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E,Z-Stereodivergent Synthesis of *N*-Tosyl α,β-Dehydroamino Esters via a Mukaiyama-Michael Addition†

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The stereodivergent synthesis of *N*-Tosyl α,β-dehydroamino esters via a Mukaiyama-Michael addition is reported. The reaction of silylketene acetals with *N*-tosylimines derived from β,γ-unsaturated α-keto esters in dichloromethane provided the corresponding (*Z*)-α,β-dehydroamino esters while the (*E*)-isomers were obtained when the reaction was carried out in the presence of 10 mol % copper(II) triflate.

α,β-Dehydroamino acid derivatives are non-proteinogenic amino acids that are often found as structural subunits in natural products produced by bacteria, fungi, marine organisms and plants, and play an important role in the biosynthesis of other non-proteinogenic amino acids and D-amino acids (Figure 1).[1] Some of these compounds have shown antibiotic and other intriguing biological activities.[2] The presence of the double bond in the dehydroamino acid residue reduces the conformational flexibility of peptides, a property that is useful for structure-activity studies and for the design of secondary structure in peptides,[3] and it also confers resistance to enzymatic degradation and alters their bioactivity.[4] These properties are affected by the *E*/*Z* configuration of the double bond of the dehydroamino acid moiety.[5] Furthermore, α,β-dehydroamino acid derivatives are widely used as starting materials in the synthesis of natural and unnatural α-amino acids through catalytic hydrogenation,[6] or conjugate addition,[7] as well as in the synthesis of heterocyclic compounds.[8] According to these pharmacological and synthetic potential, much synthetic effort has been devoted to the preparation of dehydroamino acids and their derivatives. Literature antecedents include elimination reactions of β-hydroxy-α-amino acids,[9] Horner-Wadsworth-Emmons and Wittig reactions,[10] condensation of aldehydes with *N*-protected glycine or 5-(4*H*)-oxazolone (Erlenmeyer synthesis),[11] condensation of carbonyl compounds with isocyano acetates (Schöllkopf method),[12] aminohalogenation of unsaturated esters followed by basic elimination,[13] addition of amines to alkynoates,[14] and Heck reaction.[15] In most of these procedures the thermodynamically stable *Z*-isomer is predominantly formed,[9a,10b-c,11,12b,c,13,14] while the synthesis of the *E*-isomer normally takes place with lower selectivity[9b,10a,12a] or requires the use of stereoisomerically pure starting materials that are usually prepared in multistep sequences or involves difficult isomer separation.[9c-d]

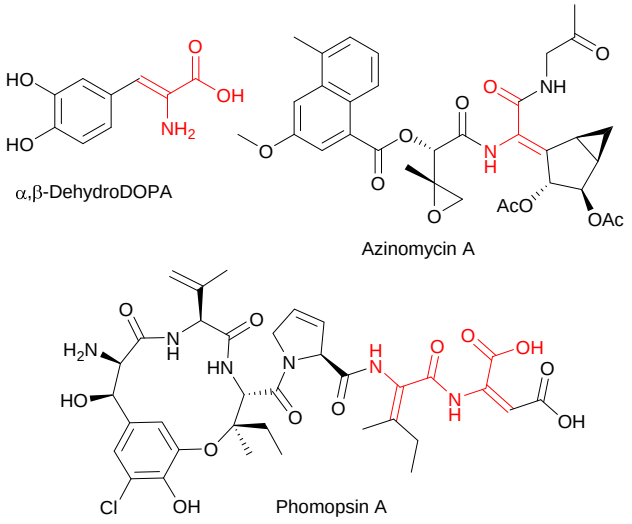

Fig. 1 Examples of natural and bioactive α,β-dehydroamino acid derivatives

Recently, Palacios described a new approach to α,β-dehydroamino acid esters consisting in the conjugate addition of dialkylzinc reagents to imines derived from β,γ-unsaturated α-keto esters catalysed by a copper(I)-fosforimidite complex.[16] A similar strategy has been reported by Liu and Hu for the construction of α-hydroxy-δ-amino esters from α-diazo esters and *N*-tosyl imines of β,γ-unsaturated α-keto esters[17] and by Kim in the rhodium-catalysed 1,4 addition of arylboronic acids

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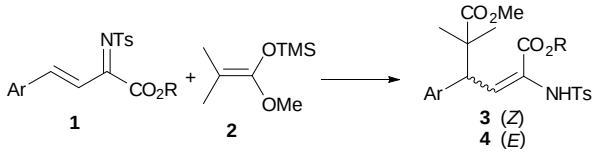
to unsaturated imino esters.[18] In all these cases the reaction takes place stereoselectively to give the corresponding dehydroamino esters with the *Z*-configuration at the double bond. However, a procedure based on this approach that led stereoselectively to the *E* or *Z* dehydroamino esters starting from a same set of reactants has not been reported to date.[19] Following our interest in nucleophilic addition reactions to unsaturated imines,[20] we report herein our preliminary results in the *E*/*Z* stereodivergent synthesis of α,β-dehydroamino esters via a Mukaiyama-Michael addition of silylketene acetals to *N*-tosyl imines of β,γ-unsaturated α-keto esters (Scheme 1).



