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Efficient synthesis of 1-heterocyclic-3-aminopyrrolidinones

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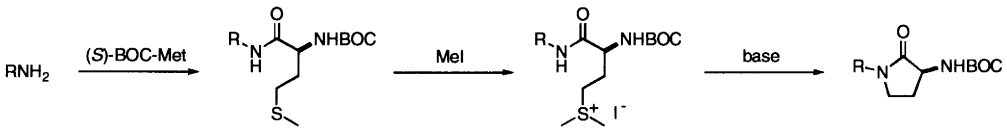
Abstract

A novel two-step synthesis of optically active 3-aminopyrrolidinones is described. The route allows access to pyrrolidinones with heterocyclic functionality that is incompatible with known methodology, and affords the final products in good to excellent yield and high enantiomeric purity. The Mitsunobu cyclodehydration is shown to be an efficient method for the formation of a variety of γ-lactams. © 2000 Published by Elsevier Science Ltd. All rights reserved.

Keywords: 3-aminopyrrolidinones; nitrogen heterocycles; Mitsunobu reaction; cyclization.

The 3-aminopyrrolidinone moiety has found widespread use in biologically-active molecules.[1,2] The most common synthetic routes to these compounds are variants of the original conditions described by Freidinger et al.,[1,3] that rely on activation of a methionine amide by treatment with excess iodomethane, followed by cyclization using sodium hydride as base (Scheme 1).



Scheme 1.

We were interested in the synthesis of enantiomerically pure 3-aminopyrrolidinones substituted with various heterocycles at the 1-position. Many of the targets contained heterocyclic functionality that was not compatible with iodomethane treatment, so we explored the alternative route shown in Scheme 2. Specifically, we planned to open a suitably protected homoserine lactone with the dimethylaluminum amide derivative of interest. We envisioned that a Mitsunobu cyclodehydration[4] of the homoserine amide would then lead to the desired γ-lactam. A similar Mitsunobu strategy has been demonstrated in the synthesis of *N*-arylpiperazinones.[5]

To our knowledge, while Mitsunobu conditions have been employed in the cyclization of β-hydroxyamides to give β-lactams,[6] the only examples utilizing γ-hydroxyamides involved the cyclization

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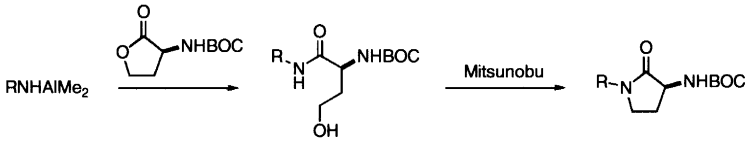


Scheme 2.

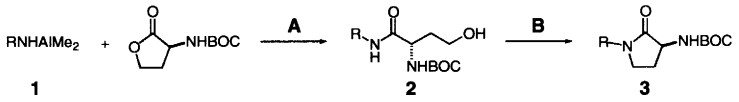
of α,α-spiro-substituted compounds or other constrained systems that were presumably predisposed to ring closure.[7] Other related examples use chemical modification at the amide nitrogen, for example in homoseryl *O*-alkyl hydroxamates, to increase the acidity of the amide N–H and hence promote cyclization.[8] We expected that the enhanced acidity of the amide functionality in an *N*-(heteroaryl)amide should also facilitate the cyclodehydration, but a range of structures, including *N*-(alkyl)amides, were investigated to assess the scope of this reaction. Another important goal of this study was to provide the 1-heterocyclic-3-aminopyrrolidinones in optically pure form, since the only published examples were synthesized as racemates.[9]

