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Synthesis of β,γ-Unsaturated *N*-Acyl-2-Oxazolidinones

Alicia Dobarro, Dolores Velasco*

Departament de Química Orgànica, Facultat de Química, Universitat de Barcelona
Martí i Franquès 1-11, E-08028 Barcelona (Spain).

Abstract: An effective imide formation method is presented, which allows the preparation of β,γ–unsaturated *N*-acyl-2-oxazolidinones with high yields and without isomerization of the double bond to give the α,β-unsaturated isomers, which are the inevitable by-products when alternative procedures are used. Copyright © 1996 Published by Elsevier Science Ltd

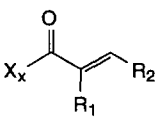
INTRODUCTION

Chiral oxazolidinones have attracted much attention since the pioneering works of Evans.[1] *N*-acyl-2-oxazolidinones have been used extensively as chiral auxiliaries in a wide variety of processes of asymmetric synthesis, like alkylations,[1] acylations,[2] aldol condensations,[3] Diels-Alder reactions[4] and 1,4-conjugated addition reactions.[5] Due to the wide application of *N*-acyl-2-oxazolidinones, their synthesis has been the subject of detailed studies. Whereas the preparation of 2-oxazolidinones has been optimized, the success of the procedures reported for *N*-acyl-2-oxazolidinones depends on the nature of the acyl part. The general procedure that Evans[4,6] reported for *N*-acyl-2-oxazolidinone derivatives is to treat the 2-oxazolidinones with n-butyllithium and the appropriate acid chlorides to afford the *N*-acyl-2-oxazolidinones in 85-100% isolated yields. However, this procedure failed[7] in the preparation of the acryloyl derivatives, due to their propensity to polymerize under these conditions. A recent paper[7] describes another method for the acylation of 2-oxazolidinones, by reacting the acid anhydride in the presence of lithium chloride using triethylamine as the base, to yield *N*-acyl-2-oxazolidinones in 84-93%. The authors report that acryloyl derivatives and other saturated or α,β-unsaturated acyl derivatives can be obtained in good yields. However, our own experiments show that none of these conditions provides a synthetic route for the preparation of *N*-acyl-2-oxazolidinones if the acyl part is β,γ-unsaturated.

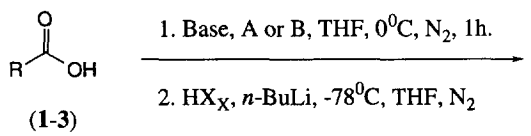
RESULTS AND DISCUSSION

When we apply the two above mentioned procedures, the one reported by Evans[4,6] and the one with the presence of lithium chloride,[7] to synthesize *N*-acyl-2-oxazolidinones from α,β-unsaturated carboxylic acids the expected *N*-acyl-2-oxazolidinones were afforded but with null or low yield due to the observed isomerization of the double bond to give the conjugated systems. This is the case with the condensation of vinylacetic acid in the presence of LiCl. The main product was not the expected *N*-acyl-2-oxazolidinone but the respective α,β–isomerizised product, only in scarce yield. In order to resolve this problem we have developed an alternative

procedure. As shown in scheme 1, the acylation is produce by the mixed anhydride previously formed from the desired acid and pivaloyl chloride. In some cases isobutyl chloroformate was used instead of pivaloyl chloride. The most appropiate activating agent should be determined in each particular case, as the regioselectivity in the attack of the conjugate base of the oxazolidinone to the mixed anhydride was found to depend on the acid.



(**7**): R_1=R_2= H; X_X= X_P
(**8**): R_1= CH_3; R_2= CH_3; X_X= X_P



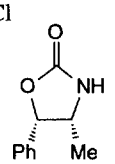
(**1-3**)

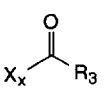
1. Base, A or B, THF, 0^0C, N_2, 1h.
2. HX_X, *n*-BuLi, -78^0C, THF, N_2

(**1**): R= $CH_2CH=CH_2$
(**2**): R= $CH(CH_3)CH=CH_2$
(**3**): R= $CH=CH_2$

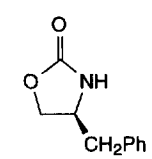
(**4**): R_1= H; X_X= X_P
(**5*R***): R_1= CH_3; X_X= X_P; 2'*R*
(**5*S***): R_1= CH_3; X_X= X_P; 2'*S*
(**6*R***): R_1= CH_3; X_X= X_N; 2'*R*
(**6*S***): R_1= CH_3; X_X= X_N; 2'*S*

