A PRACTICAL PREPARATION OF Δ^1-2-SUBSTITUTED AND Δ^1-2,3-DISUBSTITUTED PYRROLINES‡

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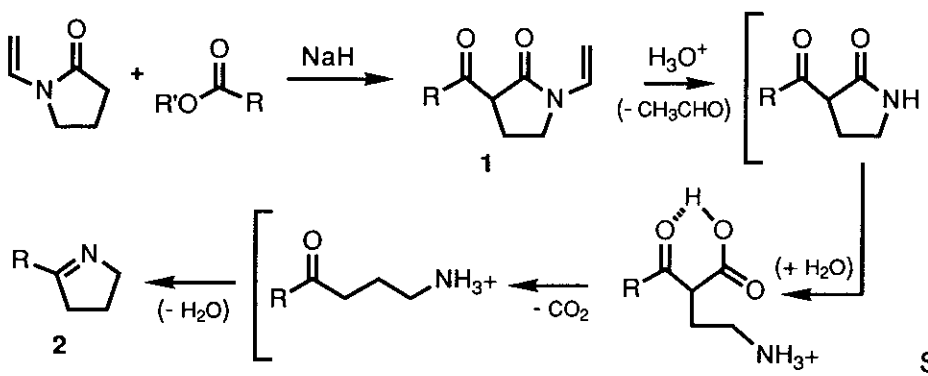
Abstract - Addition of *N*-vinylpyrrolidinone and an ester to NaH in THF effects acylation and affords keto lactams (**1**) in high yields. Hydrolysis of **1** in strong acid generates Δ^1-2-substituted pyrrolines (**2**) in good yield. Keto lactams (**1**) can be further alkylated and hydrolyzed to produce Δ^1-2,3-disubstituted pyrrolines (**4**) in good isolated yield.

We required a practical and efficient method for the large scale production of 2-phenylpyrrolidine for our development of a series of pyrroloisoquinoline antidepressants.[1] Our synthesis of 2-phenylpyrrolidine employed a catalytic hydrogenation of Δ^1-2-phenylpyrroline (**2**). The pyrroline (**2**, R = Ph) was generated using a modification of the procedure of Brandage and Lindblom.[2] Their one-pot procedure involved the sequential base-induced acylation of *N*-vinylpyrrolidinone (NVP) with an aromatic ester to afford the keto lactam intermediate (**1**, R = Ph) followed by acid-mediated hydrolysis, decarboxylation and cyclization (Scheme 1).



Scheme 1

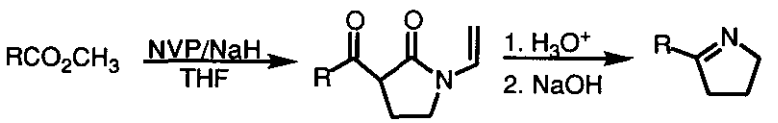
Close scrutiny of the method led us to the realization that the keto lactam intermediate (**1**) partially polymerized during the acid-mediated removal of the *N*-vinyl group. We overcame this

‡Dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday.

polymerization problem by isolating **1** (R = Ph) and performing the hydrolysis and decarboxylation under dilute conditions, in a separate step. The acylation is simply accomplished by addition of equimolar amounts of NVP and the ester to a refluxing solution of NaH in THF or toluene. The keto lactam (**1**) is isolated and purified or utilized directly in the subsequent hydrolysis step. To minimize polymerization, the hydrolysis is conducted by slow addition of **1** to refluxing 6N HCl.[1] This two-pot procedure affords Δ^1-2-phenylpyrroline (**2**, R = Ph) in 85% overall isolated yield. The potential use of pyrrolines in natural product synthesis of pyrrolizidine and indolizidine alkaloids[3] led us to explore the scope and limitation of the method for the preparation of other Δ^1-2-substituted pyrrolines.[4] Nonaromatic and enolizable esters were of prime interest because of possible competitive ester enolization, leading to unwanted chemistry (e.g., Claisen condensation), in the acylation step.