A series of heterocyclic amines were converted to the corresponding dimethylaluminum amides (**1**) (Table 1) by reaction with trimethylaluminum in CH_2Cl_2,[10] and the aluminum amides were then treated with (*S*)-BOC-homoserine lactone. The results of this study are presented in Table 1. The desired γ-hydroxyamides (**2**) were obtained in good to excellent yields, although a wide range of reactivity was noted. For example the (*R*)-tetrahydrofuran-3-yl aluminum amide (**1k**) reacted essentially quantitatively with the lactone at ambient temperature in 90 min, whereas the reaction between the pyridin-4-yl aluminum amide (**1c**) and the lactone provided only about 50% product after 48 h at 40°C. While the tetrahydrofuranyl example displays the typical reactivity profile expected for an aliphatic aluminum amide, the electron-deficient 4-pyridyl system appears to have significantly reduced nucleophilicity. Consistent with this observation are the data for the 3-pyridyl (**1b**) and 2-pyridyl (**1a**) examples, in which the yields obtained (3-pyridyl>2-pyridyl>4-pyridyl) apparently reflect the electronic-withdrawing facility of these heterocyclic systems. The data for the 5-isoquinolinyl (**1f**) and 5-quinolinyl (**1g**) examples illustrate that steric considerations are also important as the reactions with these relatively hindered aluminum amides required heating. In most cases some unreacted lactone was recovered. Attempts to increase consumption of the lactone by use of greater than 1.2 equiv. of aluminum amide were moderately successful, but led to decreases in the enantiomeric purity of the product.

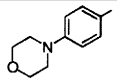
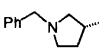
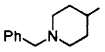
Cyclodehydration of the homoserine amides shown proceeded in excellent yield using conditions adapted from those described by Weissman et al.[5] The preformed Mitsunobu complex of di-*tert*-butyl azodicarboxylate and tri-*n*-butylphosphine was added to a solution of the alcohol in THF at 0°C, and the mixture was allowed to warm slowly to ambient temperature. In all cases, the reaction was complete after stirring for 18 h. Table 1 details the yield of each γ-lactam obtained and also the enantiomeric purity of the final product, which was determined by conversion of the deprotected 3-aminopyrrolidinone to both Mosher amide diastereomers and analysis by ^{1}H NMR spectroscopy. In general, the optical purity of the final products was excellent, although the examples that required heating in the first step tended to show some epimerization (**3c**, **3e**, and **3g**, for example).

While we had expected that γ-hydroxyamides with relatively acidic amide functionality, such as **2a**, would undergo efficient ring closure, we were gratified with the scope of the reaction and the uniformally high yields obtained. The amide groups in compounds **2k**–**2m** presumably have significantly higher pK_a values than **2a**, but the cyclizations of these substrates were still highly efficient. The lowest yield (70%) was obtained for the cyclization of the 5-quinolinyl substrate (**2g**). In this case, the balance of the material was converted to the imidate ester resulting from *O*-alkylation of the amide.[11] A small amount of *O*-

Table 1
Synthesis of 3-(*tert*-butoxycarbonylamino)pyrrolidinones



1 2 3

Entry	R	A Yield[a,b] (%)	B Yield[b,c] (%)	e.e.[d] (%)	Entry	R	A Yield[a,b] (%)	B Yield[b,c] (%)	e.e.[d] (%)
a		67[e]	95	> 99	h		88[e]	91	91
b		87[e]	93[k]	> 99	i		79[e]	93	98
c		52[f]	91	77	j		67[h]	79	96
d		64[g]	99	> 99	k		97[i]	91	> 95[n]
e		49[h]	81	80	l		83[e]	93	> 99[n]
f		77[h]	86	95	m		86[j]	78	> 99
g		54[h]	70[m]	87					

[a]All reactions performed in CH_2Cl_2 using 1.0 eq lactone and 1.2 eq of the preformed dimethylaluminum amide of interest. [b]Isolated, unoptimized yield after silica gel chromatography except as noted. [c]All reactions performed in THF using 1.3 eq n-Bu_3P and 1.3 eq DBAD. [d]e.e. of **3a-j** & **3m**. [e]Reacted for 18 h at 25°C. [f]Reacted for 48 h at 40°C. [g]Reacted for 2 h at 25°C. [h]Reacted for 18 h at 40°C. [i]Reacted for 1.5 h at 25°C. [j]Reacted for 4 h at 25°C. [k]Yield estimated by NMR spectroscopy. [m]Also isolated *O*-alkylation product (30%). [n]% d.e.

alkylation was also apparent in the case of the 5-isoquinolinyl substrate (**2f**), but this side reaction was not observed for any of the other examples.

