A Practical and Efficient Large-Scale Preparation of (4*R*,5*S*)-*N*-Propenoyl-1,5-dimethyl-4-phenylimidazolidin-2-one. A Simple Procedure for the Preparation of *N*-Acylimidazolidin-2-ones and *N*-Acylbornane 2,10-Sultams

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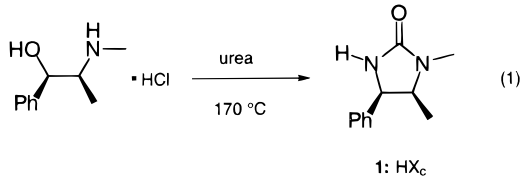
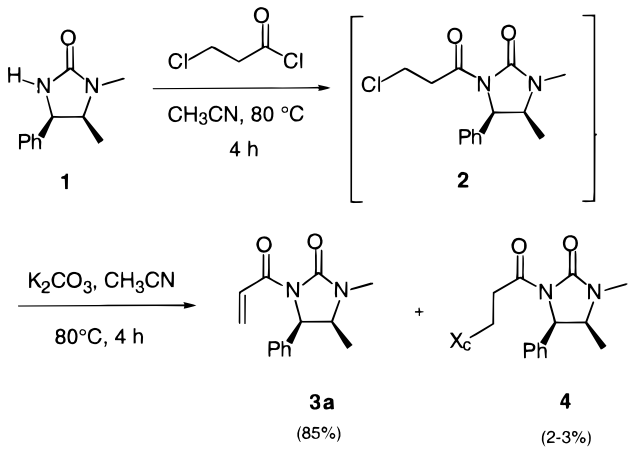
The (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one **1** is a powerful auxiliary for numerous asymmetric transformations and is readily prepared from the fusion reaction of (1*R*,2*S*)-ephedrine hydrochloride and urea (eq 1).[1,2] Excellent stereoselectivities have been observed



with **1** and its antipode in the asymmetric aldol[2] and homoaldol reactions,[3] the Diels−Alder reaction,[4] the Michael addition reaction of organometallics[5] and phthalimide,[6] and asymmetric alkylation reactions.[7] Recently as part of our endothelin receptor antagonist program, we required multikilo quantities of the *N*-propenoylimidazolidinone **3a**. Our successful efforts toward the development of an improved procedure for the large scale synthesis of **3a** will be described in this note.[8]

Scheme 1



Due to increasing emphasis for the swift development of promising new chemotherapeutics, our primary goal was to develop methodology for the preparation of **3a** which was not only inexpensive but also amenable to synthesis on a manufacturing scale. With this in mind, we wanted to avoid the use of chemistry which required special reactors, such as low-temperature chemistry (−78 °C), or costly reagents, such as alkyllithium or Grignard reagents, thus ruling out traditional metalation procedures.[2,7d−f,9] Our investigations therefore focused on simple acylation conditions of imidazolidinone **1**. Initially, reaction conditions using a tertiary amine (Et_3N, $^iPr_2NEt$) and acryloyl chloride in an aprotic solvent (CH_2Cl_2, THF) at −15 °C showed promise on a small scale. However, the exothermic reaction proved difficult to control upon scale-up (>50 g), which typically delivered **3a** in moderate yield (65−70%). In addition, chromatographic separation was required to remove polymeric material formed during the reaction.[10] We then investigated anhydride procedures developed for the Evans and Oppolzer auxiliaries, such as that reported by Ho and Mathre using LiCl/Et_3N/THF/acrylic anhydride,[11] as well as similar methodology using DABCO/Et_3N.[12] However, in both cases, low yields of **3a** were obtained due to the sluggish acylation of **1**.

We then turned to the work of Kocienski,[13] who reported that *N*-TMS-oxazolidinones and bornane 2,10-sultams undergo efficient acylation with an excess of acid chloride in the presence of catalytic copper at elevated temperatures. We reasoned that imidazolidinone **1** should exhibit similar reactivity with acid chlorides and therefore heated a solution of **1** with acryloyl chloride (1.5 equiv) in CH_3CN at 80 °C for 2 h. The reaction afforded a 1:5:1 mixture of **2**, **3a**, and the Michael adduct **4** (vide supra). Dehydrohalogenation of **2** was then achieved with K_2CO_3 (1.5 equiv) in CH_3CN heated to 80 °C for 4 h, which afforded **3a** and **4** in 75% and 12% yields, respectively (not shown).