Scheme 1 Mukaiyama-Michael reaction with *N*-tosyl imines of β,γ-unsaturated α-keto esters.

Table 1. Non-catalysed Mukaiyama Michael addition of trimethylsilyl ketene acetal **2** to *N*-tosylimines of α-keto esters **1**.[a]

Entry	**1**	Ar	R	Yield **3+4** (%)[b]	**3:4** (dr)[c]
1	**1a**	Ph	Et	84	91:9
2	**1b**	4-MeC_6H_4	Et	77	91:9
3	**1c**	4-$MeOC_6H_4$	Et	56	86:14
4	**1d**	3-$MeOC_6H_4$	Et	82	89:11
5	**1e**	2-$MeOC_6H_4$	Et	72	85:15
6	**1f**	4-ClC_6H_4	Et	80	91:9
7	**1g**	3-ClC_6H_4	Et	87	89:11
8	**1h**	2-ClC_6H_4	Et	95	87:13
9	**1i**	4-$NO_2C_6H_4$	Et	98	92:8
10	**1j**	3-$NO_2C_6H_4$	Et	99	90:10
11	**1k**	2-$NO_2C_6H_4$	Et	58	99:1
12	**1l**	2-furyl	Et	69	86:14
13	**1m**	Ph	Me	82	89:11
14	**1n**	Ph	*i*Pr	75	89:11

[a] **1** (0.25 mmol), **2** (0.6 mmol), CH_2Cl_2 (1.2 mL), rt, 20-24 h. [b] Yield of the diastereomer mixture after chromatography. [c] Determined by ^{1}H NMR

The reaction between 2-methyl-1-methoxy-1-trimethylsilyoxyprop-1-ene (**2**) and imine **1a** (Ar =Ph, R = Et) was carried out at room temperature.‡ The conjugate addition reaction proceeded smoothly in absence of any additive to give 85% yield of a mixture of two diastereomeric compounds **3a** and **4a**, differing in the geometry of the enamine double bond favouring the (*Z*)-isomer in a 91:9 ratio (Table 1, entry 1). The reaction conditions were applied to a number of *N*-tosyl imines derived from ethyl γ-aryl-β,γ-unsaturated α-keto esters **1b-k**, bearing either electron-donating or electron-withdrawing groups at the *ortho*, *metha* or *para* positions of the phenyl ring, and to an heteroaryl-substituted ester **1l**. The reaction provided the expected α,β-dehydroamino esters favouring the formation of the (*Z*)-isomers **3b-l** in all the examples studied, with diastereomeric ratios ranging from 85:15 to 99:1 (Table 1, entries 2-12). The methyl and isopropyl esters **1m** and **1n** gave similar results to ethyl ester **1a** (Table 1, entries 12-13).

Table 2. $Cu(OTf)_2$-catalysed Mukaiyama Michael addition of trimethylsilyl ketene acetal **2** to *N*-tosylimines of α-keto esters **1**.

Entry	**1**	Ar	R	Yield **3+4** (%)[b]	**3:4** (dr)[c]
1	**1a**	Ph	Et	95	3:97
2	**1b**	4-MeC_6H_4	Et	99	7:93
3	**1c**	4-$MeOC_6H_4$	Et	95	12:88
4	**1d**	3-$MeOC_6H_4$	Et	99	4:96
5	**1e**	2-$MeOC_6H_4$	Et	91	3:97
6	**1f**	4-ClC_6H_4	Et	99	6:94
7	**1g**	3-ClC_6H_4	Et	99	3:97
8	**1h**	2-ClC_6H_4	Et	99	1:99
9	**1i**	4-$NO_2C_6H_4$	Et	99	8:92
10	**1j**	3-$NO_2C_6H_4$	Et	99	6:94
11	**1k**	2-$NO_2C_6H_4$	Et	99	14:86
12	**1l**	2-furyl	Et	80	9:91
13	**1m**	Ph	Me	99	3:97
14	**1n**	Ph	*i*Pr	87	4:96

