SHORT PAPER

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Stereochemistry of aldol condensation of N,N-dialkyl amides with aromatic imines. Highly diastereoselective synthesis of β-amino acid dialkylamides†

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Aldol condensation of amide enolates with imines affords β-amino acid dialkylamides in both high yields and excellent *threo* diastereoselectivity; electronic factors seem to be of great importance for successful interaction.

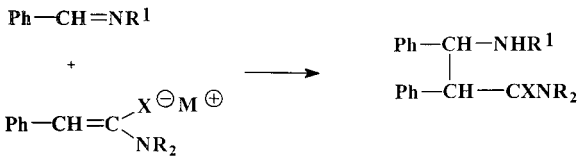
Whilst the stereochemistry of aldol condensation between metal ester enolates and imino compounds have been the object of numerous studies, mainly in relation to the synthesis of β-lactams,[1] there have been only isolated reports concerning amide enolates.[2]

Previously, one of us investigated the addition of N,N-dialkyl-phenylacetamides to benzylideneaniline in the presence of sodium amide in ether.[3] The reaction, which was not diastereoselective, was carried out under conditions where the possibility of second order asymmetric transformation existed. Although the correct conclusions were drawn, the poorly defined conditions and the lack of an accurate method of analysis before the advent of ^{1}H NMR spectroscopy made the precise investigation of the reaction stereochemistry difficult.

Further to our continuous interest in diastereoselective carbon-carbon bond formation by means of aldol type reactions,[4] we present a study of the addition of various metal enolates and titanium "ate" complexes of N,N-dialkyl phenylacetamides and thioamides to aromatic and aryl-aliphatic imines with the aim of elucidating the influence of different factors on the synthetic potential and stereochemistry of the reaction.

The reaction was examined in Et_2O and THF at constant concentration (c = 0.3 mol/L) over the temperature range of –78 to 22 °C. The synthesis with titanium "ate" complexes was carried out at –40 °C for 2 h.

The addition of N,N-dialkyl phenylacetamides to aromatic imines proceeds smoothly in good yield which increases with the temperature and the reaction time. The data obtained are summarized in Table 1. With bromomagnesium enolates a long reaction time (24 h) caused a significant decrease in the yield in favour of self-coupling products of the starting amides.



where: R: Me, Et, Pr^i, C_6H_{11}
R^1: Ph, β-*napht*, CHMePh, Me
$M^{\oplus}$: Li, Na, MgBr, $Ti(OPr^i)_4$
X: O, S

Scheme 1

N,N-Dialkylamides failed to react with aryl-aliphatic imines [R^1 = Me, CHMePh] over a wide range of reaction conditions. The same behaviour was shown by the corresponding thio analogs with both aromatic and aryl-aliphatic Schiff bases.

The failure of the reaction in some of the cases studied is due, in our opinion, to electronic reasons. The reactivity of imines is lower compared to the corresponding carbonyl compounds and decreases from aromatic to aryl-aliphatic Schiff bases. This makes the addition reaction strongly dependent on the enolate nature (X = O or S), on its substitution patterns and on the metal counterion. The diminished nucleophilicity of the thioamides compared to the oxo analogues can be explained by their softer character.[5] It is worth mentioning that in the latter case even the use of Sn(II) enolates, known to have considerable affinity towards the nitrogen atom, does not influence the condensation.[6] As it can be seen from the Table 1, small changes in the reagents' structure (compare cases 1 and 2; 1 and 4; 1 and 6) result in successful interaction.

