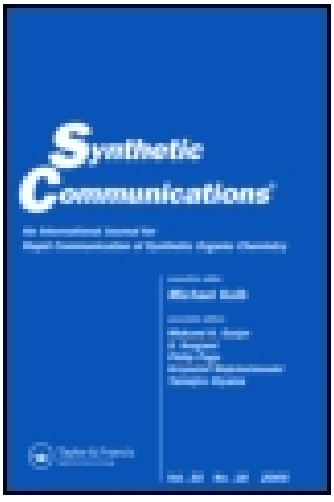

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N-Benzyl-5-hydroxy-3-pyrrolidin-2-one by Hydrogen Peroxide Oxidation of *N*-Benzyl-3-phenylseleno-2-pyrrolidinone

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Abstract: Using the known peroxide oxidation of *N*-benzyl-3-phenylseleno-2-pyrrolidinone with 30% hydrogen peroxide at −5°C after 3.5 h, we prepared the expected *N*-benzyl-3-pyrrolin-2-one. However, reaction with 30% hydrogen peroxide for 12 h (−5°C → ambient) gave the unexpected product *N*-benzyl-5-hydroxy-3-pyrrolidin-2-one in 84% isolated yield. This procedure is a new synthetic route to *N*-benzyl-5-hydroxy-3-pyrrolidin-2-one.

Keywords: elimination, lactam, peroxide, pyrrolidin-2-one, rearrangement, selenoxide

While pursuing a new approach to the synthesis of ceramides, we required *N*-benzyl-3-pyrrolin-2-one (**3**). This lactam has been reported in the literature,[1] relying on a straightforward procedure that involved syn-elimination of selenoxide **2**,[2] prepared by oxidation of *N*-benzyl-3-phenylseleno-2-pyrrolidinone, **1**. Such selenoxide elimination reactions are commonplace.[2] *N*-Benzyl-2-pyrrolidinone is readily prepared from 2-pyrrolidinone and benzyl bromide[3] or benzyl chloride.[4] The preparation of conjugated lactams is also well known, via reaction of the lactam enolate anion with PhSeBr, followed by oxidation and syn elimination of the selenoxide.[5]

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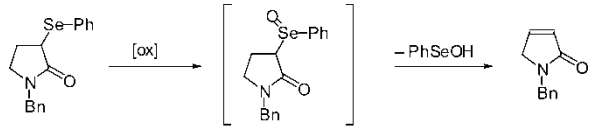
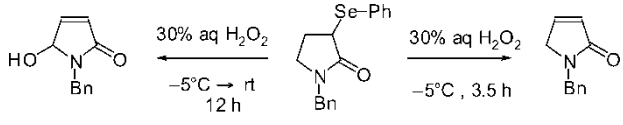


1 2 3

In this work, we prepared **1** in 52% yield by reaction of N-benzyl-2-pyrrolidinone with lithium diisopropylamide (LDA), tetrahydrofuran (THF), −78°C and with PhSeBr, THF, −78°C.[2–5] The literature procedure to prepare **3** by oxidation of **1** was repeated several times, using 30% aqueous hydrogen peroxide at −5°C, for 3.5 h. Under these conditions, we obtained **3** in 87% yield with few by-products. During the course of one oxidation with 30% hydrogen peroxide at −5°C, the solution was allowed to stir for 12 h. During this time period, the reaction mixture warmed to ambient temperatures. Upon workup, we discovered that the major product was not **3** but rather **4**.[6] This was unexpected, and such a hydroxylation reaction had not been reported previously from selenoxide elimination reactions with lactams. Lactam **4** is a known compound, however, prepared by the cerium chloride/sodium borohydride reduction of *N*-benzyl maleimide,[7] which can be prepared by reaction of maleic anhydride and benzylamine.[8]



4 1 3

Formation of **4** was unusual, given that the preparation of conjugated lactams by this method had been reported many times, and we repeated the reaction to confirm the transformation. Indeed, lactam **4** was formed in 84% isolated yield under these conditions, making this process a synthetically viable alternative to the previously reported synthesis.[7] Perhaps more important, the synthetic community should be aware of this anomalous reaction when preparing conjugated lactam compounds and also be aware of the sensitivity of the reaction to temperature and time.