A= ^{t}BuCOCl
B= ^{i}BuOCOCl

HX_X= HX_N= 



(**9**): R_3=O^{i}Bu; X_X= X_P
(**10**): R_3=^{t}Bu; X_X= X_P

HX_X= HX_P= 

Scheme 1

The use of *N*-methylmorpholine as the base in the acylation process is critical. When other bases such as triethylamine were used, some isomerization to the conjugated systems (Entries 3, 4 Table 1) was detected. Moreover, as reported elsewhere in the classical synthesis of peptides, *N*-methylmorpholine prevents racemization of chiral aminoacids during acylation using mixed anhydrides. With the acylation procedure reported here not only is double-bond isomerization inhibited, but racemization at the α-chiral position to the carbonyl center is also totally prevented. To demonstrate the generality of this procedure, two 2-oxazolidinones were used,

that were derived from (*S*)-phenylalanine and (1*S*-2*R*)-norephedrine (Entries 5, 6 Table 1). In both cases the expected β,γ-unsaturated *N*-acyl-2-oxazolidinone was obtained in high yield. The acryloyl derivative (**7**) was also obtained in good yield under these new conditions, and polymerization products were not observed (Entry 8 Table 1).

Table 1. Experimental Conditions and Results.

Entry	auxiliary	carboxylic acid	activating agent	base	yield% (comp) *N*-acyl	α,β-isomer	by-prod.
1	HX_P	**1**	isobutyl chloroformate	NMM	53 (**4**)	-	40 (**9**)
2	HX_P	**1**	pivaloyl chloride	NMM	93 (**4**)	-	-
3	HX_P	**2**	pivaloyl chloride	TEA	46 (**5**)	35.7 (**8**)	17.5 (**10**)
4	HX_P	**2**	isobutyl chloroformate	TEA	0 (**5**)	100 (**8**)	-
5	HX_P	**2**	isobutyl chloroformate	NMM	92 (**5**)	-	-
6	HX_N	**2**	isobutyl chloroformate	NMM	91(**6**)	-	-
7	HX_P	**3**	isobutyl chloroformate	NMM	51(**7**)	-	43(**9**)
8	HX_P	**3**	pivaloyl chloride	NMM	93 (**7**)	-	-

As a general procedure, the mixed anhydride was formed by reaction of the required acid in the presence of *N*-methylmorpholine at 0^0C with an acyl chloride in dry THF under N_2 atmosphere. After 1 hour the conjugate base of the appropriate oxazolidinone was added to the anhydride solution at -78^0C. The acylation was completed after warming the reaction mixture to room temperature for 4 hours, yielding the expected products, (Table 1). All products were characterizised by spectroscopic methods and their specific rotatory power was also determined (Table 2).

Table 2. Characterization of *N*-Acyl-2-Oxazolidinones

compound	m.p. (^{0}C)	$[\alpha]_D$ (c)[a]
4	oil	67.80 (1.36)
5 (R)	73-74	97.75 (1.13)
5 (S)	oil	128.35 (1.17)
6 (R)	69.5-70.5	9.20 (1.39)
6 (S)	oil	60.77 (1.60)
7	72-73	80.70 (1.01)
8	82.5-83.5	79.58 (1.19)
9	oil	30.50 (1.47)
10	87-88	42.29 (1.17)

[a]All were measured as a trichloromethane solution at 20^{0}C except **5** and **6** which were measured as ethanol solutions.

In summary, the one-pot acylation procedure presented here constitutes a useful route when *N*-acyl-2-oxazolidinones β,γ-unsaturated and *N*-acyl-2-oxazolidinones α-chiral β,γ-unsaturated are required. The mild reaction conditions prevent the racemization at the α-carbon and the isomerization processes of the double bond during the acylation reaction. The desired *N*-acyl-2-oxazolidinones β,γ-unsaturated were obtained with good yield and high optical purity.

EXPERIMENTAL

The identities of the known compounds were confirmed by comparison of the ^{1}H NMR spectra with those in literature. All solvents and reagents were purchased from commercial sources and used as received, unless otherwise indicated. Tetrahydrofuran was distilled after heating under reflux over sodium in the presence of benzophenone immediately before use. Flash chromatography was carried out on E. Merck Kieselgel 60 (230-400 mesh). Melting points are uncorrected. ^{1}H NMR spectra were recorded at room temperature in $CDCl_3$ solution on a Varian Gemini 200 spectrometer (d in ppm referred to Me_4Si). Mass spectra were measured on a Hewlett-Packard 5988-A spectrometer. Gas chromatographic system: Hewlett Packard 5890, column SE-54 (25m x 0.20mm ID), mobile phase: He (150 Kpa).