Further improvements to the reaction were made by heating a solution of **1** and 3-chloropropionyl chloride (1.3 equiv) in CH_3CN at 80 °C for 4−6 h to give **2** in >95% yield (Scheme 1). Without isolation, **2** was then treated

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(8) We have prepared in excess of 1000 kg of **3a** using this procedure.
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(10) Methodology has been reported recently using DABCO/CuCl (1.0 equiv)/Cu (1.0 equiv) and acryloyl chloride to prepare **3a** in excellent yield; however, the use of copper to inhibit polymerization made this method unattractive for our purposes. Kriel, K. N.; Emslie, N. D.; Roos, G. H. P. *Tetrahedron Lett.* **1997**, *38*, 109. See also ref 7f.
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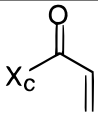
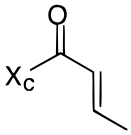
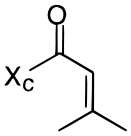
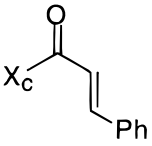
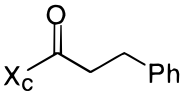
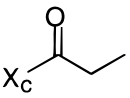
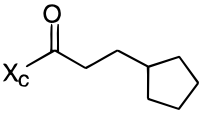
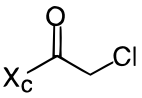
Table 1. Acylation of 1 with Acid Chlorides

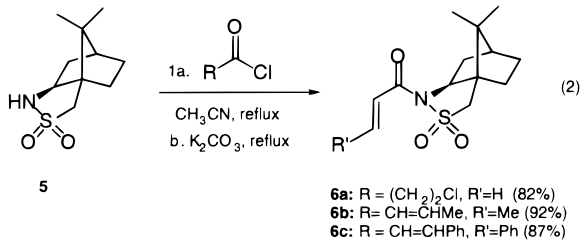
Entry	Product[a]	%Yield[b]	$[\alpha]_D^{25}$ [c]	mp (°C)
3a[d]		85	-130.2°	165.0-167.0
3b[e]		91	-102.0°	184.0-185.5
3c[f]		87	-94.6°	162.5-164.0
3d[g]		87	-29.7°	164.0-165.5
3e		81	-39.8°	120.0-122.0
3f[h]		96	-44.8°	107.0-109.0
3g		91	-37.8°	123.0-124.0
3h		93	-88.4°	89.0-90.5

[a] X_c = (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one. [b] Isolated yield. [c] *c* = 1, $CHCl_3$. [d] lit. $[\alpha]^{25}_D$ −100.6° (*c* = 1, $CHCl_3$), mp 135−140 °C (ref 7f). [e] lit. $[\alpha]^{25}_D$ −100° (*c* = 1, $CHCl_3$), mp 184 °C (ref 7e). [f] lit. $[\alpha]^{25}_D$ −105.4° (*c* = 1, CH_2Cl_2), mp 158 °C (ref 7a). [g] lit. $[\alpha]^{25}_D$ −21° (*c* = 1, $CHCl_3$), mp 184 °C (ref 7d). [h] lit. $[\alpha]^{25}_D$ −54.7° (*c* = 1, CH_2Cl_2), mp 90 °C (ref 7a).

with base to deliver **3a** in 85% yield after purification. A small amount of **4** (2−3%) was observed with these conditions; however, the byproduct was easily removed via a slurry of crude **3a** in cold (−10 °C) CH_3CN. With this procedure, **3a** was typically isolated as a white crystalline solid with >99.9% ee[14] and could be stored at room temperature for an extended period of time (>6 months) without significant decomposition.