[a] **1** (0.25 mmol), **2** (0.6 mmol), $Cu(OTf)_2$ (0.025 mmol), CH_2Cl_2 (1.9 mL), rt, 20-90 min. [b] Yield of the diastereomer mixture after chromatography. [c] Determined by ^{1}H NMR

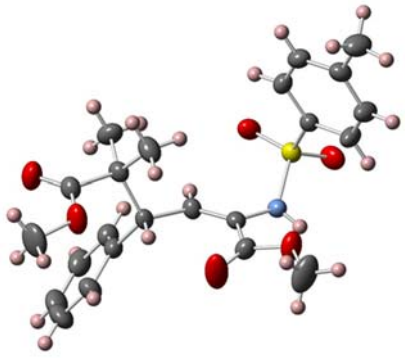


Fig. 2 Ortep plot for the X-ray structure of compound (*E*)-**4m** (copper catalysed reaction). The thermal ellipsoids are drawn at the 50% probability level.

On the other hand when the reaction between silyl ketene acetal **2** and imines **1a-n** was carried out in the presence of 10 mol % copper(II) triflate in dichloromethane at room temperature,§ a faster reaction took place to give the expected α,β-dehydroamino esters in high yield, favouring in these cases the formation of the (*E*)-isomers **4b-n** in all the examples studied (Table 2). In general, better yields and diastereoselectivities were observed for the copper-catalysed reaction compared with the non-catalysed reaction, with diastereomeric ratios (*Z*:*E*) above 10:90 in most of the cases.

Initial attempts to assign the *Z*/*E* configuration of the double bond in compounds **3** and **4** by ^{1}H NMR following spectroscopic criteria established by Mazurkiewicz et al.[21] for related *N*-acyl-α,β-dehydro-α-amino acid esters led to contradictory results (See supporting information). NOESY experiments were then carried out with samples of products

Table 3. Comparation of significative ^{1}H NMR chemical shifts for compounds (*Z*)-**3** and (*E*)-**4** (copper-catalysed reaction)[a]

Entry	3,4	Ar	R	δ_{NH} (*Z*)-**3**	δ_{NH} (*E*)-**4**	$\delta_{CH=C}$ (*Z*)-**3**	$\delta_{CH=C}$ (*E*)-**4**	δ_{ArCH} (*Z*)-**3**	δ_{ArCH} (*E*)-**4**
1	**a**	Ph	Et	6.20	6.61	7.31	7.01	4.41	4.81
2	**b**	4-MeC_6H_4	Et	6.14	6.58	7.29	6.97	4.35	4.77
3	**c**	4-MeOC_6H_4	Et	6.18	6.58	7.27	6.96	4.35	4.76
4	**d**	3-MeOC_6H_4	Et	6.18	6.59	7.27	6.97	4.37	4.79
5	**e**	2-MeOC_6H_4	Et	6.19	6.57	7.34	7.06	4.69	5.18
6	**f**	4-ClC_6H_4	Et	6.28	6.62	7.26	6.91	4.46	4.77
7	**g**	3-Cl-C_6H_4	Et	6.30	6.67	7.23	6.89	4.41	4.75
8	**h**	2-Cl -C_6H_4	Et	6.11	6.65	7.35	6.93	5.03	5.35
9	**i**	4-$NO_2C_6H_4$	Et	6.16	6.71	7.31	6.90	4.69	4.88
10	**j**	3-$NO_2C_6H_4$	Et	6.21	6.74	7.29	6.89	4.65	4.88
11	**k**	2-$NO_2C_6H_4$	Et	6.65	6.69	7.03	6.88	4.93	5.42
12	**l**	2-furyl	Et	6.40	6.71	7.04	6.69	4.56	5.04
13	**m**	Ph	Me	6.23	6.57	7.30	7.00	4.35	4.72
14	**n**	Ph	iPr	6.24	6.60	7.29	6.98	4.45	4.86

[a] ^{1}H NMR carried out in $CDCl_3$ at 300 MHz. δ values referenced to residual $CHCl_3$ (δ = 7.26 ppm).

