A High-Yielding General Synthesis of α-Lactams

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Abstract: A high-yielding general synthesis of α-lactams (aziridinones) is described. An α-haloamide precursor is cyclized by sodium hydride in the presence of 15-crown-5 ether at room temperature, using dichloromethane as the solvent. The by-products, hydrogen gas and sodium halide, are easily removed. The yields for the six known α-lactams (2b−g) chosen for this study are comparable or superior to previously reported yields, yet only short reaction times and a simple work-up is required.

Key words: aziridinones, dehydrohalogenation, heterocycles, ring closure

α-Lactams (aziridinones) are potentially useful synthons and their ring-opening reactions with various nucleophiles have been reported. Currently, there are two general methods employed for the synthesis of α-lactams, but both have drawbacks. The classical general method of dehydrohalogenating α-haloamides with potassium tert-butoxide (Scheme 1), even in its improved version (where potassium tert-butoxide was replaced by the less hygroscopic sodium tert-butoxide) is still beset by the possibility of unwanted side reactions resulting from the nucleophilicity of the base or the tert-butyl alcohol by-product. In addition, during the synthesis of 3,3-dimethyl-substituted α-lactams, the unwanted base-catalyzed rearrangement of the α-lactam to the more stable α,β-unsaturated amide can occur.

An important modification of the dehydrohalogenation reaction, reported by Scrimin et al., utilizes potassium hydroxide with 18-crown-6 ether as a phase-transfer catalyst, in benzene or toluene to cyclize α-haloamides (Scheme 2). Reaction times are between 3.5 and 12 hours, with reported yields between 50% and 94%.

However, this synthesis suffers from the disadvantage that the potassium hydroxide can hydrolyze some of the α-lactam already formed, especially when a long reaction period is required. In addition, water, a by-product of this reaction, can coagulate the potassium hydroxide, thereby extending the reaction times. This method is also unsuitable for the synthesis of phenyl-substituted α-lactams due to unacceptably low yields. Thus, regardless of the base (potassium tert-butoxide, sodium tert-butoxide, or potassium hydroxide) used to induce cyclization, undesired side reactions or follow-up reactions may occur, which can reduce the yield of the α-lactam substantially.

A second, rather restricted method used to synthesize α-lactams, first introduced in 1982, involves the cyclization of N-alkyl-N-hydroxyamides by elimination of water through treatment with trifluoromethanesulphonic anhydride and triethylamine (Scheme 3). Although this method has been used extensively to generate unstable α-lactams in situ, to date only one stable α-lactam has been synthesized by this method. This is probably due to the lack of commercial availability of N-alkyl-N-hydroxyamides, which are necessary for the synthesis of the N-alkyl-N-hydroxyamide precursors.

Therefore, we had endeavored for some time to develop a new α-lactam synthesis, which would not have the drawbacks of the above methods. As a large variety of α-haloamide precursors can easily be synthesized and then...
dehydrohalogenated, we were searching for a non-nucleophilic, non-aqueous strong base that would advantageously replace the currently used sodium tert-butoxide and potassium hydroxide.

Our attention fell on sodium hydride which has been tried as a base in the synthesis of \( \alpha \)-lactams before. In the 1950s and 1960s, the possibility that certain \( \alpha \)-haloamides may be cyclized to \( \alpha \)-lactams on dehydrohalogenation with sodium hydride in benzene had been investigated independently by two groups.\(^{16,17}\) However, in no case could an \( \alpha \)-lactam be isolated or detected as an intermediate, although the formation of all actual products could be explained through a common \( \alpha \)-lactam intermediate. Thus, the dehydrochlorination of \( \alpha \)-chloro-\( \alpha \)-diphenylacetanilide (1a) with sodium hydride gave\(^{17}\) 2-(3,3-diphenyl-2-indolinon-1-yl)-2,2-diphenylacetanilide (4) as the major product (Scheme 4), together with smaller amounts of 3,3-diphenyl-2-indolinone (5) and 1,3-diphenyl-2-indolinone (6), rather than 1,3,3-triphenylaziridinone (2a), as claimed\(^{16b}\) earlier (Scheme 3). It was later learned\(^{8}\) that the choice of an \( N \)-phenyl-\( \alpha \)-haloamide 1 as the starting substrate could only lead to unstable \( \alpha \)-lactams 2.

