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Regioselective reduction of *N*-alkyl-3-sulfonyl glutarimides. Synthesis of 3,4-dihydro-3-tosylpyridin-2-ones

Bo-Rui Chang, Chung-Yi Chen and Nein-Chen Chang*

Department of Chemistry, National Sun Yat-Sen University, Kaohsiung 804, Taiwan, ROC

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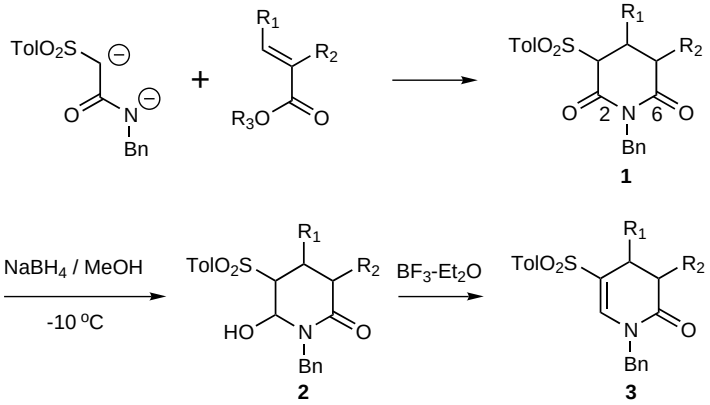
Abstract—Treatment of *N*-alkyl-3-sulfonyl glutarimides (**1**) with sodium hydride and then lithium aluminum hydride could give regioselective reduced hydroxy piperidones (**5**) which were further dehydrated to 3,4-dihydro-3-tosylpyridin-2-ones (**6**) in the presence of boron trifluoride.

N-Acyliminium ion has been used intensively in the synthesis of alkaloids and compounds with potential biological activities.[1] It is well known that hydroxy piperidone is a reasonable precursor of *N*-acyliminium ion.[2] Therefore, the regioselective reduction of asymmetrically substituted cyclic imide to their corresponding hydroxy piperidones became an interesting topic in natural products synthesis[3] and has been studied for decades. Nevertheless, it is unlikely that one soon will be able to make reliable predictions on the regiochemical outcome of reduction of more complex imide systems.[4]

Recently, we developed an efficient route to the unsymmetrical glutarimides with sulfonyl group at C-3 position.[5] We further discovered that treatment of **1** with sodium borohydride at −10°C in methanol solution gave exclusively C-2 carbonyl group reduced product **2** (Scheme 1). In the course of our study toward the synthesis of alkaloids, we needed C-6 carbonyl group reduced hydroxy piperidone **5**. Herein, we reported a general and mild route for the preparation of **5**.

As shown in Scheme 2, a mixture of glutarimide **1** and 1.2 equivalent of sodium hydride in THF was allowed to react at 25°C for 5 min, then 2 equivalent of $LiAlH_4$ was added in one portion and further stirred for 0.5–1.0 h. After normal a workup procedure, various hydroxy piperidones **5** were obtained with reduction occurring exclusively at the C-6 position. To confirm these results, hydroxy piperidones **5** were treated with boron trifluoride, the corresponding dehydration products **6** were produced in good yields (Scheme 2).



Scheme 1.

* Corresponding author.

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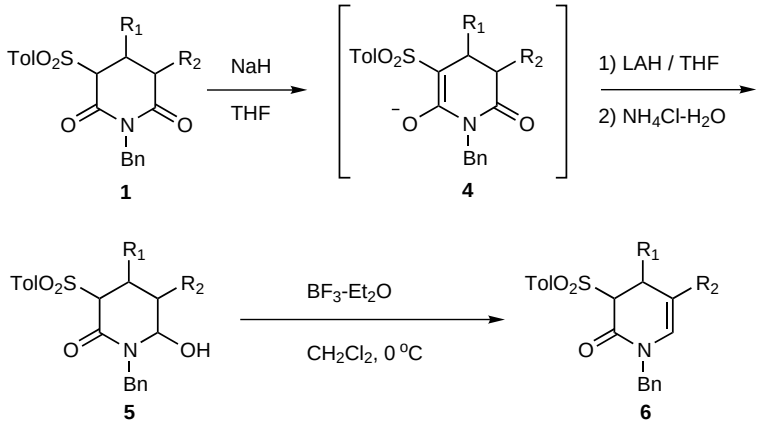
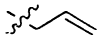
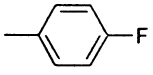


Scheme 2.

Several examples were examined and the results are listed in Table 1. Regioselective reduction of **1** could be rationalized by the formation of enolate **4**, which prevented the C-2 carbonyl group from $LiAlH_4$ reduction.

Table 1. Synthesis of **6** via regioselective $LiAlH_4$ reduction of **1**[a,b,c7]

Entry	R_1	R_2	Yield of **6** (%)
a	-H	-H	86
b	-H	$-CH_3$	85
c	-H	$-C_2H_5$	88
d	-H		86
e	-H	-Ph	80
f	-H	-Bn	90
g	$-CH_3$	-H	90
h	-Ph	-H	90
j		-H	85

[a] All the yields were based on glutarimides **1**.
[b] The structures of **6b** and **6d** were confirmed by X-ray analysis.
[c] Selected NMR spectral data for **6a**, **6b**, **6e**, **6f**, **6j**, see Ref. 8.

