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N-Acyl-5,5-dimethyl-oxazolidin-2-ones as latent aldehyde equivalents

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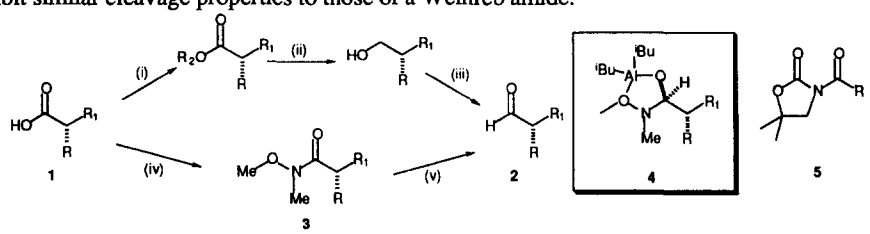
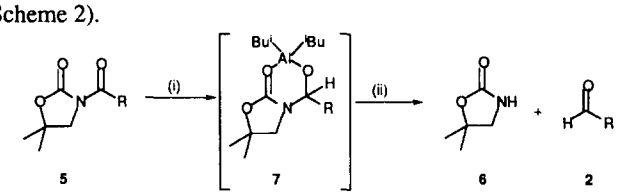
Abstract: *N*-acyl-5,5-dimethyl-oxazolidin-2-ones can function as versatile latent aldehyde equivalents - reductive cleavage with DIBAL-H affords aldehydes in good yield, while tandem DIBAL-H/Wittig methodology affords α,β-unsaturated esters. © 1999 Elsevier Science Ltd. All rights reserved.

The direct conversion of carboxylic acids which contain complex functionality to the corresponding aldehydes is a highly desirable synthetic transformation.[1] Currently, the two most popular ways of achieving this transformation are either *via* conversion of the acid **1** to an ester, reduction to its parent alcohol, followed by Swern oxidation to aldehyde **2**; or *via* conversion of the parent acid **1** to Weinreb amide **3** followed by reduction with DIBAL-H at low temperature (Scheme 1).[2] Since it is generally accepted that the reductive cleavage properties of Weinreb amides **3** arise from their ability to form chelated intermediates such as **4**, which decompose only on hydrolytic work-up, we reasoned that a suitably configured *N*-acyloxazolidin-2-one **5** would exhibit similar cleavage properties to those of a Weinreb amide.[3]



Scheme 1. *Reagents and Conditions:* (i) $SOCl_2$, MeOH; (ii) $LiAlH_4$, Et_2O; (iii) $COCl_2$, DMSO, NEt_3, CH_2Cl_2; (iv) $AlMe_3$, MeONHMe.HCl, CH_2Cl_2; (v) DIBAL-H, THF, -78°C.

The parent oxazolidin-2-one **6** was chosen as a suitable latent aldehyde equivalent primarily because attack at the oxazolidin-2-one carbonyl of **5** by DIBAL-H would be suppressed by the 5,5-*gem*-dimethyl groups, which block the trajectory of any incipient nucleophile.[4] It was also thought that a lone-pair of the oxazolidin-2-one carbonyl of **5** would have the capacity to stabilise the tetrahedral intermediate **7** arising from reduction of the *N*-acyl carbonyl of **5** (Scheme 2).



Scheme 2. *Reagents and Conditions* (i) DIBAL-H, THF, -78°C; (ii) aqueous work-up.

The parent oxazolidin-2-one **6** was prepared in 3 steps in 74% yield from glycine methyl ester according to our recently described protocol for the synthesis of the SuperQuat family of chiral auxiliaries (Scheme 3).[4] Deprotonation of oxazolidin-2-one **6** *via* treatment with *n*-BuLi in THF at -78°C, followed by reaction with the appropriate acid chloride afforded a range of *N*-acyloxazolidin-2-ones **5a-e** in good yield. Reduction of *N*-acyloxazolidin-2-ones **5a-b** and **5e** with 2 equivalents of DIBAL-H in CH_2Cl_2 at -78°C, followed by aqueous workup with saturated NH_4Cl solution, did not, however, afford the desired aldehydes **2a-b** and **5e** directly, but surprisingly gave the corresponding oxazolidin-2-one derived *N*-(1-hydroxyalkyl)oxazolidin-2-ones **8a-b** and **8e** in fair to good yield (Scheme 3, Table 1). The isolation of these *N*-(1-hydroxyalkyl)oxazolidin-2-ones

