Lithium-Initiated Imide Formation. A Simple Method for N-Acylation of 2-Oxazolidinones and Bornane-2,10-Sultam

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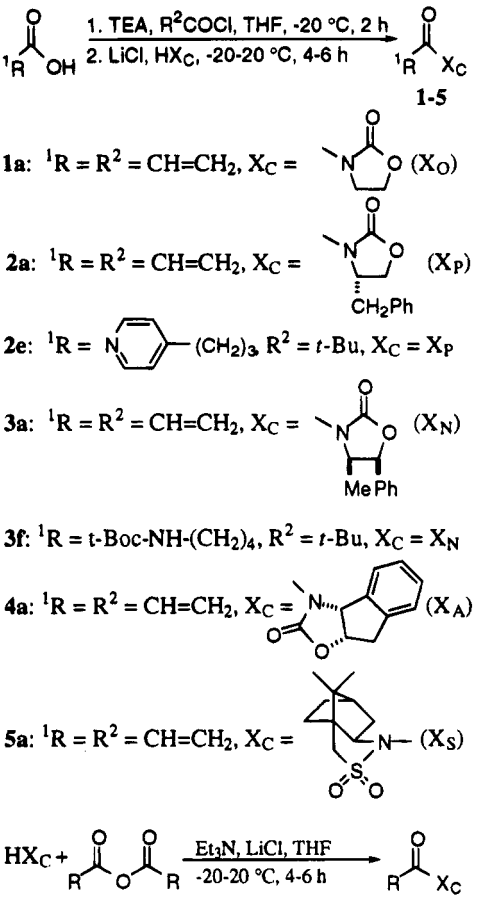
Chiral oxazolidinones have been extensively used as auxiliaries in asymmetric synthesis. As shown by the pioneering work of Evans, *N*-acyl-2-oxazolidinones have remarkable diastereoselectivity in alkylation,[1] acylation,[2] aldol condensation,[3] and the Diels–Alder reaction.[4] Traditionally, these *N*-acyloxazolidinone derivatives were prepared by lithiating the oxazolidinone with *n*-butyllithium at −78 °C, followed by acylation with an acyl chloride or an acid anhydride.[5] This procedure failed in the preparation of the acryloyl derivatives, an important class of dienophiles in asymmetric Diels–Alder reactions. Alternative methods were used to afford the acryloyloxazolidinones in moderate yields.[4,6] Similar to Evans' work, Oppolzer has used the camphor derivative, bornane-2,10-sultam, as the chiral auxiliary in asymmetric synthesis,[7] but again the preparation of the acryloyl derivative was still difficult and low yields were reported.[8] Recently, a two-step procedure was reported in which the sultam or oxazolidinone was first converted to the *N*-trimethylsilyl derivative, followed by the reaction with excess acryloyl chloride (4–6-fold) in refluxing toluene for a long reaction time.[9] However, the yields for the acryloyl oxazolidinones were still modest, and chromatographic separation of the product was required.[9] We now wish to report a simple method for the preparation of the *N*-acyloxazolidinone and sultam derivatives in high yields under mild conditions.

In an attempt to prepare acyloxazolidinones **2e** and **3f**, we developed an acylation procedure by reacting the mixed anhydride of the requisite acid and pivalic acid with the oxazolidinone in the presence of lithium chloride using triethylamine as the base, as shown in Scheme 1. This one-pot reaction is highly efficient, convenient, and suitable for large scale preparation. To demonstrate the generality of this procedure, 2-oxazolidinone (HX_O) and its derivatives from (*S*)-phenylalaninol (HX_P), (1*S*,2*R*)-norephedrine (HX_N), and (1*S*,2*R*)-1-amino-2-hydroxyindan (HX_A)[10] were converted to the 3-acyl-2-oxazolidinones **1a-b**, **2a-c,e**, **3a,d,f**, and **4a,b**. Likewise, *N*-acylsultams **5a-d** can be prepared from the corresponding (−)-bornane-2,10-sultam (HX_S).[11] Typically, the anhydride is formed by the reaction of the requisite acid and acyl chloride in THF using triethylamine as the base at ~−20 °C. After the anhydride is formed (~2 h), lithium chloride is added, followed by the oxazolidinone or the sultam. The acylation is usually complete within 4–6 h after warming to room temperature. Using this procedure, various *N*-acyloxazolidinone and sultam derivatives

