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An (*E*)-selective synthesis of trisubstituted (*E*)-α,β-unsaturated acid derivatives†

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Potassium alkoxides of *N*-acyloxazolidin-2-one derived *syn*-aldolates undergo a novel tandem intramolecular cyclisation elimination reaction to afford trisubstituted (*E*)-α,β-unsaturated amides in high d.e., which may be converted into their corresponding acids or oxazolines in good yield.

There are currently few general methods available for the diastereoselective synthesis of (*E*)-α,β-unsaturated acids/esters/amides that are substituted at both their α- and β-positions.[1] These types of trisubstituted α,β-unsaturated acid derivatives are important targets because they serve as versatile substrates for a wide range of synthetic methodology,[2] and for the construction of a wide range of natural products.[3,4] Previously, (*E*)-acid derivatives of this type have been prepared using Wittig,[3] or Horner–Emmons[4] methodology, however alternative diastereoselective protocols employing excess SmI_2[5] or $CrCl_2$[6] to effect the reductive elimination of α-halo-β-hydroxy-esters or amides have recently been described. We now report an alternative approach towards this class of acid fragment, that employs *syn*-β-hydroxy-*N*-acyloxazolidin-2-ones as substrates for a novel intramolecular cyclisation/elimination reaction to afford trisubstituted (*E*)-α,β-unsaturated amides in high d.e.

In the course of our synthetic studies we prepared nine racemic *syn*-aldolates **2a–i** in high d.e. *via* reaction of the boron enolates of *N*-acyloxazolidin-2-ones **1a–d** (**1a** R = Me; **1b** R = ^{i}Pr; **1c** R = Ph, **1d** R = $PhCH_2$–) with a series of aldehydes according to well established literature precedent.[7] It was found that treatment of these *syn*-aldolates **2a–h** with 1.5 equivalents of KHMDS in THF at −78 °C resulted in a clean elimination reaction to afford the corresponding α,β-unsaturated amides (*E*)-**3a–h** in 67–99% isolated yield, and in > 90% d.e.[8] in all cases.[9] It is noteworthy that this simple elimination methodology is general in scope, with linear and branched R-substituents being tolerated at the α-position of the *syn*-aldolates **2a–h**, and with aliphatic, unsaturated, and aromatic (neutral and electron rich) R_1-substituents being tolerated at the β-position (Scheme 1, Table 1). The only limitation of this methodology occurred during elimination of **2i** (R = Ph, R_1 = Et) which gave **3i** in a lower 47% isolated yield as a result of a competing *retro*-aldol reaction which gave (*N*-phenylacetyl)oxazolidin-2-one **1c** (R = Ph) and propionaldehyde (not isolated) as competing side-products in 32% yield.

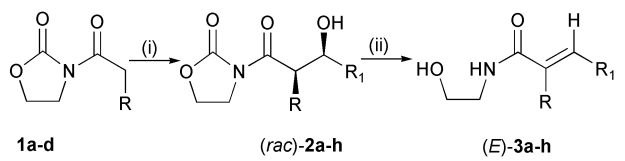
It is well known that sterically unhindered *N*-acyloxazolidin-2-ones can undergo endocyclic ring cleavage *via* either inter- or intramolecular attack of nucleophiles at their oxazolidin-2-one carbonyl groups.[10] Consequently, it was proposed that the high diastereoselectivities observed for the formation of (*E*)-α,β-unsaturated amides **3a–h** in this reaction could be explained by invoking an intramolecular endocyclic cleavage mechanism. Thus, potassium alkoxide **4** initially undergoes intramolecular attack at the oxazolidin-2-one carbonyl resulting in O–O carbonyl migration, to afford 1,3-oxazinane-2,4-dione alkoxide **5**. Subsequent anion equilibration of alkoxide **5** to enolate **6** would then enable stereoselective elimination of carbon dioxide to occur to afford the trisubstituted secondary amide (*E*)-**3** in high d.e. (Fig. 1).