Therefore, sodium hydride as a dehydrohalogenating agent in \( \alpha \)-lactam synthesis was abandoned, largely because it begins to react with \( \alpha \)-haloamides (in benzene solution) only above +40 °C, at which temperature the early \( \alpha \)-lactams were not stable.\(^{6,8}\)

Subsequent to a report by Aspinall et al.\(^{18}\) that sodium hydride in combination with the phase-transfer catalyst 15-crown-5 ether is an efficient base for the Williamson etherification of hindered alcohols, we thought the time has come to investigate the possibility whether sodium hydride and 15-crown-5 ether constitute a superior pair of agents for the synthesis of \( \alpha \)-lactams 2 from \( \alpha \)-haloamides 1.

For this study, we selected six known \( \alpha \)-lactams (Figure 1) of varying stability: \( 1-(1\text{-adamantyl})-3\text{-tert-butylaziridinone} \) (2b), \( 3\text{-tert-butyl}-1\text{-triphenylmethylaziridinone} \) (2c), \( 1,3\text{-di-tert-butylaziridinone} \) (2d), \( 3\text{-tert-butyl}-1\text{-tert-butylaziridinone} \) (2e), \( 1\text{-tert-butyl}-3\text{-dimethylaziridinone} \) (2f), and \( \text{cis}-(1,1\text{-p-menth-1,8-ylene})\text{bis}(3\text{-tert-butyl}-2\text{-aziridinone}) \) (2g). While \( \alpha \)-lactam 2f has only marginal stability\(^{6}\) (it decomposes completely after one hour refluxing in ether), all others are very stable. Following published procedures,\(^{6,7,11,19–21}\) the \( \alpha \)-bromoamide (1b–g) precursors to these \( \alpha \)-lactams (2b–g) were easily obtained in high yields with the physical and spectral properties being identical to those reported previously.

While optimizing this synthesis, it was determined that the formation of \( \alpha \)-lactams (2b–g) using sodium hydride with 15-crown-5 ether proceeds in high yield when dichloromethane was used as the solvent. Significantly

\[
\begin{align*}
\text{Scheme 3} & \quad \text{Dehydration of } N\text{-alkyl-}N\text{-hydroxyamides 3 to } \alpha\text{-lactams 2.}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 4} & \quad \text{The reaction of } \alpha\text{-chloro-} \alpha\text{-diphenylacetanilide 1a with NaH.}
\end{align*}
\]
lower yields were observed when hexane, benzene, or THF was employed. It was also observed that after several months, the 15-crown-5 ether slowly loses some of its catalytic activity due to its exposure to air. However, heating the crown ether in an oven at approximately 120 °C for 30 minutes and then cooling it in a desiccator to room temperature, fully restores its catalytic activity.

The progress of α-lactam 2 formation was followed by monitoring the disappearance of the amide carbonyl band (~1680 cm⁻¹) of the starting α-haloamide 1 and the appearance of the α-lactam carbonyl band (~1840 cm⁻¹) in the IR spectrum, taken at regular intervals during the reaction. After the reaction was complete, a water wash removed the excess sodium hydride and the sodium halide by-product, however, a significant amount of 15-crown-5 ether remained. The 15-crown-5 was easily removed by taking up the crude α-lactam 2 in hexane and washing the resulting solution with water. If difficulty is encountered in separating the aqueous from the organic layer, adding a small amount of sodium chloride (~70–80 mol%, 0.3–0.5g) allows for easy and complete separation of the two layers.