3i and **4i**[§§] obtained under non-catalytic conditions and copper catalysis, respectively. NOESY experiments with compound **3i** showed a small interaction between the NH proton (δ 6.16 ppm) and the benzylic proton (δ 4.69 ppm), which indicated the possible *Z*-geometry for the double bond in this compound. No significative interactions were found however in NOESY experiments with the Cu-catalysed reaction product **4i**. On the other hand, suitable crystals for X-ray analysis of compound **4m** (copper-catalysed reaction) could be obtained which allowed us to establish the (*E*)-configuration for the double bond in this compound (Figure 2).[§§§] On the basis of these results and ^{1}H NMR characteristic chemical shifts (Table 3) we established that all compounds **3** resulting from the non-catalysed reaction have the (*Z*)-configuration at the double bond while this has the (*E*)-configuration for the copper-catalysed reaction products **4**. Thus in all the cases the olefinic hydrogens appear at higher field for the *E*-isomer ($\delta_{CH=}{}^{Z} > \delta_{CH=}{}^{E}$) while the N-H proton appears at higher field for the *Z*-isomer ($\delta_{NH}{}^{E} > \delta_{NH}{}^{Z}$). Similarly, the benzylic proton in the β-substituent also appears at higher field for the *Z*-isomer ($\delta_{ArCH}{}^{E} > \delta_{ArCH}{}^{Z}$).

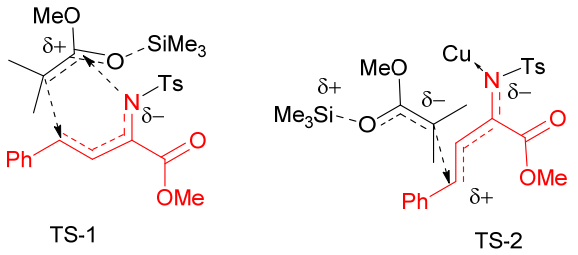


Fig. 3 TS for the Mukaiyama-Michael reaction. Non-catalysed (TS-1) and copper-catalysed (TS-2).

The results indicate that the unsaturated imine **1** adopts the s-*cis* conformation in the non-catalytic reaction while it prefers the s-*trans* conformation during the copper-catalysed reaction. Although a full explanation for this preference is not possible at this moment, our working hypothesis is that the non-catalysed reaction takes place through a cyclic Diels-Alder-like transition state (Fig. 3, TS-1) with the incipient negative charge on the nitrogen atom stabilizing the incipient positive charge at the acetal carbon, which is only possible in the s-*cis* conformation.[22] On the other hand, in the presence of copper triflate, coordination of the copper ion to the imine renders the substrate more electrophilic and the reaction takes place through an acyclic transition state (Fig. 3, TS-2) with the unsaturated imine having the s-*trans* conformation.[§§§§]

We are currently performing research addressed to study the scope of the reaction with other nucleophiles and mechanistic and theoretical studies which will be published conveniently.

Conclusions

We have developed a new procedure for the stereodivergent synthesis of *N*-Tosyl α,β-dehydroamino esters via a Mukaiyama-Michael addition. The reaction of silylketene acetals with *N*-tosylimines derived from β,γ-unsaturated α-keto esters provided the corresponding (*Z*)-α,β-dehydroamino esters. On the other hand, the (*E*)-isomers were obtained when the reaction was performed in the presence of a catalytic amount of copper triflate. This allows the stereoselective synthesis of (*E*)- or (*Z*)-α,β-dehydroamino esters from a same set of reactants, which has no precedents in the literature. We have also established a correlation between the ^{1}H NMR chemical shifts and the stereochemistry of the double bond in these compounds.

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Notes and references

‡ 2-Methyl-1-methoxy-1-trimethylsilyoxyprop-1-ene (**2**, 122 µL, 0.6 mmol) was added to a solution of imine **1** (0.25 mmol) in CH_2Cl_2 (1.2 mL) at rt under nitrogen atmosphere and the mixture was stirred overnight until the reaction was complete (20-24h). The reaction products were isolated by column chromatography on silica gel eluting with hexane/EtOAc mixtures.

§ A solution of imine **1** (0.25 mmol) in dry CH_2Cl_2 (1 mL) was added to a suspension of anhydrous $Cu(OTf)_2$ (9 mg, 0.025 mmol) in dry CH_2Cl_2 (0.9 mL) contained in a Schlenck tube under nitrogen at rt, followed by 2-methyl-1-methoxy-1-trimethylsilyoxyprop-1-ene (**2**, 122 µL, 0.6 mmol). The mixture was stirred until the reaction was complete (30-90 min). The reaction products were isolated by column chromatography on silica gel eluting with hexane/EtOAc mixtures.

§§ Compounds **3i** and **4i**, i.e. *p*-nitro derivatives, were used to avoid overlapping of ^{1}H NMR signals in the aromatic region.

§§§ CCDC 1442362

§§§§ X ray analysis of imine **1b** indicates the (*Z*)-geometry of the C=N bond and the preference of the s-*trans* conformation in the crystal structure (See S.I.). CCDC 1442206.

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