecyltrimethylammonium bromide; [c] benzyltributylammonium chloride; [d] methyltrioctylammonium choride.

Table 4. Michael addition of **1** to thiocinnamates.

Entry	R	Yield of **5** (%)[a]
1	Ph	53
2	*p*-MePh	59
3	*p*-MeOPh	80

[a] Isolated product, column chromatography on silica using hexane/acetone (8:2 v/v).

*1,4-Addition of **1** to thiocinnamates:* The addition reactions of **1** to thiocinnamates **4a**, **4b** and **4c** afforded pyrrolidinone **5**. The formation of the heterocyclic ring can be attributed to an intramolecular cyclization of the former Michael adduct. Optimization of experimental conditions led us to use toluene as solvent (again the mixture could not be stirred in absence of solvent). After vigorous stirring for 15 min. at 60 °C, compound **5** was obtained in yields ranging from 53 to 80%, depending on the thiocinnamate S-aryl group (Table 4). It is noteworthy that, for all three thiocinnamates, blank experiments, performed in the absence of catalyst, led to complete recovery of starting materials.

Part two: A study on the diastereoselectivity

*1,4-Addition of **1** to chalcone **2a***: During the monitoring of the Michael addition of **1** to chalcone (Table 2), we observed a progressive increase of product d.e. during the course of reaction. In order to further investigate this effect, we decided to collect data until the d.e. value was constant (Table 5).

Table 5. Values of d. e. for the Michael addition of **1** to chalcone **2a**.

Entry	Time (h)	d. e. (%) for **3a**	
		Absence of TEBAC	Presence of TEBAC
1	2	34	85
2	4	52	90
3	6	100	100

Except for a reaction time of 6 hours (entry 3), when for both reactions (in the presence or absence of TEBAC) only one diastereoisomer was formed, the reaction afforded a mixture of two stereoisomers (unknown configuration) with one as the major product, which we did not manage to separate by column chromatography. As can be seen, d.e. increases with increasing reaction time, and it seems reasonable to suggest that the retro-Michael reaction of the minor diastereomer, leading to starting materials, allows for the conversion to the thermodynamically more stable component. This process seems to be more efficient for the catalyzed reaction (Table 5, entries 1 and 2), as expected for a lower energy transition state.

It should be mentioned that when the reaction was conducted in the absence of solvent for 15 min., d. e. was higher (75%) as compared to the analogous reaction in toluene (Table 2, entry 2). In order to account for these results, two points should be taken into consideration: (i) in a solvent free system, chalcone produces a "polar medium"; (ii) the intermediate for the Michael reaction has anionic character. Invoking the Hammond postulate, we propose that stabilization of the transition state, favored in polar medium, is responsible for the observed increase of d.e. value in solvent-free conditions.

*1,4-Addition of **1** to benzalketone **2b**:* A similar stereochemical behavior was observed when the Michael addition was performed using benzalketone instead of chalcone. Thus, for two hours of reaction time we could observe that **3b** was produced with a higher d.e. value (30%) in presence of catalyst (TEBAC), as compared to the uncatalysed reaction (20%). Likewise, for a longer reaction time (4 h), only one diastereoisomer was obtained in the presence or absence of catalyst.

*1,4-Addition of **1** to thiocinnamates **4a**, **4b**, **4c**:* Under similar conditions, pyrrolidinone **5** was obtained as a mixture of two diastereoisomers in low d.e. values ($\leq$ 9%). The major diastereoisomer could be separated by column chromatography on silica using hexane/acetone (8:2 v/v). It seems reasonable to admit that the cyclization of the Michael adduct may occur as soon as it was produced. Thus, no retro-Michael should occur in this case, explaining the low d. e. values.

In summary, we have demonstrated that after careful examination of various parameters, unnatural α-amino acid esters could be obtained in good yields by Michael addition of ethyl N-acetylaminocyanoacetate to α-enones and thiocinnamates under PTC conditions. In addition, based on the reversibility of the Michael reaction, we have devised an explanation for diastereoselectivity profiles in the formation of α-enones and thiocinnamates Michael adducts. Further studies on the aforementioned reactions, using asymmetric phase transfer catalysis, are under investigation.