The method has also proven to be a general procedure for the acylation of **1**, affording excellent yields (>80%) of the *N*-acylimidazolidinones **3b**−**h** shown in Table 1. In the α,β-unsaturated acid chloride examples, a K_2CO_3 charge was required to dehydrohalogenate the β-chloro-*N*-acylimidazolidinone formed during the acylation, whereas the reaction with saturated acid chlorides did not require base treatment. In all cases, complete acylation was obtained after 4−6 h of heating at 80 °C in CH_3CN with 1.25−1.50 equiv of the acid chloride. The crude product was then easily purified by recrystallization from $EtOH/H_2O$ or flash column chromatography to deliver the *N*-acylimidazolidinone in excellent yield and purity.

The remarkably simple procedure is also effective with Oppolzer's bornane 2,10-sultam auxiliary **5** (eq 2). With



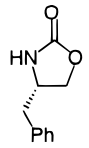
(2)

5

6a: R = $(CH_2)_2Cl$, R'=H (82%)
6b: R= CH=CHMe, R'=Me (92%)
6c: R = CH=CHPh, R'=Ph (87%)

the acid chlorides attempted, i.e., 3-chloropropionyl chloride, *trans*-crotonyl chloride, and cinnamoyl chloride, efficient acylation was observed after 8−10 h of heating at reflux in CH_3CN. After base treatment, the α,β-unsaturated *N*-acylbornane sultams were delivered in excellent yields and purities comparable to earlier reported procedures.[11,13]

In contrast to **1** and **5**, the Evans 2-oxazolidinone auxiliary **7** did not succumb to simple acylation with acid chlorides. For example, heating a solution of **7** with cinnamoyl chloride or propionyl chloride in CH_3CN at reflux for 24 h gave only recovered starting material. Presumably, the lower reactivity of **7** with acid chlorides is due to a greater delocalization of the urethane nitrogen lone pair relative to the imidazolidinone and bornane 2,10-sultam auxiliaries.



7

In conclusion, we have developed a simple and effective procedure for the synthesis of *N*-acylimidazolidinones and *N*-acylbornane 2,10-sultams amenable for large-scale synthesis. The method utilizes the modest nucleophilicity of the respective auxiliaries which undergo acylation with acid chlorides in high yield at elevated temperatures in polar solvents.

Experimental Section

All commercially available reagents were purchased from Aldrich Chemical Co. and were used without further purification except *trans*-crotonyl chloride, which was distilled prior to use. All solvents were high-performance liquid chromatography (HPLC) grade and used without further purification. Unless otherwise indicated, all reactions were magnetically stirred and monitored by reverse-phase HPLC using a Supelcosil ABZ+ column. Yields refer to chromatographically and spectroscopically pure compounds. Melting points are uncorrected. ^1H and

(14) Enantiomeric purity of **3a** was determined by chiral HPLC using Daicel Chiralpak AD column (9:1 hexane/2-propanol, 1 mL/min, 210 nm) with retention times of 8.73 min (**ent-3a**) and 14.08 min (**3a**).

^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Infrared spectra were recorded on an FT-IR spectrometer using KBr plates with film or in solution.

(−)-(4*R*,5*S*)-*N*-(Propenoyl)-1,5-dimethyl-4-phenylimidazolidin-2-one (3a).[7f] To a 12-L three-necked flask equipped with an air-driven mechanical stirrer, thermometer, and reflux condenser was charged (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one (**1**) (710 g, 3.74 mol), CH_3CN (7 L), and 3-chloropropionyl chloride (500 mL, 5.24 mol) under nitrogen. The suspension was heated to 80 °C for 6 h and then cooled to room temperature, and K_2CO_3 (1032 g, 7.48 mol) added portionwise over 10 min. The mixture was stirred for 0.5 h at ambient temperature and heated to 80 °C for 5−6 h, followed by filtration of the inorganics at room temperature. The filter cake was washed with CH_3CN (7 L), the filtrate was transferred to a 12-L three-necked flask, and 1500 mL of solvent was removed via distillation under reduced pressure (20 mmHg). The slurry was cooled to −15 °C for 3 h and filtered, and the filter cake was washed with cold (0 °C) *n*PrOH/heptane (1:9, 500 mL) and dried under vacuum (20 mmHg) at 25 °C to afford **3a** as a white crystalline solid (769 g, 85%). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H 6.60; N 11.47. Found: C, 69.10; H, 6.66; N 11.50.