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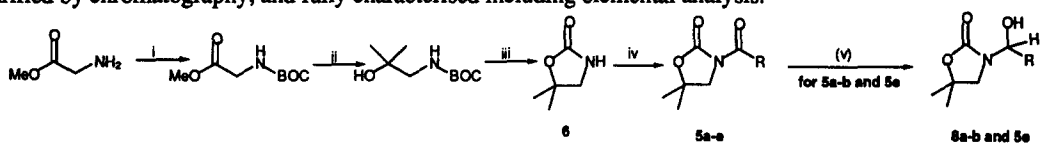
8a-b and **8e** provides compelling evidence of the kinetic stability of species such as **7** under the reaction conditions in preventing further reduction of these systems by DIBAL-H. Although these *N*-(1-hydroxyalkyl) derivatives were rather sensitive to decomposition, *N*-(1-hydroxydihydrocinnamyl)oxazolidin-2-one **8a** could be purified by chromatography, and fully characterised including elemental analysis.

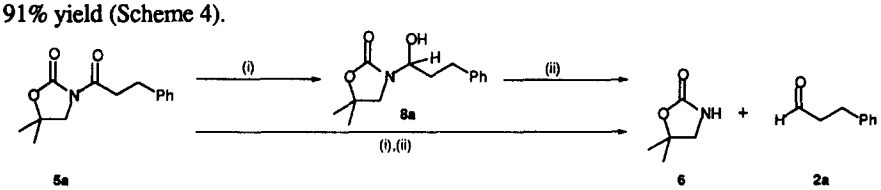


Scheme 3: *Reagents and Conditions:* (i) Boc_2O, K_2CO_3, MeOH; (ii) 4 equivs MeMgBr, THF; (iii) *t*-BuOK, THF; (iv) *n*-BuLi, RCOCl, THF; (v) DIBAL-H, CH_2Cl_2, -78°C.

R	*N*-Acyl oxazolidin-2-one	% Yield	*N*-(1-hydroxyalkyl) oxazolidin-2-ones	% Yield
$PhCH_2CH_2$-	**5a**	84%	**8a**	79%
$CH_3CH_2CH_2$-	**5b**	88%	**8b**	94%
CH_2=$CHCH_2$-	**5c**	97%	--	--
$(CH_3)_2CHCH_2$-	**5d**	62%	--	--
^{t}Bu-CH_2CH_2-	**5e**	93%	**8e**	59%

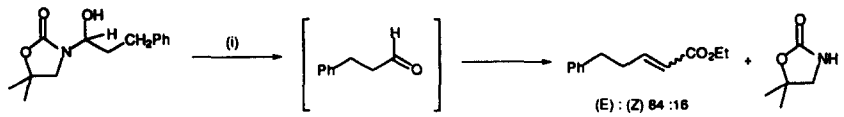
Table 1: Yields for acylations of **6** and DIBAL-H reduction of *N*-acyloxazolidin-2-ones **5a-b** and **5e**.

Treatment of *N*-(1-hydroxydihydrocinnamyl)oxazolidin-2-one **8a** with a range of bases resulted in decomposition to give a complex mixture of products, including a low yield of the desired aldehyde **2a**. Since aldehydes such as **2a** are often unstable under basic conditions as a result of aldol type reaction processes, the synthetic protocol was modified to trap aldehyde **2a** *in situ*, *via* formation of an intermediate bisulfite adduct. Therefore, treatment of *N*-(1-hydroxydihydrocinnamyl)oxazolidin-2-ones **8a** with sodium hydroxide (adjusted to pH 9.0) in the presence of sodium hydrogen sulphate gave, after chromatography, aldehyde **2a** in 91% yield. This procedure was incorporated into a 'one-pot' procedure where consecutive treatment of **5a** with DIBAL-H in CH_2Cl_2 at -78°C, followed immediately by alkaline hydrolysis with $NaOH/NaHSO_3$ afforded aldehyde **2a** in an overall 91% yield (Scheme 4).



Scheme 4: *Reagents and Conditions:* (i) DIBAL-H, THF, -78°C; (ii) NaOH, $NaHSO_3$.