We now report that the base-induced acylation of NVP with a variety of alkyl esters affords the key intermediate keto lactams (**1**), and that the subsequent acid-mediated transformation of the keto lactams provides good yields of Δ^1-2-substituted pyrrolines (**2**). Our preliminary results are summarized in Table 1.[5,6]

Table 1. Preparation of Δ^1-2-Substituted Pyrrolines



1 **2**

Entry	R	Yield **1** (%)[a]	Yield **2** (%)[b]
1	Ph	85	85
2[c]	$PhCH_2$-	96	66
3	*c*-C_3H_5-	75	0
4	*c*-C_6H_{11}-	99	73
5	$CH_3(CH_2)_8$-	99	81
6	$BzlO(CH_2)_3$-	96	95[d]
7	$(CH_3)_2CH$-	99	98
8	$(CH_3)_3C$-	96	73

a. Crude yield.

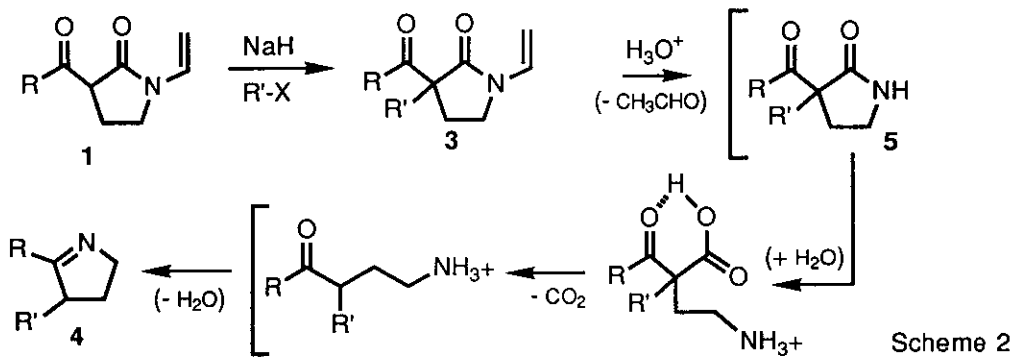
b. Overall isolated purified yield from NVP.

c. Two equiv of NaH used.

d. Benzyl group was removed in the reaction.

Thus, several enolizable esters acylate NVP to afford excellent yields of the desired keto lactams (**1**) (Table 1, Entries 2-7). No evidence was found for competitive enolization of the esters, although 2 equivalents of NaH were needed for the acylation involving ethyl phenylacetate (Table 1, Entry 2).

Sterically congested esters also react with NVP to give keto lactams in high yields (Table 1, Entries 4,7,8). However, low yields or no identifiable acylated products were found with base-sensitive esters, such as methyl methacrylate or methyl crotonate (not listed); likewise, lactones fail to react under these conditions. In general, when **1** is refluxed with 6N HCl for several hours, good to excellent yields of Δ^1-2-substituted pyrrolines are produced (Table 1, Entries 1,2,4-8). No pyrroline-like product was detected in the case of the cyclopropyl keto lactam (**1**, Table 1, Entry 3).
The method was extended to include the preparation of Δ^1-2,3-disubstituted pyrrolines (**4**) by alkylation of **1** followed by hydrolysis of the resulting substituted keto lactam **3** (Scheme 2).