Experimental Section

General

NMR spectra were recorded on a Bruker DRX 500 spectrometer operating at 500 MHz for proton and 125 MHz for ^{13}C spectra. IR spectra were run on a Perkin-Elmer 1000 FT-IR spectrometer using KBr pellets. Melting points were determined on a Mettler FP5 apparatus and are uncorrected. Microanalyses were performed on a Perkin Elmer 2400 B CHN elemental analyzer. Gravity column chromatography was performed on Merck Kieselgel 60 (70 – 230 mesh). Thiocinnamates **4a**,**4b**,**4c** were prepared according to literature procedures [11].

General procedure for the Michael addition of ethyl N-acetylaminocyanoacetate **1** *to α-enones* **2a**, **2b** *and thiocinnamates* **4a**, **4b** *and* **4c**

A mixture of ethyl N-acetylaminocyanoacetate (1.5 mmol), α-enone (1.5 mmol) or thiocinnamate (1.5 mmol), KOH (0.15 mmol) and tetraalkylammonium salt (0.15 mmol), in toluene or in absence of solvent, was stirred vigorously by a mechanical stirrer at 60 °C in reaction time that varied from 5 min. to 6 h. The reaction mixture was diluted with dichloromethane (30 ml), the organic extract was treated with water, and then dried over anhydrous sodium sulfate. After removal of solvent, under reduced pressure, the crude product was purified by column chromatography using (A) dichlorometane/acetone (9:1 v/v) or (B) chloroform/ethyl acetate (1:1 v/v) or (C) hexane/acetone (8:2 v/v) to yield, in sequence, products **3a**, **3b** and **5**. The diastereomeric excess (d.e.) values for **3a** obtained after column chromatography are summarized in Table 5. A similar stereochemical behavior was observed for **3b**, while **5** was obtained with low d. e. values ($\leq$ 9%).

*Ethyl 2-acetylamino-2-cyano-3,5-diphenyl-5-oxopentanoate (**3a**)*

IR (KBr): ν = 3357, 2366, 1756 (C=O), 1688 (C=O), 1451, 1239 cm^{-1}. – ^{1}H NMR ($CDCl_3$), major/minor isomer: $\delta = 0.82/1.22$ (t, J = 7.0 Hz, 3 H, *Me*CH_2O), 2.05/1.96 (s, 3 H, MeCO), 3.71/4.16 (dq, J = 10.6, 7.2 Hz, 1 H, CH_2O), 3.88 – 3.93/4.28 (m, 1 H, CH_2O/dq, J = 10.6, 7.2 Hz, 1 H, CH_2O), 3.88/3.75 – 3.93 (dd, J = 18.0, 3.0 Hz, 1 H, CH_2COPh/m, 2 H, CH_2COPh), 3.84 – 3.93/4.28 (m, 1 H, CH_2O/dq, J = 10.6, 7.2, 1 H, CH_2O), 3.96/4.02 – 4.08 (dd, J = 8.0, 3.0 Hz, 1 H, CH/m, 1 H, CH), 4.05 (dd, J = 18.0, 8.0 Hz, 1 H, CH_2COPh), 7.24 – 7.99/6.39 – 7.99 (m, 10 H, all arom. H), 8.26/8.26 (s, 1 H, NH). – ^{13}C{^{1}H} NMR ($CDCl_3$), major/minor isomer: $\delta = 13.28/13.71$ (*Me*CH_2), 22.42/22.42 (Me), 42.67/40.06 (CH_2COPh), 44.90/45.13 (CH), 62.90/60.63 (CH_2O), 63.33/63.69 (Cq), 116.14/116.24 (C=N), 128.41/128.11, 128.73/128.71, 128.81/128.79, 128.86/128.93, 128.88/129.12, 134.44/133.83, 135.53/135.91, 136.85/136.02 (all arom. C), 165.81/165.53 (COOEt), 170.18/169.57 (CONH), 200.04/196.91 (COPh). – $C_{22}H_{22}N_2O_4$ (378.4): calcd. C 69.84, H 5.82, N 7.41; found C 69.92, H 6.21, N 7.32.