In conclusion, a novel two-step synthesis of optically active 3-aminopyrrolidinones has been developed. This route should be a useful complement to the known methodology, especially for structures which contain functionality with undesirable reactivity towards iodomethane. The variety of substituents tolerated on the amide nitrogen highlights the versatility of the Mitsunobu ring closure in the formation of γ-lactams.

1. Representative experimental procedures

(*S*)-2-(*tert*-Butoxycarbonylamino)-4-hydroxy-*N*-pyridin-2-ylbutyramide (**2a**). To a stirred solution of 2-aminopyridine (126 mg, 1.34 mmol) in dry CH_2Cl_2 (3 mL) at ambient temperature, under argon, was added trimethylaluminum (0.67 mL of a 2.0 N solution in hexane, 1.34 mmol) dropwise. The resulting

mixture was stirred for 15 min, then (*S*)-*N*-(*tert*-butoxycarbonyl)homoserine lactone[12] (224 mg, 1.11 mmol) in CH_2Cl_2 (3 mL) was added slowly and stirring was continued at ambient temperature for 18 h. The reaction was quenched carefully with 10% aqueous citric acid (1 mL) and, after effervescence had stopped, the mixture was partitioned between saturated aqueous potassium sodium tartrate (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted further with CH_2Cl_2 (2×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica, eluting with a gradient of EtOAc–20 to 10% hexane to yield the amide as an oil (221 mg, 67%). ^{1}H NMR ($CDCl_3$) δ 9.69 (1H, br s), 8.31 (1H, dd, *J*=4.8, 0.9 Hz), 8.20 (1H, d, *J*=8.1 Hz), 7.70 (1H, ddd, *J*=8.4, 7.3, 1.8 Hz), 7.04 (1H, ddd, *J*=7.3, 4.9, 0.9 Hz), 6.05 (1H, br d, *J*=5.1 Hz), 4.62 (1H, m), 3.93 (1H, m), 3.79 (2H, m), 2.14 (1H, m), 1.96 (1H, m), 1.48 (9H, s). MS (EI) *m*/*z*=295 (M^+=$C_{14}H_{21}N_3O_4$). HPLC purity=91.7% (215 nm).

(*S*)-3-(*tert*-Butoxycarbonylamino)-2-oxo-1-(2-pyridyl)pyrrolidine (**3a**). Tri-*n*-butylphosphine (0.208 mL, 0.83 mmol) was added to a solution of di-*tert*-butyl azodicarboxylate (191 mg, 0.83 mmol) in dry THF (2 mL) at ambient temperature. The resulting mixture was stirred for 5 min, then added dropwise to a solution of (*S*)-2-(*tert*-butoxycarbonylamino)-4-hydroxy-*N*-pyridin-2-ylbutyramide (190 mg, 0.64 mmol) in THF (1 mL) at 0°C, under argon. The reaction mixture was allowed to warm slowly to ambient temperature and stirred for 18 h, then partitioned between saturated aqueous $NaHCO_3$ (5 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted further with CH_2Cl_2 (10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica, eluting with a gradient of hexane–20 to 40% EtOAc to yield the lactam as a white solid (169 mg, 95%). ^{1}H NMR ($CDCl_3$) δ 8.38 (1H, d, *J*=8.4 Hz), 8.37 (1H, ddd, *J*=4.8, 1.8, 0.7 Hz), 7.71 (1H, ddd, *J*=8.5, 7.3, 2.0 Hz), 7.06 (1H, ddd, *J*=7.2, 4.9, 0.9 Hz), 5.16 (1H, br s), 4.42 (1H, m), 4.27 (1H, dd, *J*=11.0, 9.2 Hz), 3.82 (1H, td, *J*=11.1, 6.4 Hz), 2.75 (1H, m), 1.91 (1H, m), 1.44 (9H, s). MS (EI) *m*/*z*=277 (M^+=$C_{14}H_{19}N_3O_3$). HRMS (EI) calculated for $C_{14}H_{19}N_3O_3$ *m*/*z*=277.1426; found *m*/*z*=277.1425. HPLC purity=100.0% (215 nm). Mosher amide analysis of this product by ^{1}H NMR indicated less than 0.5% of the undesired isomer.[13]