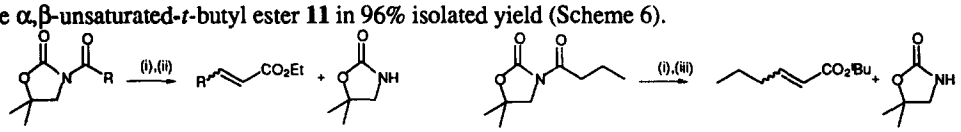
Since aldehydes such as **2a** are normally generated as synthetic intermediates, a tandem DIBAL-H/Wittig strategy for the deployment of *N*-acyloxazolidin-2-ones **5a-d** to α,β-unsaturated esters was also developed. It was reasoned that deploying the lithium anion of a phosphonate such as **9a** to deprotonate *N*-(1-hydroxydihydrocinnamyl)oxazolidin-2-one **8a**, would afford aldehyde **2a**, which would be immediately trapped *in situ* by excess **9a** to afford α,β-unsaturated ester **10a**.[5] Thus, treatment of **8a** with 2.5 equivalents of **9a** gave a mixture of the parent oxazolidin-2-one **6** and the chromatographically separable (*E*)- and (*Z*)-α,β-unsaturated esters **10a** in 70% yield.[6] The yield obtained and the *E*-:*Z*- ratio of 87:13 for ester **10a** were identical to those observed for reaction of the parent aldehyde **2a** with **9a** (Scheme 5)



8a 2a 10a 6

Scheme 5: *Reagents and Conditions:* (i) $EtO_2CCH(Li)PO(OEt)_2$ **9a** (2.5eq), THF, -78°C.

Having demonstrated the feasibility of the DIBAL-H/Wittig methodology for the preparation of α,β-unsaturated ester **10a**, a 'one-pot' protocol involving sequential treatment of *N*-acyloxazolidin-2-ones **5a-d** with DIBAL-H and **9a** to afford α,β–unsaturated esters **10a-d** in an overall 45-69% yield (Scheme 6, Table 2) was developed. ^{1}H NMR spectroscopic analysis of the crude reaction mixtures arising from these reactions, in conjunction with losses in mass balance during purification, led us to believe that the moderate yields obtained for pure ethyl esters **10a-10d** were a result of their volatility. As a result the tandem DIBAL-H/Wittig protocol was repeated on *N*-acyloxazolidin-2-one **5b** using the lithium anion of *t*-butyl dimethylphosphonoacetate **9b** to afford the less volatile α,β-unsaturated-*t*-butyl ester **11** in 96% isolated yield (Scheme 6).



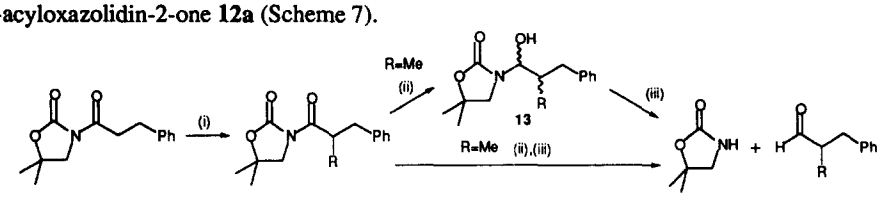
5a-d 10a-d 6 5b 11 6

Scheme 6: *Reagents and Conditions:* (i) DIBAL-H, THF, -78°C; (ii) $EtO_2CCH(Li)PO(OEt)_2$ **9a** (2.5eq); (iii) $^tBuO_2CCH(Li)PO(OMe)_2$ **9b** (2.5eq).

5	R	Phosphonate	α,β-unsaturated ester	Yield	(E):(Z) ratio
a	$PhCH_2CH_2$-	9a	10a	70%	87:13
b	$CH_3CH_2CH_2$-	9a	10b	45%	95:5
c	CH_2=$CHCH_2$-	9a	10c	69%	91:9
d	$(CH_3)_2CHCH_2$-	9a	10d	51%	92:8
b	$CH_3CH_2CH_2$-	9b	11	96%	84:16

Table 2: Yields of esters **10a-d** and **11** from tandem *in situ* DIBAL-H/Wittig reaction of *N*-acyloxazolidin-2-ones **5a-d**

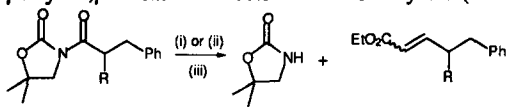
Latent aldehyde equivalents which are compatible with enolate methodologies, which Weinreb amides are not, provide a particularly useful synthetic methodology. Thus, treatment of the dihydrocinnamoyl derived *N*-acyloxazolidin-2-one **5a** with LHMDS in THF followed by either methyl iodide or allyl bromide afforded the α-substituted products **12a** and **12b** in good yield. Treatment of **12a** with DIBAL-H in CH_2Cl_2 at -78°C gave a stable, diastereomeric mixture (3:1) of *N*-(1-hydroxyalkyl)oxazolidin-2-ones **13**. Treatment of this mixture of *N*-(1-hydroxyalkyl)oxazolidin-2-ones **13** with NaOH/$NaHSO_3$ afforded the desired aldehyde **14** in 91% isolated yield. The corresponding 'one pot' procedure afforded aldehyde **14** in 83% yield directly from α-methyl-*N*-acyloxazolidin-2-one **12a** (Scheme 7).