Scheme 1



1b: R = Et, $X_C = X_O$
2b: R = Et, $X_C = X_P$
2c: R = *trans* CH=CHMe, $X_C = X_P$
3d: R = $CMe=CH_2$, $X_C = X_N$
4b: R = Et, $X_C = X_A$
5c: R = *trans* CH=CHMe, $X_C = X_S$
5d: R = $CMe=CH_2$, $X_C = X_S$

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(11) Bornane-2,10-sultam was prepared by borane reduction of the camphorsulfonimine, which was synthesized by the known procedure.[12] In comparison with the lithium aluminum hydride reduction,[12] the borane reduction has the advantage of simplicity, in which no aqueous workup is needed. The reaction is quenched with methanol after reduction is complete, and the product is crystallized from ethanol after removal of the volatiles. Alternatively, the sulfonimine can be reduced by Raney nickel-catalyzed hydrogenation (50 w % Ni, 3 atm, 20 °C, 20 h in 2-methoxyethanol).

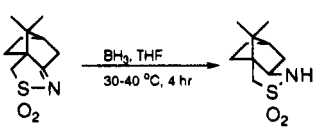

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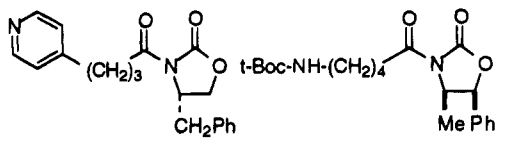
Table 1. Synthesis of *N*-Acyl-2-oxazolidinones and Sultams

auxiliary	product	yield (%)	mp (°C)	lit. mp (°C)	$[\alpha]_D$ (*c*)[a]	lit. $[\alpha]_D$ (*c*)[b]
HX_O	**1a**	84	83–84	82–83[6]		
HX_O	**1b**	85	85–86			
HX_P	**2a**	90	72–73	73–74	+110° (0.980)	+71.9° (2.41)[4]
HX_P	**2b**	93	44–45	45–46	+84.1° (1.02)	+80.7° (1.00)[c]
HX_P	**2c**	88	84–85	85–86	+106° (1.07)	+94.6° (1.65)[4]
HX_P	**2e**	91	73–74		+61.2° (1.15)	
HX_N	**3a**	88	oil	oil	+20.5° (1.28)	+29.0° (2.61)[4]
HX_N	**3d**	91	79–80	80–81	+35.3° (1.23)	+36.8° (1.27)[4]
HX_N	**3f**	92	103–104			
HX_A	**4a**	84	141–142		+406° (1.36)	
HX_A	**4b**	92	128–129	130	+296° (1.00)	+268° (2.4)[10]
HX_S	**5a**	89	184 dec	>170 dec	−98.5° (1.05)	−100.9° (0.983)[9]
HX_S	**5b**	95	151–152	153–154	−113° (1.34)	−108.4° (2.65)[15]
HX_S	**5c**	87	182–183	186–187	−82.3° (1.15)	−99.5° (1.04)[16]
HX_S	**5d**	95	147–148		−95.6° (1.23)	+93° (1.00)[d]

[a] Measured as a dichloromethane solution at 20 °C. [b] All literature values were reported as that of $CHCl_3$ solution unless specified. [c] In CH_2Cl_2, ref 5. [d] Enantiomer of **5d**, ref 8c.

have been prepared in high yields (Table 1). The presence of lithium chloride (1.1–1.2 equiv) is essential for the acylation to occur, possibly due to the chelate of the lithium ion which results in the activation of the acid anhydride. Alternatively, the acidity of the amide (sultam) may increase by interaction with lithium ion. However, other metal halides, such as magnesium bromide, failed to initiate the reaction under similar conditions.