Acylation of 2-oxazolidinones. General procedure.

The mixed anhydride was formed by reaction of the required acid (1.2 eq.) in the presence of *N*-methylmorpholine (1.2 eq.) at 0°C with pivaloyl chloride (or isobutyl chloroformate) (1.2 eq.) in dry THF under N_2 atmosphere and then stirred for 1 hour at -78°C. Simultaneously the oxazolidinone (1 eq.) was treated with n-BuLi (1 eq.) at -78°C for 30 minutes in dry THF under N_2 atmosphere and added to the anhydride solution. After 1 hour at -78°C the reaction mixture was warmed to room temperature for 4 hours, yielding the expected products, (Table 1). The reaction was monitored by TLC and quenched by the addition of a saturated aqueous solution of NH_4Cl. All products were isolated and purified by flash chromatography on silica gel with CH_2Cl_2 as eluent, except for the diastereoisomers (**5**) and (**6**), for which a mixture CH_2Cl_2/hexane/EtOAc 5.6:4.0:0.4 was used.[8]

(4S)-3-(3-Butenoyl)-4-(phenylmethyl)-2-oxazolidinone (4).

Oxazolidinone HX_p (177 mg, 1 mmol) was acylated with the mixed anhydride formed from vinylacetic acid and pivaloyl chloride using the method described above to give (**4**) (227 mg, 93%), (Entry 2, Table 1).

When isobutyl chloroformate was used as activating agent 53% of (**4**) was isolated and 40% of the compound (**9**) was obtained as by-product (Entry 1, Table 1).

(**4**): ^{1}H NMR: δ 7.25 (m, 5H), 6.01 (m, 1H), 5.24 (m, 2H), 4.67 (m, 1H), 4.18 (m, 2H), 3.73 (t, 2H, J = 5.7 Hz), 3.30 (dd, 1H, J = 3.3, 13 Hz), 2.77 (dd, 1H, J = 9.6, 13 Hz).

(**9**), *4S)-3-(carboisobutyloxi)-4-(phenylmethyl)-2-oxazolidinone* .

^{1}H NMR: δ 7.25 (m, 5H), 4.51 (m, 1H), 4.12 (m, 4H), 3.37 (dd, 1H, J = 3.3, 13 Hz), 2.81 (dd, 1H, J = 9.6, 13Hz), 2.01 (m, 1H), 1.02 (d, 6H, J = 7.4 Hz). EM-EI (m/z): 277 ($M^{+\cdot}$, 5%), 221 (M-C_4H_8, 18%), 177 (M-$C_5H_8O_2$, 5%).

*(4S)-3-(2-Methyl-3-butenoyl)-4-(phenylmethyl)-2-oxazolidinone (**5**).*

Oxazolidinone HX_P (177 mg, 1 mmol) was acylated with the mixed anhydride formed from 2-methyl-3-butenoic acid and isobutyl chloroformate following the method described above. NMM was used as base to give (**5**) (238 mg, 92%), (Entry 5, Table 1). The diastereoisomers (**5*R***) and (**5*S***) were separated by flash cromatography using CH_2Cl_2/hexane/EtOAc 5.6:4.0:0.4 as eluent.

When pivaloyl choride was used as acylating agent and TEA as base, only 46% of the product (**5**) was obtained. Under these conditions the by-products (**8**) (97 mg, 35.7%) and (**10**) (45.5 mg, 17.5%) were also obtained, (Entry 3, Table 1).

When isobutyl chloroformate was used as acylating agent and TEA as base, only the by-product **8** was obtained quantitatively, (Entry 4, Table 1).

(**5*S***): ^{1}H NMR: 7.2-7.4 (m, 5H), 5.98 (m, 1H), 5.17 (m, 2H), 4.66 (ddt, 1H, *J* =9.6 Hz, 6.6 Hz, 3.3 Hz), 4.46 (q, 1H, *J* = 6.9 Hz), 4.18 (m, 2), 3.28 (dd, 1H, *J* =13 Hz, 3.3 Hz), 2.78 (dd, 1H, *J* =13 Hz, 9.6 Hz), 1.34 (d, 3H, *J* = 6.9 Hz). EM-CI-NH_3 (m/z): 294 (M+35, 8%), 277 (M+18, 100%), 260 (M+1, 10%).