The stereochemical ratios were constant under a wide range of reaction conditions. Strict kinetic control over the product configuration was assured by short time experiments (15 s). The observed *threo* predominance was found to be independent of the solvent, temperature and reaction time but

Table 1 Addition of metal enolates and titanium "ate" complexes of N,N-dialkyl pnenylacetamide to aromatic imines

Case	R	R^1	M^+	Yield (%)[a]	*E*/*T*[b]
1	Me	Ph	Li, Na	traces	–
2	Me	Ph	MgBr[c]	42	0/100
3	Me	Ph	$Ti(OPr^i)_4$	30	5/95
4	Me	β-napht	Li	70	0/100
5	Me	β-napht	$Ti(OPr^i)_4$	65	5/95
6	Et	Ph	Li	92	0/100
7	Et	Ph	Na	55	30/70
8	Et	Ph	MgBr	40	0/100
9	Et	Ph	$Ti(OPr^i)_4$	66	6/94
10	Et	β-napht	Li	95	0/100
11	Et	β-napht	$Ti(OPr^i)_4$	83	8/92
12	$Pr^{i,d}$	Ph	Li	92	0/100
13	Pr^i	Ph	Na	58	40/60
14	Pr^i	Ph	MgBr	40	0/100
15	Pr^i	Ph	$Ti(OPr^i)_4$	92	0/100
16	Pr^i	β-napht	Li	82	0/100
17	Pr^i	β-napht	$Ti(OPr^i)_4$	75	5/95

[a]Yields in THF for 1h at 22 °C in the case Li, Na and MgBr and for 2 h at –40 °C in the case of $Ti(OPr^i)_4$. Yields in Et_2O do not differ significantly. [b]The stereochemical ratios are constant with the solvent, the reaction time and the temperature. [c]MgBr enolates do not react at low temperature. [d]The same results are obtained when R=C_6H_{11}.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

A *(erythro)* B *(threo)*

Fig. 1

depended significantly on the metal counterion (cases 7 and 13). It varied from exclusive with lithium and bromomagnesium enolates and excellent with the titanium "ate" complexes to moderate with a sodium counterion.

The kinetic *threo* predominance is in good agreement with a chelated transition state, proposed for aldol reactions,[7] where both chair and boat arrangements of the reagents are considered.[8] For *Z*-configurated metal enolates[9] and the *E*-configurated imines[10] (Fig. 1) a boat *A* over a chair transition structure is preferred for the formation of the *erythro* isomer because of more convenient mode of chelation. However, the unfavourable eclipsing interactions Ph/Ph and NR_2/R^1 in the transition structure *A* resulted in a preference for the chair transition state *B*, thus leading to the predominance of the *threo* adduct.

Bearing in mind that titanation does not affect the enolate geometry,[11] an analogous transition states must operate with titanium "ate" complexes.[12]

The lower kinetic diastereoselectivity with sodium enolates can be rationalized in terms of less "tight" transition structures because of the lower coordination ability of sodium, where the effective bulk of the substituents is decreased.[13]

The observed constancy of the diastereoisomeric ratios raised the important question about the reversibility of the reaction. The condensation of zinc amide enolates with imines was believed to be under kinetic control (48 h, room temperature).[2] With the lithium enolates the reversibility was unambiguously proved by a concurrent synthesis which involved the addition of methyl iodide to aldolate reaction mixtures. Instead of N-alkylated adducts, the corresponding hydratropic acid dialkylamides were isolated, obviously through reverse aldolization. In general, the equilibrium with sodium enolates is reached more rapidly.[14] In the case of bromomagnesium enolates, the decrease in the yields observed after a long period of time which was accompanied by the formation of coupling products of the amides, is indirect evidence of