2e **3f**

In summary, this one-pot synthesis provides a convenient route for the preparation of *N*-acyloxazolidinones and sultams in high yields. Acyloxazolidinones having additional functional groups, *e.g.*, **2e** and **3f**, can be prepared in high yields under mild reaction conditions. Especially notable for this method is the preparation of the acryloyl derivatives **1**–**5a** in which the products were formed in good yields and easily isolated.

Experimental Section

The identities of the known compounds were confirmed by comparison of the ^1H NMR spectra with those in literature. Melting points were uncorrected. All reagents were purchased from Aldrich and used as received except for methacrylic anhydride and crotonic anhydride, which were distilled before used. THF (inhibitor-free) was dried over 4 Å molecular sieves under nitrogen.

Method A. General procedure for the Acylation of 2-Oxazolidinones and Bornane-2,10-sultam with Acid Anhydrides. To the solution of the oxazolidinone or sultam (0.20 M, 1 equiv), lithium chloride (1.1 equiv), and triethylamine (1.3 equiv) in THF was added the acid anhydride (1.2 equiv) at −20 °C. The mixture was allowed to warm to room temperature and stirred for 4 h. THF was removed *in vacuo*, and the residue was partitioned between ethyl acetate and 0.2 N aqueous hydrochloric acid. The organic layer was subsequently washed with brine, 1 M sodium bicarbonate, and brine. The organic solution was then dried over sodium sulfate and filtered. The ethyl acetate was removed *in vacuo*, and the residue was crystallized by trituration with boiling hexane.

Method B. General Procedure for the Preparation of the *N*-Acryloyl-2-oxazolidinones and Sultam. To the solution of acrylic acid (1.3 equiv) and triethylamine (2.5 equiv) in THF (volume corresponded to 0.2 M of the oxazolidinone or sultam substrate) was added acryloyl chloride (1.2 equiv) at −20 °C. A white solid was formed instantaneously. The mixture was stirred at ~−20 °C for 1 h.[13] Lithium chloride (1.1 equiv) was added, followed by the oxazolidinone or sultam (1 equiv). The mixture was allowed to warm to room temperature and stirred for 4 h. The reaction was quenched by addition of 0.2 N HCl (2 equiv), and THF was removed *in vacuo*. The residue was partitioned between ethyl acetate and 0.2 N HCl. The organic layer was washed subsequently with 0.2 N HCl, brine, 1 M sodium bicarbonate (2×), and brine. The organic solution was then dried over sodium sulfate and filtered. Ethyl acetate was removed *in vacuo*, and the residue was dissolved in toluene. The toluene solution was filtered through a silica gel bed, and the cake was washed with toluene. Concentration to dryness afforded the desired product which was crystallized by trituration with boiling hexane.

3-Propenoyl-2-oxazolidinone (1a).[6] Oxazolidinone HX_O (3.50 g, 40 mmol) was converted to **1a** using method B (4.73 g, 84%).

3-Propionyl-2-oxazolidinone (1b). Oxazolidinone HX_O (1.75 g, 20 mmol) was acylated with propionyl anhydride using method A to give **1b** (2.43 g, 85%). ^1H NMR: δ 4.39 (t, 2 H, J = 8.1 Hz), 4.00 (t, 2 H, J = 8.1 Hz), 2.91 (q, 2 H, J = 7.4 Hz), 1.15 (t, 3 H, J = 7.4 Hz). Anal. Calcd for $C_6H_9NO_3$: C, 50.35; H, 6.33; N, 9.79. Found: C, 50.19; H, 6.40; N, 9.72.

(4*R*)-3-Propenoyl-4-(phenylmethyl)-2-oxazolidinone (2a).[4] Oxazolidinone HX_P (3.54 g, 20.0 mmol) was converted to **2a** using method B (4.15 g, 90%).