*Ethyl 2-acetylamino-2-cyano-3-phenyl-5-oxohexanoate (**3b**)*

IR (KBr): ν = 3303, 2362, 1752 (C=O), 1717 (C=O), 1665 (C=O), 1665, 1456, 1248 cm^{-1}. – ^{1}H NMR ($CDCl_3$), major/minor isomer: $\delta = 0.80/1.25$ (t, J = 7.0 Hz, 3 H, *Me*CH_2), 2.03/1.90 (s, 3 H, MeCONH), 2.24/2.14 (s, 3 H, MeCO), 3.29/3.34 (dd, J = 19.0, 3.0 Hz, 1 H, *CH*$_2$COMe/dd, J = 18.0, 6.0 Hz, 1 H, *CH*$_2$COMe), 3.56/3.17 (dd, J = 19.0, 8.5 Hz, 1 H, *CH*$_2$COMe/dd, J = 18.0, 7.0 Hz, 1 H, *CH*$_2$COMe), 3.70/3.81(dd, J = 8.5, 3.0 Hz, 1 H, CH/dd, J = 7.0, 6.0 Hz, 1 H, CH), 3.64 – 3.68/4.19 (m, 1 H, CH_2O/dq, J = 12.0, 7.0 Hz,1 H, CH_2O), 3.87/4.25 (dq, J = 12.0, 7.0 Hz, 1 H, CH_2O), 7.24 – 7.31/7.25 – 7.38(m, 5 H, all arom. H), 8.10/8.10 (s, 1 H, NH). – ^{13}C{^{1}H} NMR ($CDCl_3$), major/minor isomer: $\delta = 13.34/13.83$ (*Me*CH_2), 22.42/22.42 (*Me*CONH), 30.43/30.47 (MeCO), 44.80/44.80 (CH), 47.31/44.91 (*CH*$_2$COMe), 62.98/63.72 (CH_2O), 63.15/60.65 (Cq), 116.098/116.19 (C=N), 128.79/128.96, 128.82/129.24, 128.90/129.48, 136.50/135.92 (all arom. C), 165.79/165.55 (COOEt), 170.35/169.77 (CONH), 209.34/205.91 (COMe). – $C_{17}H_{20}N_2O_4$ (316.3): calcd. C 64.56, H 6.33, N 8.86; found C, 64.34, H 6.24, N 9.12.

*N-Acetyl-5-cyano-5-ethoxycarbonyl-4-phenyl-2-pyrrolidinone (**5**)*

IR (KBr): ν = 2367, 1765 (C=O), 1703 (C=O), 1249 cm^{-1}. – ^{1}H NMR ($CDCl_3$), major/minor isomer: $\delta = 0.81/1.35$ (t, J = 7.0 Hz, 3 H, *Me*CH_2), 2.65/2.64 (s, 3 H, MeCO), 2.97/3.05 (dd, J = 17.0, 8.0 Hz, 1 H, CH_2CO), 3.37/3.30 (dd, J = 17.0, 13.0 Hz, 1 H, CH_2CO), 3.72 – 3.84 (m, 1 H, CH_2O), 3.91 – 4.05 (m, 1 H, CH_2O), 4.22/4.43 (dd, J = 13.0, 8.0 Hz, 1 H, CH), 7.34 – 7.42 (m, 5 H, all arom. H). – ^{13}C{^{1}H} NMR ($CDCl_3$), major/minor isomer: $\delta = 13.48/14.11$ (*Me*CH_2), 24.99/24.99 (MeCO), 34.99/36.69 (CH_2CO), 46.13/46.30 (CH), 63.91/64.38 (CH_2O), 65.64/67.38 (Cq), 116.00/113.83 (C=N), 128.31/128.43, 129.28/129.33, 129.67/129.84, 131.54/132.43 (all arom. C), 163.85/165.17 (COOEt), 170.37/170.16 (COMe), 171.45/171.20 ($COCH_2$). – $C_{16}H_{16}N_2O_4$ (330.3): calcd. C 64.00, H 5.33, N 9.33; found C 64.04, H 5.56, N 9.46.

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