Table 2 Physical, analytical and ^{1}H NMR data for compounds **1**–**7**

Compound	R	R^1	Mp(*T*/°C) (solvent)	R_f[a] (Et_2O: LP ratio)	Found (required) (%) C	H	δH
(1)-E[b]	Me	Ph	236-237 (EtOH)	0.4 (2:1)	80.16 (80.20)	7.01 (7.02)	2.66, 2.73 [6H, d, $N(CH_3)_2$], 3.98 (1H, broad s, NH), 4.12 (1H, d, *J* = 9.5 Hz, H-3), 5.02 (1H, d. *J* = 9.4 Hz, H-2), 6.35–7.51 (15H, m, $3xC_6H_5$)
(1)-T	Me	Ph	184-185 (heptane)	0.4 (2:1)	80.12 (80.20)	7.32 (7.02)	2.65, 2.85 [6H, d, $N(CH_3)_2$], 4.26 (1H, d, *J* = 4.8 Hz, H-3), 4.84 (1H, d, *J* = 4.8 Hz, H-2), 6.17–7.50 (16H, m, $3xC_6H_5$+NH)
(2)-E[b]	Et	Ph	180-182 (EtOH)	0.73 (1:1)	80.59 (80.61)	7.34 (7.58)	0.81 (3H, t, CH_2CH_3), 0.87 (3H, t, CH_2CH_3), 2.97–3.14 (1H, m, CH_2CH_3), 3.22–3.36 (1H, m, CH_2CH_3), 3.97 (1H, d, *J* = 9.6 Hz, H-3), 5.04 (1H, d, *J* = 9.5 Hz, H-2), 6.20-7.61 (15H, m, $3xC_6H_5$)
(2)-T	Et	Ph	165-166 (EtOH)	0.48 (1:1)	80.60 (80.61)	7.56 (7.58)	0.75 (3H, t,CH_2CH_3), 1.00 (3H, t, CH_2CH_3), 2.78–2.93 (1H, m, CH_2CH_3), 2.96–3.11 (1H, m, CH_2CH_3), 3.26 (2H, q, CH_2CH_3), 4.18 (1H, d, *J* = 3 Hz, H-3), 4.8 (1H, d, *J* = 5 Hz, H-2), 6.44–7.52 (15H, m, $3xC_6H_5$)
(3)-E	Pr^i	Ph	176-178 (Et_2O/hexane)	0.25 (1:8)	80.78 (80.96)	7.93 (8.05)	0.66, 0.69 [3H, d, $CH(CH_3)_2$], 0.85, 0.88 [3H, d, $CH(CH_3)_2$], 1.14, 1.16 [3H, d, $CH(CH_3)_2$, 1.18, 1.12 [3H, d, $CH(CH_3)_2$], 3.05–3.27 [1H, m, $CH(CH_3)_2$], 3.50 (1H, broad s, NH), 3.95–4.00 [1H, m, $CH(CH_3)_2$], 4.06 (1H, d, *J* = 9.58 Hz, H-3), 5.85 (1H, d, *J* = 9.56, H-2), 6.32–7.53 (15H, m, $3xC_6H_5$)
(3)-T	Pr^i	Ph	105-107 (Et_2O/hexane)	0.34 (1:8)	80.83 (80.96)	7.86 (8.05)	0.74, 0.77 [3H, d, $CH(CH_3)_2$], 0.77, 0.80 [3H, d, $CH(CH_3)_2$], 1.21, 1.24 [3H, d, $CH(CH_3)_2$, 1.34, 1.37 [3H, d, $CH(CH_3)_2$], 3.29 [1H, m, $CH(CH_3)_2$], 3.78 [1H, m, $CH(CH_3)_2$], 4.22 (1H, d, *J* = 4.69 Hz, H-3) 4.81 (1H, d, *J* = 4.69, H-2), 6.42–7.39 (15H, m, $3xC_6H_5$)
(4)-T	C_6H_{11}	Ph	148-150 (EtOH)	0.58 (1:8)	82.24 (82.46)	8.12 (8.39)	0.89–3.29 (22H, m, $2xC_6H_{11}$), 4.22 (1H, d, *J* = 4.9 Hz, H-3), 4.82 (1H, d, *J* = 4.84 Hz, H-2), 6.26–7.36 (15H, m, $3xC_6H_5$)
(5)-T	Me	β-napht	230-232 (EtOH)	0.33 (2:1)	82.13 (82.20)	6.60 (6.64)	2.71, 2.91 [6H, d, $N(CH_3)_2$], 4.44 (1H, broad s, H-3), 4.97(1H, d, *J* = 5.15 Hz, H-2), 6.42–7.96 (17H, m, $2xC_6H_5$ + $C_{10}H_7$)
(6)-T	Et	β-napht	146-148 (EtOH)	0.36 (1:2)	82.18 (82.43)	7.06 (7.16)	0.78 (3H, t, CH_2CH_3), 1.03 (3H, t, CH_2CH_3), 2.82–2.94 (1H, m, CH_2CH_3), 3.00–3.15 (1H, m, CH_2CH_3), 3.29 (2H, q, CH_2CH_3), 4.26 (1H, broad s, H-3), 4.93 (1H, d, *J* = 4.3 Hz, H-2), 6.48–7.67 (17H, m, $2xC_6H_5$ + $C_{10}H_7$)
(7)-T	Pr^i	β-napht	96-98 (EtOH)	0.35 (1:5)	82.48 (82.63)	7.48 (7.61)	0.69, 0.72 [3H, d, $CH(CH_3)_2$], 0.82, 0.85 [3H, d, $CH(CH_3)_2$], 1.23, 1.26 [3H, d, $CH(CH_3)_2$], 1.37, 1.40 [3H, d, $CH(CH_3)_2$], 3.35 [1H, broad s, $CH(CH_3)_2$], 3.73–3.84 [1H, m, $CH(CH_3)_2$], 4.36 (1H, d, *J* = 3.96 Hz, H-3), 4.9 (1H, d, *J* = 3.72 Hz, H-2), 6.10-7.51 (17H, m, $2xC_6H_5$ + $C_{10}H_7$)