General Procedure for α,β-Unsaturated *N*-Acylimidazolidin-2-ones (3b−3d). To a CH_3CN (50 mL) suspension of **1** (5.0 g, 26.3 mmol) was added the acid chloride (39.7 mmol) in one portion at 25 °C. The mixture was heated to 80 °C for 4−6 h under nitrogen and cooled to room temperature, and K_2CO_3 (3.6 g, 26.3 mmol) was added portionwise over 10 min. The mixture was heated to 80 °C for 2−4 h and cooled to room temperature, and the inorganics were removed via filtration. The filtrate was then concentrated under reduced pressure; the residue was partitioned between CH_2Cl_2 and H_2O; and the organic phase was washed with saturated Na_2CO_3 and saturated NaCl, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified via recrystallization from EtOH/H_2O (9:1, 5 mL/g substrate) at 0 °C or flash column chromatography [SiO_2, EtOAc/hexane (1:1)] unless otherwise indicated.

(4*R*,5*S*)-*N*-(*trans*-Crotonyl)-1,5-dimethyl-4-phenylimidazolidin-2-one (3b).[7e] White solid (6.1 g, 91%) after flash chromatography. Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.68; H, 7.01; N, 10.67.

(4*R*,5*S*)-*N*-(3,3-Dimethylacryloyl)-1,5-dimethyl-4-phenylimidazolidin-2-one (3c).[7a] White crystalline solid (6.2 g, 87%) after recrystallization. Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.4; N, 10.29. Found: C, 70.60; H, 7.32; N, 10.24.

(4*R*,5*S*)-*N*-(*trans*-Cinnamoyl)-1,5-dimethyl-4-phenylimidazolidin-2-one (3d).[7d] Recrystallization from EtOAc (5 mL/g substrate) at −10 °C afforded **3d** as white flakes (7.3 g, 87%). Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 75.20; H, 6.32; N, 8.68.

General Procedure for Saturated *N*-Acylimidazolidin-2-ones (3e−3h). To a CH_3CN (50 mL) suspension of **1** (5.0 g, 26.3 mmol) was added the acid chloride (32.9 mmol) in one portion at 25 °C. The mixture was heated to 80 °C for 4−6 h under nitrogen and cooled to room temperature, and the solution was concentrated under reduced pressure. The residue was then partitioned between CH_2Cl_2 and H_2O, and the organic phase was washed with saturated Na_2CO_3 and brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified via recrystallization from EtOH/H_2O (9:1, 5 mL/g substrate) at 0 °C or flash column chromatography [SiO_2, EtOAc/hexane (1:1)].

(4*R*,5*S*)-*N*-(3-Phenylpropionyl)-1,5-dimethyl-4-phenylimidazolidin-2-one (3e). White solid (6.9 g, 81%) after recrystallization. **3e:** IR (Nujol) 1760, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8 (d, 3H, J = 6.6 Hz), 2.8 (s, 3H), 2.9 (m, 2H), 3.3 (m, 2H), 3.9 (dq, 1H, J = 6.6, 8.5 Hz), 5.3 (d, 1H, J = 8.5 Hz), 7.10−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.9, 28.1, 30.6, 37.3, 53.9, 59.3, 125.9, 126.9, 128.0, 128.3, 128.5 (2C), 136.8, 140.1, 156.0, 172.0. Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.36; H, 6.87; N, 8.64.

(4*R*,5*S*)-*N*-(Propionyl)-1,5-dimethyl-4-phenylimidazolidin-2-one (3f).[7a] White solid (6.2 g, 96%) after recrystallization. Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.44; H, 7.27; N, 11.43.

(4*R*,5*S*)-*N*-(3-Cyclopentylpropionyl)-1,5-dimethyl-4-phenylimidazolidin-2-one (3g). White solid (7.5 g, 91%) after recrystallization. **3g:** IR (Nujol) 1760, 1740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.8 (d, 3H, J = 6.6 Hz), 1.1 (m, 2H), 1.4−1.8 (m, 9H), 2.8 (s, 3H), 3.0 (m, 2H), 3.9 (dq, 1H, J = 6.6, 8.5 Hz), 5.3 (d, 1H, J = 8.5 Hz), 7.15 (m, 2H), 7.20−7.35 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.9, 25.1, 28.1, 30.8, 32.4 (2C), 35.0, 53.9, 59.3, 126.9, 127.9, 128.4, 136.8, 155.9, 172.9. Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.79; H, 8.28; N, 8.87.