The reaction times and yields with this new method versus previously reported reaction times and yields of α-lactams 2b–g are listed in Scheme 5 and Scheme 6. As shown in Scheme 5 and Scheme 6, yields of all the α-lactams synthesized by the use of NaH with 15-crown-5 are comparable or superior to those reported elsewhere. However, only short reaction times were necessary, especially when compared to the method which utilizes potassium tert-butoxide. The reaction times, easy work-up, high yields, and the ability to synthesize α-lactams containing a phenyl substituent, we find the method described herein to be superior to the previous published syntheses of α-lactams.

The by-products of this synthesis, hydrogen gas and sodium bromide, are easily removed. In addition, in the case of 1-tert-butyl-3,3-dimethyloxazolidinone (2f), sodium hydride does not catalyze the isomerization of this α-lactam to N-tert-butylmethacrylamide, which has been observed when potassium tert-butoxide is used. Finally, this method works well in the presence of phenyl substituents as evidenced by the synthesis of α-lactam 2c.

In order to test the versatility of this method and to determine if α-chloroamides would also be suitable starting reagents, a new α-lactam, 1-(1-adamantyl)-3-phenylaziridine (2h) was prepared by cyclizing N-(1-adamantyl)-2-chloro-2-phenylethanamide (1h) (Scheme 7).

The yield of crude 2h, as determined by ¹H NMR, was 91.3%. Attempts to purify 2h by low temperature recrystallization or by column chromatography proved unsuccessful due to the instability of the α-lactam. However, crude 2h was isolated and reacted with the nucleophile, benzylamine. N-Benzyl-2-(1-adamantylamino)-2-phenylethanamide (7) was isolated in 67.1% yield (Scheme 7). Assignment of structure 7 was based on the peak at m/z = 240 in the mass spectrum and the methylene protons of the benzyl group appearing at δ = 4.45–4.54 in the ¹H NMR spectrum. The rationale for this assignment is discussed elsewhere.

Therefore, owing to short reaction times, easy work-up, high yields, and the ability to synthesize α-lactams containing a phenyl substituent, we find the method described herein to be superior to the previous published syntheses of α-lactams.

Melting points are uncorrected and were measured on a Thomas-Hoover capillary melting point apparatus. TLC was performed with Analtech silica gel glass backed plates (250 microns) and recorded as a function of Rf values. Flash chromatographic separations were performed using silica gel (JT Baker, 40 µm) as the stationary phase. IR spectra were recorded on a Perkin Elmer Fourier Transform (FT-IR) Spectrum 1000 Spectrophotometer. NMR spectra (¹H and ¹³C) were obtained on a 400 MHz Bruker Spectrometer with TMS as the internal standard. Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, Georgia). MS spectra

Scheme 5 The synthesis of α-lactams 2b–f.

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Current Procedure Reaction Time and Yield</th>
<th>Lit.² Reaction Time and Yield</th>
<th>Lit.³ Reaction Time and Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>C(CH₃)₃</td>
<td>H</td>
<td>Ada</td>
<td>2 h, 96%</td>
<td>N.R., 65%⁹</td>
</tr>
<tr>
<td>2c</td>
<td>C(CH₃)₃</td>
<td>H</td>
<td>Tr⁵</td>
<td>1 h, 96%</td>
<td>2.5 h, 93%⁷</td>
</tr>
<tr>
<td>2d</td>
<td>C(CH₃)₃</td>
<td>H</td>
<td>C(CH₃)₃</td>
<td>4 h, 98%</td>
<td>0.25 h, 68%²⁰</td>
</tr>
<tr>
<td>2e</td>
<td>Ada</td>
<td>H</td>
<td>C(CH₃)₃</td>
<td>0.5 h, 98%</td>
<td>0.42 h, 56%²¹</td>
</tr>
<tr>
<td>2f</td>
<td>CH₃</td>
<td>CH₃</td>
<td>C(CH₃)₃</td>
<td>3 h, 55%</td>
<td>1 h, 54%⁶</td>
</tr>
</tbody>
</table>

³ Ad = adamantyl; Tr = trityl.
⁴ Using tBuO²
⁵ Using KOH/18-crown-6.
⁶ N.R. = not reported.