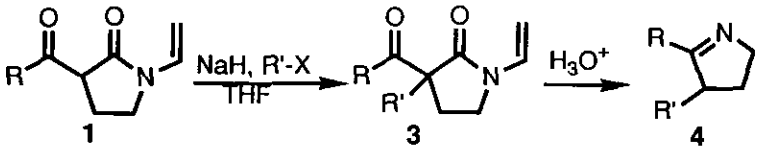


Scheme 2

Treatment of the sodium enolate of **1** in THF at room temperature with an alkylating agent provides the substituted keto lactams (**3**) in excellent yield. We found that benzyl bromide and methyl iodide are effective in the alkylation of **1**; however n-butyl bromide and 1-bromo-3-chloropropane were not. We observed no evidence for *O*-alkylation involving the sodium enolate of **1**. As with lactam (**1**), treatment of **3** in refluxing 6N HCl effects a rapid and quantitative removal of the *N*-vinyl group followed by hydrolysis, decarboxylation and cyclization to furnish the disubstituted pyrrolines (**4**) in moderate to excellent yield. Table 2 summarizes our preliminary results.[5,7] The sterically crowded keto lactams hydrolyzed very slowly. In fact, *t*-butylbenzyl lactam (**3**) (Table 2, Entry 3) yields only a trace of the pyrroline even after several days of refluxing. The major product is lactam (**5**) (95%). The lower yields encountered with the *t*-butyl- and isopropylpyrrolines (Table 2, Entries 3,5-6) may reflect product loss during isolation due to the volatile nature of the products or to incomplete hydrolysis of the intermediate lactam (**5**).

The present investigation clearly expands the Brandage/Lindblom methodology to include the preparation of Δ^1-2-substituted pyrrolines and Δ^1-2,3-disubstituted pyrrolines. We are currently using more highly functionalized esters applicable to the synthesis of pyrroline, pyrrolidine, and pyrrole based natural products.

Table 2. Preparation Δ^1-2,3-Disubstituted Pyrrolines (**4**).



1 **3** **4**

Entry	R	R'	Yield **3** (%)[a]	Yield **4** (%)[b]
1	Ph	$PhCH_2$-	99 [70]	94[c]
2	Ph	CH_3-	99	87
3	$(CH_3)_3C$-	$PhCH_2$-	99	trace
4	$(CH_3)_3C$-	CH_3-	97	82
5	$(CH_3)_2CH$-	$PhCH_2$-	99	77
6	$(CH_3)_2CH$-	CH_3-	77	51

[a] Crude yield. Bracketed yield is after purification by crystallization.

[b] Overall isolated purified yield from **1**.

[c] Yield from purified **3**.

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2. S. Brandage and L. Lindblom, Acta Chem. Scand. B, 1976, 30, 93. Also see: P. Jacob, III., J. Org. Chem., 1982, 47, 4165.

3. For reviews see; (a) M. Ikeda, T. Sato, and H. Ishibashi, Heterocycles, 1988, 27, 1465. (b) S. Rajeswari, S. Chandrasekharan, and T. Govindachari, Heterocycles, 1987, 25, 659.

4. For a comparison study involving preparation of Δ^1-2-substituted pyrrolines using organolithium reagents and NVP see: J. Bielawski, S. Brandage, and L. Lindblom, J. Heterocycl. Chem., 1978, 15, 97.

5. All compounds had satisfactory spectral data, including ^1H and ^{13}C nmr, mass spectra, and ir.

6. Typical procedure: Preparation of Δ^1-2-isopropylpyrroline (Table 1, Entry 7). A mixture of

freshly distilled *N*-vinylpyrrolidinone (8.3 g, 75 mmol) and methyl isobutyrate (9.2 g, 90 mmol) in THF (20 ml) is added slowly to 95% NaH (4.8 g, 190 mmol) in refluxing THF (80 ml). The mixture is refluxed for 4 h, cooled to room temperature, diluted with saturated ammonium chloride and extracted with ether (3x75 ml). The ether extracts are dried ($MgSO_4$) and solvent removed in vacuo to afford crude keto lactam (**1**) [R = isopropyl] as an amber oil (13.6 g, 99%): ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.10 (d, J = 6.90 Hz, 3H), 1.18 (d, J = 6.90 Hz, 3H), 2.08-2.23 (m, 1H), 2.52-2.62 (m, 1H), 3.20 (dq, J = 6.90, 6.90 Hz, 1H), 3.44-3.65 (m, 2H), 3.88 (dd, J = 5.57, 9.24 Hz, 1H), 4.46 (d, J = 16.10 Hz, 1H), 4.50 (d, J = 8.77 Hz, 1H), 7.01 (dd, J = 8.77, 16.10, 1H); ^{13}C nmr (75 MHz, $CDCl_3$) δ 17.01, 18.54, 19.77, 40.05, 43.11, 53.17, 95.41, 129.01, 168.45, 208.98. Crude **1** (7.2 g, 40 mmol) is dissolved in THF (10 ml) and slowly added to refluxing 6N HCl (50 ml). After refluxing 16 h the solution is cooled to 0° C, basified (pH 12) with 50% NaOH, and extracted with methylene chloride (3x50 ml). The combined organics are dried ($MgSO_4$) and concentrated in vacuo to give 4.35 g (98% yield) of pyrroline [**2**, R = isopropyl]: ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.46 (d, J = 6.93 Hz, 6H), 1.82-1.87 (m, 2H), 2.48 (t, J = 7.90 Hz, 2H), 2.61 (h, J = 6.93 Hz, 1H), 3.78 (t, J = 7.48 Hz, 2H); ^{13}C nmr (75 MHz, $CDCl_3$) δ 19.90 (CH_3), 23.38 (CH_2), 32.38 (CH), 34.44 (CH_2), 60.42 (CH_2), and 182.66 (C_q).