(4*R*)-3-Propionyl-4-(phenylmethyl)-2-oxazolidinone (2b).[5] Oxazolidinone HX_P (0.887 g, 5.0 mmol) was acylated with propionyl anhydride using method A to give **2b** (1.09 g, 93%).

(4*R*)-3-((*E*)-2-Butenoyl)-4-(phenylmethyl)-2-oxazolidinone (2c).[4] Oxazolidinone HX_P (0.887 g, 5.0 mmol) was acylated with crotonic anhydride using method A to give **2c** (1.08 g, 88%).

(4*R*)-3-(4-(4′-Pyridyl)butyloyl)-4-(phenylmethyl)-2-oxazolidinone (2e). To the suspension of the 4-(4′-pyridyl)butyric acid hydrochloride[14] (2.02 g, 10.0 mmol) and triethylamine (4.05 g, 40 mmol) in 120 mL of THF was added pivalyl chloride (1.21 g, 10.0 mmol) at −20 °C. The mixture was stirred for 2 h at ~−20 °C. Lithium chloride (0.47 g, 10 mmol) was added, followed by oxazolidinone HX_P (1.77 g, 10 mmol). The mixture was warmed to room temperature and further stirred for 4 h. THF was removed *in vacuo*. The residue was partitioned between ethyl acetate (80 mL) and water (40 mL). The organic layer was washed with 1 M sodium bicarbonate (2 × 40 mL) and brine (40 mL). The solvent was evaporated *in vacuo*, and an oil was obtained. The oil crystallized upon standing overnight (2.96 g, 91%). Mp: 73–74 °C. ^1H NMR: δ 8.50 (d, 2 H, J = 5.9 Hz), 7.25 (m, 7 H), 4.65 (m, 1 H), 4.20 (m, 2 H), 3.30 (dd, 1 H, J

(13) Alternatively, the acryloyl anhydride and lithium chloride can be generated as the following. To the suspension of lithium acrylate (1.87 g, 24 mmol) in THF (100 mL) was added acryloyl chloride (2.18 g, 24 mmol) at 0 °C. The mixture was warmed to 20 °C and aged until the solid dissolved (~2 h).

(14) Prepared by the reaction of diethyl malonate and 4-vinylpyridine, followed by hydrolysis and decarboxylation. For similar reactions, see: Boekelheide, V.; Rothchild, S. *J. Am. Chem. Soc.* **1947**, *71*, 978.

= 3.3, 13 Hz), 3.0 (m, 2 H), 2.73 (m, 3 H), 2.08 (m, 2 H). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.10; H, 6.38; N, 8.50.

(4*R*,5*S*)-3-Propenoyl-4-methyl-5-phenyl-2-oxazolidinone (3a).[4] Oxazolidinone HX_N (0.885 g, 5.0 mmol) was converted to the acryloyl derivative **3a** using method B. A slightly yellow oil was obtained after removal of the solvent under high vacuum (1.09 g). It was further purified by flash chromatography on silica gel (1:3 ethyl acetate/hexane) to afford **3a** as a colorless oil (0.98 g, 85%).

(4*R*,5*S*)-3-(2-Methylpropenoyl)-4-methyl-5-phenyl-2-oxazolidinone (3d).[4] Oxazolidinone HX_N (0.886 g, 5.0 mmol) was converted to **3d** using method A (1.10 g, 90%).