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were recorded on a Hewlett Packard® GI800A GCD System. The reagents benzylamine (freshly distilled before use), 1-adamantanamine, 15-crown-5 ether, NaH (60% dispersion in mineral oil), EtN, and THF were obtained from Aldrich® (Milwaukee, WI). EtOAc and CH₂Cl₂ were obtained from J.T. Baker® (Phillipsburg, NJ). Hexane was obtained from VWR (Plainfield, NJ). 1-Chlorophenylacetyl chloride was obtained from Fluka (Milwaukee, WI). Tritylamine was obtained from Alfa Aesar (Ward Hill, MA) and trimethylacetic acid was obtained from Lancaster (Windham, NH).

α-Bromoamides 1b–g
All of the known α-bromoamides (1b–g) were synthesized using published procedures[6,7,10,19–21] with their physical and spectral properties being identical to those reported earlier.

N-(1-Adamantyl)-2-chloro-2-phenylethanamide (1b)
Following the general procedure of Lengyel and Aaronson[22], a solution of α-chlorophenylacetyl chloride (32.4 g, 0.171 mol) in CH₂Cl₂ (90 mL) was added dropwise at 0°C to a suspension of 1-adamantanamine (25.9 g, 0.174 mol) and Et₃N (17.4 g, 0.174 mol) in CH₂Cl₂ (160 mL). The reaction mixture was stirred for 20 h at rt, washed with distilled H₂O (3 × 200 mL), 2 N HCl (2 × 60 mL), and again with distilled H₂O (2 × 200 mL). The organic layer was dried with Na₂SO₄ and the CH₂Cl₂ removed under reduced pressure to yield crude N-(1-Adamantyl)-2-chloro-2-phenylethanamide (1b). After recrystallization from MeCN, pure 1b (36.0 g, 69.1%, mp 152–154 °C) was obtained.

IR (CCl₄): 3411 (N–H), 3035 (Ar C–H), 2911 and 2852 (aliphatic C–H), 1683 (C=O, amide) cm⁻¹.

1H NMR (CDCl₃): δ = 1.69 [s, CH₃(Ad), 6 H], 2.04 [s, CH₃(Ad), 6 H], 2.09 [s, CH(Ad), 3 H], 5.24 [s, CHCl, 1 H], 6.44 [s, NH, 1 H], 7.37 (m, Ph, 5 H).

13C NMR (CDCl₃): 6 = 29.40 [CH(Ad)], 36.24 [CH₃(Ad)], 41.24 [CH₂(Ad)], 52.58 [C(Ad)], 61.93 (CHCl), 127.75, 128.83, 128.90 (2 × Ph₉), 137.66 [Cl(Ph)], 166.09 (C=O).

Anal. Calc. for C₁₈H₂₃ClNO: C, 71.16; H, 7.34; N, 4.61; Cl, 11.43. Found: C, 70.99; H, 7.34; N, 4.61; Cl, 11.43.

α-Lactams (2b–f); General Procedure
A suspension of NaH (60% dispersion in mineral oil) (6.0 mmol) and 15-crown-5 ether (0.5 mmol) in CH₂Cl₂ (50 mL) was stirred for 20 minutes and then the α-haloamide (1b–f) (2.0 mmol) was added. The reaction mixture was stirred for an additional 0.5–3 h, washed with distilled H₂O (3 × 50 mL), dried with Na₂SO₄, and the CH₂Cl₂ removed under reduced pressure. The resulting crude α-lactam (2b–f) was taken up in hexane (50 mL), washed with distilled H₂O (3 × 50 mL), dried with Na₂SO₄, and the hexane removed under reduced pressure to afford pure α-lactam (2b–f), with comparable physical and spectral properties reported elsewhere.[5,7,10,19–21]

2f
The reaction was done at 0 °C and the product yield was based on 1H NMR (it was impure with starting α-bromoamide 1f).