Desulfonation of **5b** and **5d** using sodium amalgam in methanol furnished the corresponding hydroxy lactam **7b** and **7d**, respectively. In general, these products cannot be obtained by direct reduction of the corresponding unsymmetrical glutarimides **9**.[6] It was reported that unsymmetrical glutarimides **9** seem to be preferentially reduced at the less hindered carbonyl group[4b] to furnish **10** (Scheme 3). The structures of **7b** and **7d** were further confirmed by transformation to the corresponding elimination enamides **8b** and **8d**, respectively.

In conclusion, we have developed general ways of regioselective reduction of unsymmetical 3-sulfonyl glutarimides. The application of these results in indolizidines, quinolizidines, isoquinolines and indole alkaloids synthesis is currently underway in our laboratory.

Acknowledgements

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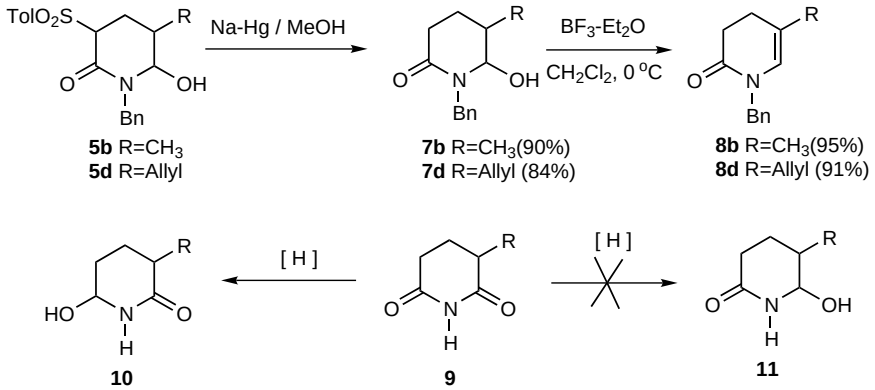

Scheme 3.

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7. Standard procedure: A solution of **1a** (357 mg, 1.0 mmol) in THF (10 mL) was added to a rapidly stirred suspension of sodium hydride (60% dispersion in mineral oil, 1.2 mmol). After the reaction mixture was stirred at room temperature for 5 min, 2.0 mmol of $LiAlH_4$ was then added and the resulting reaction mixture was stirred for 1.0 h, quenched with a saturated ammonium chloride solution (1 mL) and extracted with AcOEt (3×20 mL). The organic layers were washed with brine (2×10 mL), dried with anhydrous $MgSO_4$, filtered and evaporated. Without purification, crude **5a** was treated with boron trifluoride (cat.) in 20 mL of CH_2Cl_2 for 1 day, water (20 mL) was then added. After extraction with CH_2Cl_2 (2×20 mL), the organic layers were washed with brine (2×10 mL), dried with anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography (hexane/AcOEt = 4/1) to afford dehydration product **6a** (293 mg, 86%).
8. Selected spectral data of **6a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.5 Hz, 2H), 7.35–7.26 (m, 7H), 5.95 (dd, J = 8.0, 3.0 Hz, 1H), 5.15–5.12 (m, 1H), 4.70 (d, J = 15.0 Hz, 1H), 4.61 (d, J = 15.0 Hz, 1H), 4.05 (dd, J = 8.0, 3.0 Hz, 1H), 3.21 (ddd, J = 19.0, 5.0, 3.0 Hz, 1H), 2.88–2.81 (m, 1H), 2.42 (s, 3H); **6b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 8.0 Hz, 2H), 7.35–7.26 (m, 7H), 5.66 (s, 1H), 4.65 (d, J = 15.0 Hz, 1H), 4.57 (d, J = 15.0 Hz, 1H), 4.05 (dd, J = 8.0, 3.0 Hz, 1H), 3.01 (dd, J = 18.5, 3.0 Hz, 1H), 2.83 (dd, J = 18.5, 8.0 Hz, 1H), 2.43 (s, 3H), 1.72 (s, 3H); **6e**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 8.0 Hz, 2H), 7.37–7.23 (m, 12H), 6.21 (d, J = 2.5 Hz, 1H), 4.72 (s, 2H), 4.20 (dd, J = 8.0, 3.5 Hz, 1H), 3.59 (dd, J = 18.0, 3.5 Hz, 1H), 3.25 (ddd, J = 18.0, 8.0, 2.5 Hz, 1H), 2.42 (s, 3H); **6f**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 8.5 Hz, 2H), 7.35–7.23 (m, 10H), 7.134 (d, J = 7.0 Hz, 2H), 5.75 (d, J = 1.0 Hz, 1H), 4.69 (d, J = 15.0 Hz, 1H), 4.59 (d, J = 15.0 Hz, 1H), 4.00 (dd, J = 8.5, 3.5 Hz, 1H), 3.34 (S, 2H), 2.96 (dd, J = 18.5, 3.5 Hz, 1H), 2.70 (dd, J = 18.5, 1.0 Hz, 1H), 2.42 (s, 3H); **6j**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.0 Hz, 2H), 7.39–7.30 (m, 7H), 7.00–6.97 (m, 2H), 6.92–6.88 (m, 2H), 6.21 (d, J = 7.5 Hz, 1H), 5.31 (dd, J = 7.5, 6.5 Hz, 1H), 4.88 (d, J = 14.5 Hz, 1H), 4.57 (d, J = 6.5 Hz, 1H), 4.54 (d, J = 14.5 Hz, 1H), 4.00 (s, 1H), 2.44 (s, 3H); **8b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–7.21 (m, 5H), 5.74 (s, 1H), 4.63 (s, 2H), 2.56 (t, J = 8.0 Hz, 2H), 2.22 (t, J = 8.0 Hz, 2H), 1.65 (s, 3H).