5a 12a R=Me 12b R=allyl 6 14

Scheme 7: *Reagents and Conditions:* (i) LHMDS, MeI or allyl bromide, THF, 0°C; (ii) DIBAL-H, CH_2Cl_2, -78°C; (iii) NaOH, $NaHSO_3$.

When the tandem DIBAL-H/Wittig reaction was repeated using **12a** as a substrate, the corresponding α,β-unsaturated ester **15a** (*E*:*Z* ratio 4:1) was isolated in 71% yield. Treatment of the α-allylated *N*-acyloxazolidin-2-one **12b** under these conditions afforded only recovered starting material with no evidence of any of the desired α,β-unsaturated ester **15b**. The sluggishness of **12b** towards reduction with DIBAL-H was overcome by increasing its reactivity *via* precoordination of **12b** with the Lewis acid $ZnCl_2$, which facilitated the reduction process to afford the desired γ-allyl-α,β-unsaturated ester **15b** in 82% yield (*E*:*Z* ratio 3:1) (Scheme 8).



12a or 12b 6 15a R=Me, conditions (i)
15b R-Allyl, conditions (ii)

Scheme 8: *Reagents and Conditions:* (i) DIBAL-H, THF, 0°C; (ii) $ZnCl_2$; DIBAL-H, THF, -30°C; (iii) $EtO_2CCH(Li)PO(OEt)_2$ **9a**.

In conclusion, we have demonstrated that *N*-acyl-5,5-dimethyl-oxazolidin-2-ones **5** can function as versatile latent aldehyde equivalents. Unlike the corresponding Weinreb amides, enolates derived from *N*-acyloxazolidin-2-ones can be usefully deployed in alkylation reactions. Reductive cleavage of these substrates with DIBAL-H in CH_2Cl_2 in the presence of alkaline $NaHSO_3$ affords aldehydes, while tandem DIBAL-H/Wittig methodology allows direct access to α,β-unsaturated esters **10** and **15**.

Acknowledgements. Financial support by Zeneca Pharmaceuticals (HJS) and the Catalonian Government (JB) is gratefully acknowledged.

References.

1. (a) Evans, D. A.; Ng, H. P. *Tetrahedron Lett.*, 1993, **34**, 14, 2229; (b) Hori, K.; Hikage, N.; Inagaki, A.; Mori, S.; Nomura, K.; Yoshii, E. *J. Org. Chem.* 1992, **57**, 2888; (c) Evans, D. A.; Polniaszek, R. P.; DeVries, K. M.; Guinn, D. E.; Mahre, D. J. *J. Am. Chem. Soc.*, 1991, **113**, 7613; (d) Andersen, M. W.; Hildebrandt, B.; Dahmann, G.; Hoffmann, R. W. *Chem. Ber.*, 1991, **124**, 2127; (e) Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.*, 1990, **112**, 2998.

2. For leading references see Larock, R. C. *Comprehensive Organic Transformations*, VCH: New York, 1989; Chandrasekar, S.; Kumar, M. S.; Muralidhar, B. *Tetrahedron. Lett.*, 1998, **39**, 909; Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.*, 1981, **22**, 39, 3815; Sibi, M. P. *Org. Prep. Proced. Int.*, 1993, **25**, 15; Mentzel, M.; Hoffman, H. M. R. *J. Prakt. Chem.*, 1997, **339**, 517

3. While oxazolidin-2-thiones have been shown to exhibit the cleavage properties of Weinreb amides, to the best of our knowledge there are no reports on the use of oxazolidin-2-ones to this end. (a) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fusita, E. *J. Org. Chem.*, 1986, **51**, 2391; (b) Izawa, T.; Mukaiyama, T.; *Bull. Chem. Soc. Jpn.*, 1979, **52**, 2, 555.

4.(a) Bull, S. D.; Davies, S. G.; Jones, S.; Sanganee, H. J. *J. Chem. Soc. Perkin Trans.1*, 1999, 387 (b). Bull, S. D.; Davies, S. G.; Jones, S.; Polywka, M. E. C.; Prasad, R. S.; Sanganee, H. J. *Synlett*, 1998, 519; (c) Davies, S. G.; Sanganee H. J. *Tetrahedron : Asymmetry*, 1995, **6**, 671.

5. Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler R. *J. Am. Chem. Soc.*, 1990, **112**, 5290.

6. All (*E*:*Z*) mixtures of α,β-unsaturated esters were determined by ^1H (400MHz) NMR spectroscopic analysis of the crude reaction mixture and could easily be separated to homogeneity by column chromatography.