It has been reported previously that reaction of the Zn enolate of α-bromo-*N*-acyl-oxazolidin-2-one **7** with benzaldehyde did not afford the expected aldolate product, but instead gave a mixture of rearranged 1,3-oxazinane-2,4-dione diastereoisomers **8** and **9** in good yield (Scheme 2).[11] Since this implied that Zn alkoxides of β-hydroxy-*N*-acyloxazolidin-2-ones underwent rearrangement to their corresponding 1,3-oxazinane-2,4-diones, we treated *syn*-aldolate **2f** with 10 mol% of Et_2Zn in CH_2Cl_2 at room temperature to cleanly afford its corresponding 1,3-oxazinane-2,4-dione **10** in 88% yield.[12] Subsequent treatment of **10** with KHMDS in THF at −78 °C gave (*E*)-**3f** in > 90% d.e., thus providing good evidence that the potassium alkoxide of

Table 1 Synthesis of (*E*)-α,β-unsaturated amides **3a–h**

Entry	Aldolate	R	R_1	Product	d.e.[a]	% Yield[b]
1	**2a**	Me	Ph	**3a**	> 95	89
2	**2b**	Me	Et	**3b**	> 95	67
3	**2c**	$PhCH_2$–	$Me(CH_2)_6$–	**3c**	92	99
4	**2d**	^{i}Pr	cyclohexyl	**3d**	93	76
5	**2e**	^{i}Pr	(*E*)-Ph(CH=CH)–	**3e**	> 95	95
6	**2f**	^{i}Pr	Et	**3f**	> 95	99
7	**2g**	^{i}Pr	Ph	**3g**	92	94
8	**2h**	^{i}Pr	*p*-MeOPh–	**3h**	90	79
9	**2i**	Ph	Et	**3i**	> 95	47

[a] All diastereoselectivities were determined *via* ^{1}H NMR spectroscopic analysis (300 MHz) of the crude reaction product. [b] Yields are for pure (*E*)-diastereoisomers isolated after chromatographic purification.



Scheme 1 *Reagents and conditions:* (i) 9-BBNTf, $^i Pr_2NEt$, CH_2Cl_2, 0 → −78 °C; R_1CHO, CH_2Cl_2; (ii) KHMDS (1.5 eq.), THF, −78 °C.

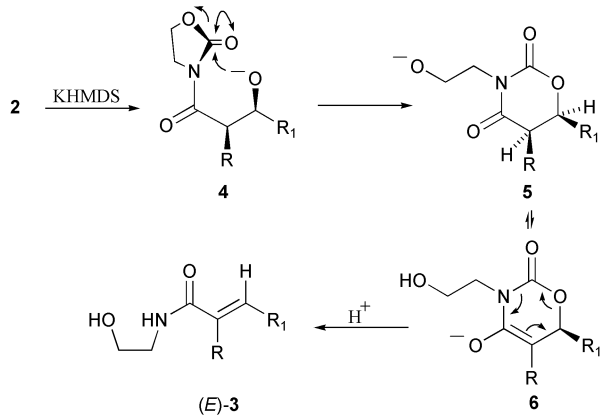


Fig. 1 Intramolecular cyclisation/elimination mechanism for the formation of (*E*)-α,β-unsaturated amides **3**.

† Electronic supplementary information (ESI) available: synthesis and spectroscopic details for compounds **3a** and **12a**. See http://www.rsc.org/suppdata/cc/b3/b304213h/

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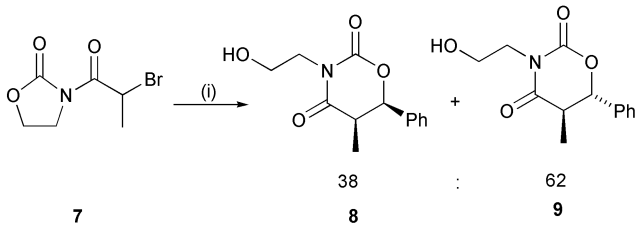
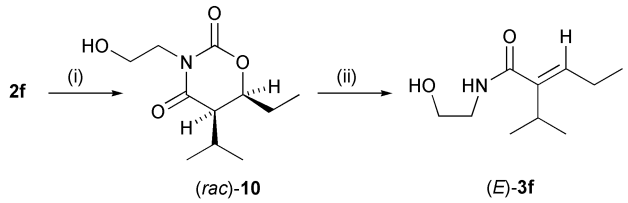


Scheme 2 *Reagents and conditions:* (i) Zn, THF, −78 °C, PhCHO.