The mechanism of the hydroxylation is unknown at this time, but allylic oxidation of **3**, or rearrangement from an intermediate that is as yet undefined, are possibilities. However, mechanistic analogies suggested by literature precedent do not adequately explain this transformation. One possibility is the Evans–Mislow rearrangement of allylic sulfides,[9] which involves a [2,3]-sigmatropic rearrangement. Reich and Yelm reported a similar [2,3]-sigmatropic rearrangement of selenoxides,[10] which they stated was facile at temperatures hotter than −50°C. Sharpless and Lauer showed that oxidation of allylic selenides gave rearrangement to alcohols via a [2,3]-sigmatropic rearrangement.[11] To invoke such a mechanism, however, requires initial formation of an allylic selenide, which seems unlikely in this

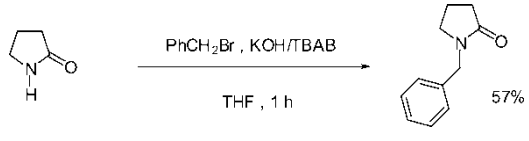
case. Benzeneselenic acid is a by-product of the selenoxide elimination and can add to alkenes as reported by Sharpless, who showed that cyclooctene reacted with benzeneselenic acid to give the hydroxy-selenide.[12] Subsequent oxidation with *tert*-butylhydroperoxide gave cyclooct-2-en-1-ol. Such an addition–elimination sequence involving **3** would not lead to **4** directly but may lead to an intermediate that rearranges to **4**. This is, of course, speculative. The allylic oxidation of alkenes with selenium dioxide[13] involving an initial ene reaction followed by a [2,3]-sigmatropic rearrangement[14] is another possible analogy. There is no evidence of selenium dioxide in the reaction of **1**, but reaction of the S=O unit of the PhSeOH by-product with **3** may be possible. If so, rearrangement and conversion to **4** in the aqueous medium is possible. All of this is speculative, of course, and a detailed mechanistic study is required. Such speculation has some value in that it points to a working hypothesis that formation of **4** may involve initial formation of **3** followed by a reaction with PhSeOH in the presence of the aqueous hydrogen peroxide.

Apart from the mechanistic speculation, the reaction of **1** with aqueous hydrogen peroxide under these conditions is a synthetically useful route to hydroxy-lactam **4**. From a practical standpoint, formation of **4** should be considered a competitive sidereaction for the preparation of conjugated lactams by selenoxide elimination that is dependent upon temperature control and reaction time.

EXPERIMENTAL

All glassware was flame-dried under nitrogen, and all reactions were performed under nitrogen. All chemicals were purchased from the Aldrich Chemical Co. and used without further purification. The tetrahydrofuran was dried over sodium–benzophenone and distilled immediately prior to its use. The ^{1}H NMR (400 MHz) and the ^{13}C NMR (100.65 MHz) were recorded on a Brücker DRX-400 instrument, in $CDCl_3$, and all chemical shifts are reported in δ, relative to tetramethylsilane (TMS) as an internal standard. Infrared spectra were recorded on a Jasco FT/IR-410 instrument and are reported in centimeters^{-1}. Mass spectra were recorded on a Hewlet-Packard 5970 GC/MS instrument.

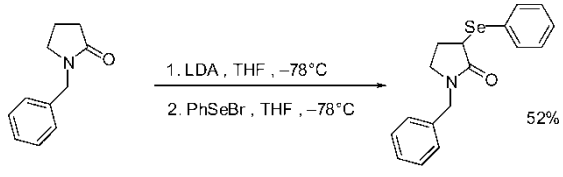
Preparation of *N*-Benzyl-2-pyrrolidinone