(4*R*,5*S*)-3-(5-(*N*-Boc-amino)valeryl)-4-methyl-5-phenyl-2-oxazolidinone (3f). To the solution of 5-(*N*-Boc-amino)valeric acid (1.80 g, 8.3 mmol) and triethylamine (2.13 g, 21 mmol) in 50 mL of THF was added pivaloyl chloride (1.01 g, 8.3 mol) at −25 °C. The resulting mixture was stirred at ~−20 °C for 2 h. Lithium chloride (0.39 g, 9.1 mmol) was added, followed by oxazolidinone HX_N (1.42 g, 8.0 mmol). The mixture was warmed to room temperature and further stirred for 4 h. THF was removed *in vacuo*, and the residue was partitioned between ethyl acetate (50 mL) and 5% potassium hydrogen sulfate (30 mL). The organic layer was further washed with potassium hydrogen sulfate (30 mL), brine (30 mL), 1 M sodium bicarbonate (2 × 30 mL), and brine (30 mL). The ethyl acetate solution was dried over sodium sulfate and filtered. Evaporation of ethyl acetate afforded **3f** as a colorless oil, which solidified upon standing (2.92 g, 92%). Mp: 103−104 °C. ^{1}H NMR: δ 7.35 (m, 5 H), 5.67 (d, 1 H, J = 13 Hz), 4.75 (m, 1 H), 4.62 (br, 1 H), 3.18 (m, 2 H), 2.95 (m, 2 H), 1.72 (m, 2 H), 1.58 (m, 2 H), 1.45 (s, 9 H), 0.9 (d, 3 H, J = 8 Hz). Anal. Calcd for $C_{20}H_{28}N_2O_5$: C, 63.81; H, 7.49; N, 7.44. Found: C, 63.49; H, 7.63; N, 7.32.

***N*-Propenoyltetrahydroindeno-2-oxazolidinone (4a).** Oxazolidinone[10] HX_A (0.876 g, 5.0 mmol) was acylated using method B to give **4a** as a white crystalline solid (0.963 g, 84%). ^{1}H NMR: δ 7.68 (d, 1 H, J = 7 Hz), 7.50 (dd, 1 H, J = 10, 17 Hz), 7.30 (m, 3 H), 6.64 (dd, 1 H, J = 2, 17 Hz), 6.60 (d, 1 H, J = 7 Hz), 5 93 (dd, 1 H, J = 2, 10 Hz), 5.33 (m, 1 H), 3.40 (d, 2 H, J = 3.5 Hz). Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.83; N, 6.11. Found: C, 67.96; H, 4.90; N, 6.04.

***N*-Propionyltetrahydroindeno-2-oxazolidinone (4b).**[10] Oxazolidinone HX_A (0.876 g, 5.0 mmol) was acylated using method A to give **4b** (1.06 g, 92%) as a white crystalline solid. ^{1}H NMR: δ 7.65 (d, 1 H, J = 8 Hz), 7.30 (m, 3 H), 5.94 (d, 1 H, J = 7 Hz), 5.37 (m, 1 H), 3.38 (d, 2 H, J = 3.5 Hz), 2.95 (q, 2 H, J = 7.3 Hz), 1.20 (t, 3 H, J = 7.3 Hz).

(−)-*N*-Propenoylbornane-2,10-sultam (5a).[8b,9] Sultam HX_S (1.72 g, 8.0 mmol) was acylated using method B. Crystallization of the crude product from toluene/hexane gave **5a** as a white crystalline solid (1.71 g, 79%). A second crop was obtained by evaporating the filtrate and triturating with boiling hexane (0.215 g, 10%).

(−)-*N*-Propionylbornane-2,10-sultam (5b).[15] Sultam HX_S (1.08 g, 5.0 mmol) was acylated using method A to give **5b** as a white crystalline solid (1.29 g, 95%).

(−)-*N*-(E)-2-Butenoylbornane-2,10-sultam (5c).[16] Sultam HX_S (1.08 g, 5.0 mmol) was acylated using method A to give **5c** as a white crystalline solid (1.23 g, 87%).

(−)-*N*-(2-Methylpropenoyl)bornane-2,10-sultam (5d).[17] Sultam HX_S (1.08 g, 5.0 mmol) was acylated using method A to afford **5d** as a white crystalline solid (1.35 g, 95%).

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(17) The preparation of the enantiomer has been reported; see ref 8c.