2g
NaH (60% dispersion in mineral oil) (12 mmol) and 15-crown-5 (0.50 mmol) were used with 1g (2 mmol) and the reaction mixture stirred for 48 h. Pure 2g was obtained by flash chromatography.[11]

1-(1-Adamantyl)-3-phenylaziridinone (2h)
A suspension of NaH (60% dispersion in mineral oil) (0.24 g, 6.0 mmol) and 15-crown-5 ether (0.38 g, 0.5 mmol) in CH₂Cl₂ (50 mL) was stirred for 20 minutes and then N-(1-adamantyl)-2-chloro-2-phenylethanamide (1h) (0.606 g, 2.0 mmol) was added. The reaction mixture was stirred for an additional 1.5 h and then was washed with distilled H₂O (3 × 50 mL), dried with Na₂SO₄, and the CH₂Cl₂ removed under reduced pressure. The resulting crude α-lactam (2h) was taken up in hexane (50 mL), washed with distilled H₂O (3 × 50 mL), dried with Na₂SO₄, and the hexane removed under reduced pressure to afford a solid (0.56 g), 91.3% based on 1H NMR.

IR (CCl₄): 1849 (C=O, lactam) cm⁻¹.

1H NMR (CDCl₃): δ = 3.90 (s, CH of lactam ring).

Bis-α-lactams 1g
NaH (0.24 g, 6.0 mmol) and MeOCl were added to 2g (2 mmol) and the reaction mixture stirred at rt for 1 h. The THF was removed under reduced pressure and the

N-Benzyl-2-(1-adamantylamino)-2-phenylethanamide (7)
Crude 1-(1-adamantyl)-3-phenylaziridinone (2h) (0.54 g, 2.0 mmol), determined to be 91.3% pure, based on 1H NMR, was dissolved in THF (30 mL) and a soln of benzylamine (0.858 g, 8.0 mmol) in THF (10 mL) was added. The reaction mixture stirred at rt for 1 h. The THF was removed under reduced pressure and the

Scheme 6 The synthesis of bis-α-lactam 2g.[11]

Scheme 7 Synthesis and reaction of 1-(1-adamantyl)-3-phenylaziridinone (2h).
resulting solid was purified by flash chromatography (Hexane–EtOAc, 70:30) to afford pure \( N \)-benzyl-2-amino-(1-adamantyl)-2-phenylethanamide (7), (0.46 g, 67.1% mp 156–157°C).

IR (CCl\(_4\)): 3355 (N–H), 3088, 3066, 3031 (Ar C–H), 2910 and 2851 (aliphatic C–H), 1679 (C=O amide) cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)): \( \delta = 1.40 \) (s, NH amide, 1 H), 1.50–1.67 [m, \( CH_2 \) (Ad), 12 H], 2.09 [s, CH(Ad), 3 H], 4.49 (dd, \( J = 5.82, 14.75 \) Hz, \( CH_HHPh \), 1 H), 4.49 (s, CH, 1 H), 4.54 (dd, \( J = 6.30, 14.75 \) Hz, \( CH_HHPh \), 1 H), 7.37 (m, 2 \( Ph \), 10 H), 8.23 (s, NH, 1 H).

\(^{13}\)C NMR (CDCl\(_3\)): \( \delta = 29.64 \) [\( CH(Ad) \)], 36.62 [\( CH_2 \) (Ad)], 43.17 [\( CH_2 \) (Ad)], 52.21 [\( C1(Ad) \)], 59.85 (CH), 127.46, 127.54, 127.88, 128.03, 128.79, 129.11 (4 \( Ph \) ortho, 4 \( Ph \) meta, 2 \( Ph \) para), 138.79, 141.96 (C1Ph), 174.25 (C=O).

GCMS: \( m/z \) 374 [M\(^+\), (C\(_{25}\)H\(_{30}\)N\(_2\)O)\(^+\); 240 base peak, (C\(_{6}\)H\(_{5}\)CHNHC\(_{10}\)H\(_{15}\)\(^+\)]; 135 (C\(_{10}\)H\(_{15}\)\(^+\)).


References

(1) Part of this work was presented at the 223\(^{rd}\) National Meeting of the American Chemical Society, Orlando, FL, April 7-11, 2002, Division of Organic Chemistry, Abstract 350.
(12) Unpublished results from the authors’ laboratory.