Addition of benzyl bromide (18 mL, 151 mmol) and 2-pyrrolidinone (12.75 g, 150 mmol) to a mixture of pulverized KOH (8.30 g, 149 mmol) and

tetrabutylammonium bromide (TBAB, 7.09 g, 22 mmol) in 100 mL of THF, in a 500-mL, three-neck, round-bottom flask fitted with an overhead mechanical stirrer, was followed by stirring of the reaction mixture for 1 h at ambient temperature. During the addition and subsequent reaction, the reaction flask was immersed in a Bransonic 220 ultrasonic bath. Filtration of the precipitate and concentration of the reaction mixture in vacuo led to an oil, which was treated with 100 mL of diethyl ether. The precipitated TBAB was filtered, the organic layer dried with $MgSO_4$, and the solution filtered and concentrated in vacuo. Purification by silica-gel chromatography (ether/hexane) gave 15.0 g of *N*-benzyl-2-pyrrolidinone[3] (86.0 mmol, 57%). ^{1}H NMR: δ 7.27–7.19 (m, 5H), 4.40 (s, 2H), 3.17 (t, 2H), 2.33 (t, 2H), and 1.94 ppm (m, 2H); ^{13}C NMR: δ 174.5 (S), 136.7 (s), 128.4 (d), 128.3 (d), 128.1 (d), 127.8 (d), 127.5 (d), 46.4 (t), 46.3 (t), 30.8 (t), and 17.6 ppm (t); IR (neat): 3030, 2915, 1687, 1429, 1286, and 702 cm^{-1}; MS (m/z, rel. int.), 176 (67, P), 146 (44), 118 (19), 104 (38), 91 (100, B), 65 (35), and 51 (15).

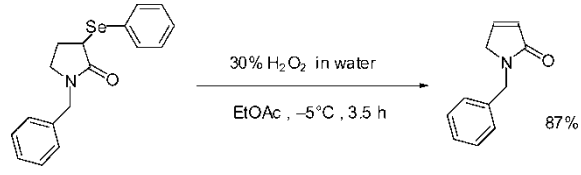
Preparation of *N*-Benzyl-3-phenylseleno-2-pyrrolidinone



A 250-mL, three-neck, round bottom flask was charged with 2.63 mL of diisopropylamine (18.8 mmol) dissolved in 20 mL of dry THF, at room temperature. The reaction flask was immersed in a dry-ice bath, and the solution was stirred for 5 min at -78°C). Addition of 15.85 mL of butyllithium in hexane (1.2 M, 19.3 mmol) to the diisopropylamine solution was accomplished via cannula. The reaction mixture was stirred for 15 min at -78°C, and 2.74 mL of 1-benzyl-2-pyrrolidinone (16.8 mmol) dissolved in 20 mL of THF was transferred to the reaction mixture via cannula. The reaction mixture was stirred for 1 h at -78°C, and 4.638 g of phenylselenenyl bromide (19.3 mmol) dissolved in 20 mL of THF was transferred to the reaction mixture. The reaction mixture was stirred for 30 min at -78°C, and 10 mL of saturated aqueous ammonium chloride was added. The reaction mixture was stirred while the reaction mixture warmed to ambient temperature, and 100 mL of ethyl acetate and 50 mL of distilled water were added to the reaction. After separation of the organic phase, it was washed with brine, dried with magnesium sulfate, and concentrated in vacuo. The crude product was purified with silica column chromatography using 25% ethyl acetate in hexane to give 2.94 g of 3-phenylselenopyrrolidin-2-one[3,5] (10.0 mmol, yield 51.9%).

GC/MS (m/z): 51, 65, 91 (b), 157, 174, 250, 331 (M^+), ^{1}H NMR: δ 2.05–2.13 (1H, m), 2.44–2.54 (1H, m), 2.93–2.99 (1H, m), 3.06–3.11 (1H, m), 3.94–3.98 (1H, dd, *J* 8.83 Hz, *J* 4.37 Hz), 4.34–4.43 (2H, dd, *J* 21.8 Hz, *J* 16.7 Hz), and 7.15–7.68 ppm (10H, m).