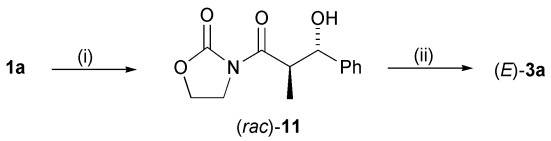


Scheme 3 *Reagents and conditions:* (i) Et_2Zn (10 mol%), CH_2Cl_2, 0 °C; (ii) KHMDS, THF, −78 °C.

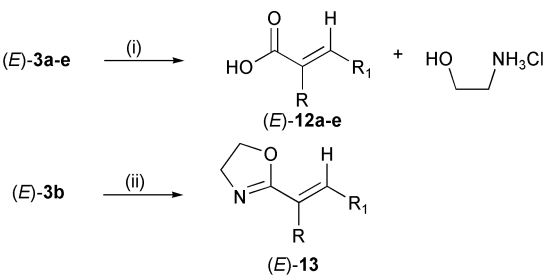
1,3-oxazinane-2,4-dione **5** is a key intermediate in controlling diastereoselectivity during stereoselective elimination of the potassium alkoxides of *syn*-aldolates **2a–h** (Scheme 3).

We next explored elimination of the corresponding *anti*-aldolate **11** which was prepared *via* treatment of **1a** with $MgCl_2$, TMSCl, Et_3N and benzaldehyde in EtOAc according to Evans' recently published procedure.[13] Treatment of *anti*-aldolate **11** with KHMDS in THF at −78 °C afforded amide (*E*)-**3a** in > 95% d.e. identical to that observed previously for elimination of *syn*-**2a** under the same conditions (Scheme 4). This is consistent with the key elimination step of both *syn*-**2a** and *anti*-**11** occurring *via* an E1cB-type mechanism, to afford a common enolate intermediate **6** that decomposes to afford α,β-unsaturated amide (*E*)-**3a** in high d.e.

In order to demonstrate the synthetic utility of this methodology, a range of diastereomerically pure trisubstituted secondary amides (*E*)-**3a–e** were hydrolysed to their parent acids **12a–e** by refluxing in 6 M HCl for two hours in 91–99% yield.† Importantly, no evidence of any products resulting from double bond migration were observed in the ^{1}H NMR spectra of the crude hydrolysis products of **3a–e** (Scheme 5, Table 2, entries 1–5).[14] The potential synthetic versatility of this methodology arising from the presence of the *N*-hydroxyalkyl substituent of α,β-unsaturated amides **3a–e** was also demonstrated *via*



Scheme 4 *Reagents and conditions:* (i) $MgCl_2$, Et_3N, TMSCl, PhCHO, EtOAc, rt; (ii) KHMDS, THF, −78 °C.



Scheme 5 *Reagents and conditions:* (i) 6 M HCl, Δ; (ii) $SOCl_2$, rt.

Table 2 Yields of (*E*)-α,β-unsaturated acids **12a–e** and (*E*)-oxazoline **13**

Entry	Amide	R	R_1	Product	% Yield
1	**3a**	Me	Ph	**12a**	99
2	**3b**	Me	Et	**12b**	91
3	**3c**	$PhCH_2$–	$Me(CH_2)_6$–	**12c**	99
4	**3d**	^{i}Pr	cyclohexyl	**12d**	99
5	**3e**	^{i}Pr	(*E*)-Ph(CH=CH)–	**12e**	99
6	**3b**	Me	Et	**13**	88

conversion of **3b** to its corresponding trisubstituted-α,β-unsaturated oxazoline (*E*)-**13** on treatment with thionyl chloride in 88% yield (Scheme 5, Table 2, entry 6).[15]

In conclusion, we have demonstrated that treatment of easily prepared *N*-acyloxazolidone-*syn*-aldolates with KHMDS affords an alkoxide intermediate which undergoes a stereoselective base mediated elimination reaction to afford trisubstituted (*E*)-α,β-unsaturated amides in high d.e.

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