7. Typical procedure: Preparation of Δ^1-3-benzyl-2-isopropylpyrroline (**4**, Table 2, Entry 5). Keto lactam [**1**, R = isopropyl] (4.1 g, 23 mmol) in THF (5 ml) is added slowly to stirring 95% NaH (0.6 g, 25 mmol) in THF (100 ml) at room temperature. The mixture is stirred for 15 min and benzyl bromide (4.2 g, 25 mmol) is added dropwise. After stirring overnight, the reaction is quenched with saturated ammonium chloride and extracted with ether (2x75 ml). The ether extracts are dried ($MgSO_4$) and solvent removed in vacuo to afford crude keto lactam (**3**) [R = isopropyl, R' = benzyl] as an off white solid (6.2 g, 99%): ^{1}H nmr (300 MHz, $CDCl_3$) δ1.02 (d, J = 6.70 Hz, 3H), 1.10 (d, J = 6.70 Hz, 3H), 1.89-1.94 (m, 1H), 2.55-2.71 (m, 2H), 2.98 and 3.45 (abq, J = 13.72 Hz, 2H), 3.16-3.22 (m, 1H), 3.37 (dq, J = 6.70, 6.70 Hz, 1H), 4.26 (d, J = 16.10 Hz, 1H), 4.44 (d, J = 9.10 Hz, 1H), 7.04 (dd, J = 9.10, 16.10 Hz, 1H), 7.12-7.26 (m, 5H); ^{13}C nmr (75 MHz, $CDCl_3$) δ 17.20, 19.58, 20.23, 36.06, 39.18, 41.79, 63.94, 95.46, 126.92, 128.26, 128.30, 129.00, 129.81, 135.76, 170.97, 211.11. Crude **3** (1.0 g, 3.7 mmol)) is dissolved in THF (10 ml) and slowly added to refluxing 6N HCl (35 ml). After refluxing 24 h the solution is cooled to 0°C, basified (pH 12) with 50% NaOH, and extracted with methylene chloride (3x50 ml). The organics are dried ($MgSO_4$) and concentrated in vacuo to give 0.57 g (77% yield) of pyrroline (**4**) [R = isopropyl, R' = benzyl]: ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.17 (d, J = 6.87 Hz, 3H), 1.24 (d, J = 6.87, 3H), 1.59-1.63 (m, 1H), 1.82-1.94 (m, 1H), 2.38-2.47 (m, 1H), 2.67-2.70 (m, 1H), 3.04-3.15 (m, 2H), 3.58-3.77 (m, 2H), 7.16-7.32 (m, 5H); ^{13}C nmr (75 MHz, $CDCl_3$) δ 19.51 (CH_3), 20.5 (CH_3), 29.11 (CH_2), 29.85 (CH), 37.75 (CH_2), 49.79 (CH), 58.33 (CH_2), 126.05, 12.79, 128.32 (3 CH), 140.04, (C_q), 184.02 (C_q).

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