# REARRANGEMENT OF N-(p-TOLUENESULFONYLOXY)-2-PYRROLIDINONE

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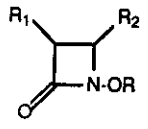
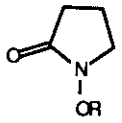
Abstract - Base induced rearrangement of N-(p-toluenesulfonyloxy)-2-pyrrolidinone provides 3-(p-toluenesulfonyloxy)-2-pyrrolidinone by an apparent nitrogen analog of the Favorskii rearrangement.

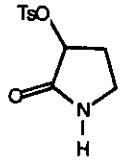
Variously substituted N-hydroxy-2-azetidinones (**1**) have been found to undergo interesting molecular rearrangements.[1] Since substituted pyrrolidinones are useful intermediates for the synthesis of a number of nitrogen heterocycles, we decided to study the possibility of inducing rearrangements in the corresponding N-hydroxy-2-pyrrolidinones (**2**). Herein we report that treatment of N-(p-toluenesulfonyloxy)-2-pyrrolidinone (**3**) with base initiates a smooth rearrangement to the corresponding 3-(p-toluenesulfonyloxy)-2-pyrrolidinone (**4**).




**1**




**2, R = H**
**3, R=pTs**




**4**

4-Chlorobutyro-O-benzylhyroxamate, **7**, was prepared by reaction of the corresponding acid choride, **5**, with O-benzylhydroxylamine, **6**, and then cyclized with NaH in methylene chloride to provide N-benzyloxy-2-pyrrolidinone, **8**, in 65% yield (Scheme 1). Attempting the same cyclization in DMF/$CH_2Cl_2$ (1:1) produced a mixture of N- and O-alkylated isomers (hydroximates) with the desired pyrrolidinone **8** being produced in only 20% yield. Hydrogenolysis ($H_2$/Pd-C, 1 atmosphere in ethanol) of **8** provided N-hydroxy-2-pyrrolidinone, **9**.[2] Treatment of **9** with 110 mole % of p-toluenesulfonyl chloride in pyridine at 5°C for 10 h provided the desired tosylate, **3**[3] (89% yield). Crystalline pyrrolidinone **3** (100 mg, 0.39 mmole) was dissolved in 10 ml of dry THF and 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU, 59 µl, 0.39 mmole) was added. After 30 min at room temperature, all of the starting material was

consumed. The THF was evaporated and the resulting mixture was subjected to column chromatography on silica gel to provide 3-(p-toluenesulfonyloxy)-2-pyrrolidinone, **4**[3], as a white crystalline solid in 60% yield. The structure of **4** was unambiguously established by an alternative preparation from 3-hydroxy-2-pyrrolidinone **11**.[4] Milder amine bases (pyridine, N-methylmorpholine, and triethylamine) did not induce the rearrangement of **3** to **4**. Interestingly, similar subjection of N-(p-toluenesulfonyloxy)-2-piperidinone **12** and N-(p-toluenesulfonyloxy)-2-azetidinone **13** to the same conditions (DBU/THF/room temperature) induced no rearrangement. Heating these same solutions of **12** and **13** led to decomposition. While mechanistic details are yet to be worked out, the net result of the rearrangement of **3** to **4** is similar to the Favorskii rearrangement[5] and may proceed through the aziridinone **10**. However, attempts to trap **10** with nucleophilic solvent (methanol) failed and again only the tosylate **4** was isolated. The rearrangement of **3** to **4** provides a novel route to substituted 3-hydroxy-2-pyrrolidinones which are useful synthetic intermediates and also of pharmacological interest as cognition activators.[4d,6]

ACKNOWLEDGEMENTS

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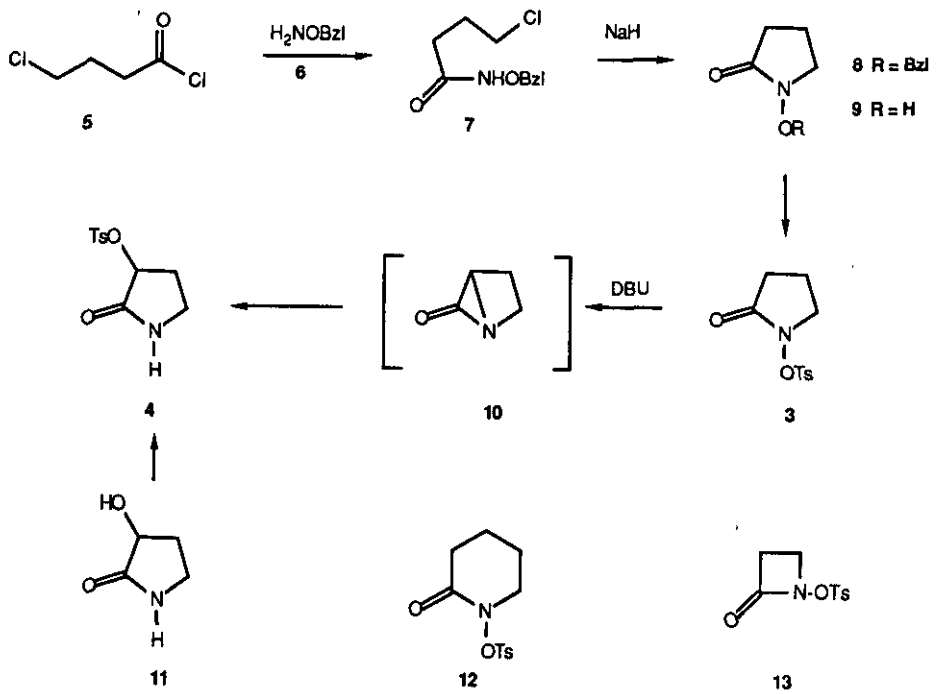
**Scheme 1**



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3. Selected characterization data include **3** mp 108-111°C; $^1$H NMR ($CDCl_3$) δ 2.15 (m, 4H) 2.4 (s, 3H), 3.5 (s, 2H), 7.35 (d, 2H), 7.9 (d, 2H); ir ($CH_2Cl_2$) 1750 $cm^{-1}$. Anal. calcd. for $C_{11}H_{13}NO_4S$: C (51.75), H (5.13), N (5.49). Found: C (51.61), H (5.07), N (5.26). **4**: mp 137-139°C; $^1$H nmr ($CDCl_3$) δ 2.36 (m, 1H), 2.44 (s, 3H), 2.56 (m, 1H), 3.33 (m, 1H), 3.45 (m, 1H), 4.91 (t, 1H), 6.6 (br s, 1H), 7.36 (d, 2H), 7.88 (d, 2H); ir (KBr) 1720 $cm^{-1}$. Anal. calcd. for $C_{11}H_{13}NO_4S$: C (51.75), H (5.13), N (5.49). Found: C (51.87), H (5.02), N (5.41).

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