(**5*R***): ^{1}H NMR: 7.2-7.4 (m, 5H), 5.98 (m, 1H), 5.17 (m, 2H), 4.66 (ddt, 1H, *J* =9.6 Hz, 6.6 Hz, 3.3 Hz), 4.48 (q, 1H, *J* = 6.9 Hz), 4.18 (m, 2), 3.23 (dd, 1H, *J* = 13 Hz, 3.3 Hz), 2.74 (dd, 1H, *J* = 13 Hz, 9.6 Hz), 1.30 (d, 3H, *J* = 6.9 Hz).

(**8**), *(4S)-3-(2-Methyl-2-butenoyl)-4-(phenylmethyl)-2-oxazolidinone.*

^{1}H NMR: δ 7.25 (m, 5H), 6.21 (q, 1H, *J* = 8 Hz), 4.67 (m, 1H), 4.18 (m, 2H), 3.35 (dd, 1H, *J* = 3.3, 13 Hz), 2.81 (dd, 1H, *J* = 9.6, 13 Hz), 1.90 (s, 3H), 1.80 (d, 3H, *J* = 8 Hz). EM-EI (m/z): 259 ($M^{+\cdot}$, 27%), 244 (M-CH_3, 69%), 168 (244-Ph, 16%). EM-CI-NH_3 (m/z): 294 (M+35, 5%), 277 (M+18, 100%), 259 ($M^{+\cdot}$, 18%).

(**10**), *(4S)-3-(2,2-Dimethyl-propionyl)-4-(phenylmethyl)-2-oxazolidinone.*

^{1}H NMR: δ 7.25 (m, 5H), 4.69 (m, 1H), 4.16 (m, 2H), 3.21 (dd, 1H, *J* = 3.3, 13 Hz), 2.75 (dd, *J* = 9.6, 13 Hz), 1.40 (s, 9H). EM-EI (m/z): 261 ($M^{+\cdot}$, 16%), 246 (M-CH_3, 1%), 204 (M-C_4H_9, 19%).

*(4R,5S)-3-(2-Methyl-3-butenoyl)-4-methyl-5-phenyl-2-oxazolidinone (**6**).*

Oxazolidinone HX_N (1.120 g, 6.32 mmol) was acylated with the mixed anhydride formed from 2-methyl-3-butenoic acid and isobutyl chloroformate following the method described above. NMM was used as base to give (**6**) (1.490 g, 91%), (Entry 6, Table 1). The diastereoisomers (**6*R***) and (**6*S***) were separated by flash cromatography using CH_2Cl_2/hexane/EtOAc 5.6:4.0:0.4 as eluent.

(**6*R***): ^{1}H NMR: δ 7.2-7.5 ppm (m, 5H), 5.98 (m, 1H), 5.66 (d, 1H, J = 7.2 Hz), 5.18 (m, 2H), 4.74 (dq, 1H, J =7.2 Hz, 6.6Hz), 4.48 (m, 1H), 1.31 (d, 3H, J = 6.9 Hz), δ 0.90 (d, 3H, J = 6.6 Hz).

(**6*S***): ^{1}H NMR : δ 7.2-7.5 ppm (m, 5H), 6.00 (m, 1H), 5.67 (d, 1H, J = 7.2 Hz), 5.18 (m, 2H), 4.79 (q, 1H, J = 6.6Hz), 4.48 (q, 1H J = 7.0 Hz), 1.31 (d, 3H, J = 7.0 Hz), δ 0.87 (d, 3H, J = 6.6 Hz).

*(4S)-3-Propenoyl-4-(phenylmethyl)-2-oxazolidinone (**7**)* [7]

Oxazolidinone HX_P (177 mg, 1 mmol) was converted to (**7**) using the method described above (215 mg, 93%), (Entry 8, Table 1).

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8. The purity of two diastereomeric products was monitored by G.C. Retention time for products (**5*R***), (**5*S***), (**6*R***) and (**6*S***) are respectively: t_1, 17.5 min; t_2, 17.8 min t_3, 40.9 min; t_4, 41.8 min. Gas chromatographic system: Hewlett Packard 5890; column: SE-54 (25m x 0.20mm ID); mobile phase: He (23 psi); temperature: 200°C (isotherm) for products (**5*R***) and (**5*S***); T_i=170°C, t_i=45 min.,T_f=200°C, ΔT=5°C/min. for products (**6*R***) and (**6*S***).

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