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11. Structures of the *N*-alkylation and *O*-alkylation products confirmed by HRMS, ^{1}H NMR, ^{13}C NMR and NOE experiments.
12. Synthesized by EDC/HOBT-mediated cyclization of (*S*)-*N*-(*tert*-butoxycarbonyl)homoserine.
13. Representative determination of enantiomeric purity (for **3a**): A solution of (*S*)-3-(*tert*-butoxycarbonylamino)-2-oxo-1-(2-pyridyl)pyrrolidine (**3a**) (65 mg) in EtOAc (5 mL) at 0°C was saturated with HCl (g). The mixture was stood at 0°C for 15 min, then concentrated in vacuo to provide (*S*)-3-amino-2-oxo-1-(2-pyridyl)pyrrolidine dihydrochloride as a white solid (59 mg, 100%). ^{1}H NMR (CD_3OD) δ 8.43 (1H, ddd, *J*=5.1, 1.9, 0.8 Hz), 8.29 (1H, dt, *J*=8.6, 0.9 Hz), 7.96 (1H, ddd, *J*=8.5, 7.4, 1.8 Hz), 7.29 (1H, ddd, *J*=7.3, 5.1, 1.1 Hz), 4.37 (1H, dd, *J*=11.0, 8.8 Hz), 4.33 (1H, ddd, *J*=10.5, 9.2, 1.1 Hz), 3.82 (1H, td, *J*=10.5, 6.7 Hz), 2.70 (1H, m), 2.16 (1H, m). (*S*)-3-Amino-2-oxo-1-(2-pyridyl)pyrrolidine dihydrochloride (23 mg) was dissolved in CH_2Cl_2 (1 mL) and Et_3N (45 μL), and (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid chloride (19 μL) was added. The mixture was stood at ambient temperature for 30 min, then partitioned between EtOAc (5 mL) and sat. aq. $NaHCO_3$ (3 mL). The organic layer was washed with sat. aq. NH_4Cl (3 mL), then brine (3 mL), then dried over Na_2SO_4 and concentrated to dryness in vacuo to give (*S*,*S*)-α-methoxy-*N*-[2-oxo-1-(2-pyridyl)pyrrolidin-3-yl]-α-trifluoromethylphenylacetamide which was sufficiently pure for NMR spectroscopic analysis. ^{1}H NMR ($CDCl_3$) δ 8.38–8.34 (2H, m), 7.70 (1H, ddd, *J*=8.4, 7.3, 1.8 Hz), 7.59–7.56 (2H, m), 7.44–7.38 (3H, m), 7.32 (1H, br d, *J*=5.5 Hz), 7.07 (1H, ddd, *J*=7.2, 4.9, 0.9 Hz), 4.68 (1H, ddd, *J*=11.4, 8.4, 6.0 Hz), 4.29 (1H, ddd, *J*=10.3, 9.1, 0.9 Hz), 3.87 (1H, td, *J*=11.0, 6.6 Hz), 3.40 (3H, q, *J*=1.3 Hz), 2.81 (1H, m), 1.94 (1H, m). The (*S*,*R*)-diastereomer was also synthesized (by the same method but using the (*S*)-Mosher's acid chloride) for comparison purposes.