[a]LP=Light petroleum (b.p. 40–70°C).
[b]Obtained according to **(3)**.

reversibility. Hence, the observed constancy of the stereochemical ratios is one more example of coincidence of kinetic and thermodynamic diastereoselectivity.[15]

The predominance of *threo* aldol at equilibrium has been explained by smaller non-bonding interactions in the chelated *threo* aldolate compared to the *erythro* intermediate.[14] The results with sodium enolates (cases 7 and 13) emphasize the role of the metal counterion indicating that, in the case of sodium, chelation is not important.

Experimental

All reactions were carried out under an argon atmosphere. The solvents used were dry and freshly distilled over $LiAlH_4$ prior to use. The ^1H NMR spectra were recorded on a Bruker WM-spectrometer at 250 MHz with Me_4Si as the internal standard. Melting points were measured on a Kofler apparatus and are uncorrected. Analytical TLC investigations were performed on Merk Kieselgel $60F_{254}$.

The relative configurations of compounds **1** and **2** are known.[3] The stereostructural assignment of compounds **3–7** was done using the ^1H NMR correlation between H-2 proton chemical shifts and the stereostructure found for *E/T* pairs of compounds **1** and **2**, obtained as previously described.[3] The difference in the location of the same proton signals was used to determine the *E/T* ratios.

Enolization: The lithium enolates were prepared by the use of LDA at 20 °C. Thus, 1 mmol of N,N-dialkylamide, dissolved in 1 mL of THF or Et_2O was added dropwise to 1.1 mmol of LDA in 1 ml of the corresponding solvent and the reaction mixture was kept at stirring for 15 min. The sodium enolates were generated with $NaNH_2$ as metallating agent according to.[4(a)] The bromomagnesium enolates were obtained from the lithium enolates by metal exchange with equimolar quantity of $MgBr_2$. The titanium "ate" complexes were generated from the lithium enolates by the addition of 1 equivalent of neat $Ti(O\text{-}Pr^i)_4$ at –40 °C for 30 min.

Synthesis–General procedure: To a solution of 1 mmol of the enolate or titanium "ate" complex was added 1 mmol of the imine dissolved in 1 mL of the chosen solvent at the desired temperature. At the end of the reaction time (varying from 15 s to 24 h) the mixture was quenched with an aqueous NH_4Cl solution. After a standard work up procedure, the reaction yields were determined by preparative TLC.

Physical, analytical and ^1H NMR data for compounds 1–7 are given in Table 2.

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