(4*R*,5*S*)-*N*-(Chloroacetyl)-1,5-dimethyl-4-phenylimidazolidin-2-one (3h). White flakes (6.5 g, 93%) after recrystallization. **3h:** IR (Nujol): 1725, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8 (d, 3H, J = 6.6 Hz), 2.8 (s, 3H), 3.9 (dq, 1H, J = 6.6, 8.5 Hz), 4.75 (AB q, 2H, J = 19.5, 15.2 Hz), 5.3 (d, 1H, J = 8.5 Hz), 7.15 (m, 2H), 7.20−7.35 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 14.8, 28.1, 43.8, 54.4, 59.5, 126.9, 128.2, 128.5, 135.8, 155.2, 165.2. Anal. Calcd for $C_{13}H_{15}N_2O_2Cl$: C, 58.54; H, 5.67; N, 10.50. Found: C, 58.79; H, 5.61; N, 10.44.

(+)-*N*-Propenoylbornane 2,10-Sultam (6a).[13] To a solution of (1*R*)-(+)-2,10-bornane sultam **5** (500 mg, 2.32 mmol) in CH_3CN (10 mL) under nitrogen was added 3-chloropropionyl chloride (0.28 mL, 2.90 mmol) and the solution was heated to reflux for 10 h. The solution was cooled to room temperature and charged with K_2CO_3 (640 mg, 4.64 mmol), and heating was continued for 4 h. After cooling to ambient temperature, the mixture was partitioned with CH_2Cl_2 and H_2O, and the organic phase was washed with saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was chromatographed [SiO_2, EtOAc/hexane (1:1)] to afford **6a** as a white solid (510 mg, 82%): mp 200 °C dec (lit. mp 180 °C dec); $[\alpha]^{25}_D$ +100.9° (*c* 1.1, $CHCl_3$), [lit. $[\alpha]^{25}_D$ +102° (c 1.7, $CHCl_3$)]. Anal. Calcd for $C_{13}H_{19}NSO_3$: C, 57.97; H, 7.11; N, 5.20. Found: C, 58.09; H, 7.18; N, 5.21.

(+)-*N*-(2-Butenoyl)bornane 2,10-Sultam (6b).[13] The sultam **5** (500 mg, 2.32 mmol) was acylated with *trans*-crotonyl chloride (0.33 mL, 3.48 mmol) using the procedure described above to give **6b** as a white solid (610 mg, 92%): mp 180−182 °C (lit. mp 181−183 °C); $[\alpha]^{25}_D$ +100.2° (*c* 1.04, $CHCl_3$), [lit. $[\alpha]^{25}_D$ +102° (*c* 1.6, $CHCl_3$)]. Anal. Calcd for $C_{14}H_{21}NSO_3$: C, 59.34; H, 7.47; N, 4.94. Found: C, 59.52; H, 7.35; N, 4.79.

(+)-*N*-(3-Phenylpropenoyl)bornane 2,10-Sultam (6c).[13] To a solution of (1*R*)-(+)-2,10-bornane sultam **5** (500 mg, 2.32 mmol) in CH_3CN (10 mL) under nitrogen was added cinnamoyl chloride (502 mg, 3.02 mmol), and the solution was heated to reflux for 10 h. After the solution cooled to ambient temperature, the CH_3CN was removed in vacuo. The residue was diluted with EtOAc, and the organic phase was washed with saturated Na_2CO_3 and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was chromatographed [SiO_2, EtOAc/hexane (1:1)] to afford **6c** as a white solid (700 mg, 87%): mp 188−189.5 °C (lit. mp 187−189); $[\alpha]^{25}_D$ +97.2° (*c* 1.1, $CHCl_3$), [lit. $[\alpha]^{25}_D$ +98° (*c* 1.7, $CHCl_3$)]. Anal. Calcd for $C_{19}H_{23}NSO_3$: C, 66.06; H, 6.71; N, 4.05. Found: C, 66.14; H, 6.71; N, 4.01.

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