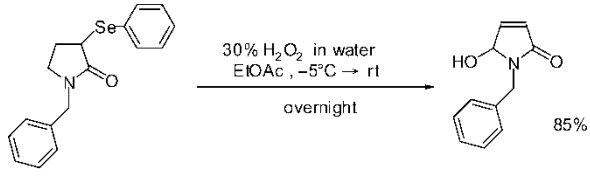
Preparation of *N*-Benzyl-3-pyrrolin-2-one



A 25-mL, three-neck, flask containing 525 mg of 3-phenylseleno-2-pyrrolidinone (1.59 mmol) dissolved in 5 mL of ethyl acetate was immersed in a salt-ice bath and stirred for 5 min at -10°C. Slow addition of 0.9 mL of 30% aqueous hydrogen peroxide was followed by stirring at -5°C until the 3-phenylseleno-2-pyrrolidinone disappeared, as monitored by thin-layer chromatography (TLC) (about 4 h). After the completion of the reaction, the ice bath was removed, and 10 mL of ethyl acetate and 5 mL of brine were added to the reaction mixture. Extraction was followed by separation of the organic layer. The organic layer was washed with 5 mL of saturated aqueous sodium bicarbonate solution and then 5 mL of brine. Drying of the organic layer with $MgSO_4$ was followed by filtration and concentration in vacuo. The crude product was purified with silica column chromatography (50% ethyl acetate in hexane) to give 238 mg of 1-benzyl-3-pyrrolin-2-one[3,5] (1.38 mmol, 87%).

GC/MS (m/z): 51, 65, 91 (B), 144, and 173 (M^+); ^{1}H NMR: δ 3.80 (2H, s, 5H), 4.57 (2H, s), 6.15–6.17 (1H, dt, *J* 6.0 Hz, *J* 1.8 Hz), 6.97–6.99 (1H, dt, *J* 6.0 Hz, *J* 1.6 Hz, 3H), and 7.16–7.28 ppm (5H, m); ^{13}C: δ 45.97, 52.27, 127.58, 127.94, 128.00, 128.76, 137.30, 142.83, and 171.36 ppm; IR (neat): 3082, 1703, and 1677 cm^{-1}.

Preparation of *N*-Benzyl-5-hydroxy-3-pyrrolin-2-one



A 25-mL, three-neck flask was charged with 525 mg of *N*-benzyl-3-phenylseleno-2-pyrrolidinone (1.59 mmol) dissolved in 5 mL of ethyl acetate and

immersed in a salt-ice bath. After stirring for 5 min at -10°C, 0.9 mL of 30% aqueous hydrogen peroxide solution was slowly added to the solution. The reaction mixture was stirred at -5°C until the *N*-benzyl-3-phenylseleno-2-pyrrolidinone disappeared as monitored by TLC (about 4 h). The reaction mixture was stirred overnight with slow elevation of temperature from -5°C to room temperature. At this time, 10 mL of ethyl acetate and 5 mL of brine were added to the reaction mixture, and the organic layer was separated. The organic layer was washed with 5 mL of saturated aqueous sodium bicarbonate solution and then 5 mL of brine, dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified with silica column chromatography (100% ethyl acetate) to give 254 mg of *N*-benzyl-5-hydroxy-3-pyrrolin-2-one[7] (1.34 mmol, 84%).

GC/MS (m/z): 55, 65, 79, 91, 106 (B), 189 (M^+); ^{1}H NMR (400 MHz): δ 3.56–3.59 (1H, d, *J* 10.9 Hz), 4.14–4.18 (1H, d, *J* 14.9 Hz), 4.81–4.85 (1H, d, *J* 14.9 Hz), 5.16–5.19 (1H, d, *J* 10.9 Hz), 6.03–6.05 (1H, d, *J* 5.9 Hz), 6.84–6.86 (1H, d, *J* 5.9 Hz), and 7.18–7.25 ppm (5H, m); ^{13}C NMR (100.65 MHz): δ 43.1, 83.1, 128.1 (2C), 128.7 (2C), 129.2 (2C), 137.5, 146.5, and 170.0 ppm; IR (KBr): 3178, 2963, 1662, 1591 cm^{-1}.

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