COMMUNICATION

# Regioselective reduction of maleimide and citraconimide derivatives: general preparation of 5-hydroxy-1,5-dihydropyrrol-2-one

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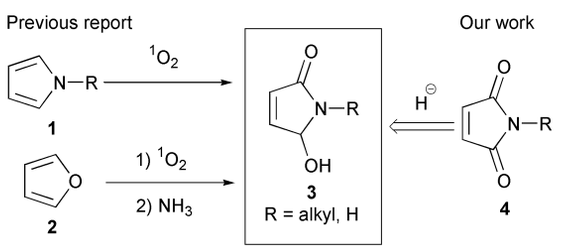
**$NaBH_4$ reduction of citraconimide derivatives regioselectively afforded 5-hydroxy-4-methyl-1,5-dihydropyrrol-2-ones, whereas $NaBH_4$–$CeCl_3$ or DIBAL-H reduction gave 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-ones.**

## Introduction

5-Hydroxy-1,5-dihydropyrrol-2-one derivatives **3** are important building blocks[1] for the preparation of a wide variety of natural products with potential pharmaceutical applications. Generally, 5-hydroxy-1,5-dihydropyrrol-2-one derivatives **3** are synthesized by photooxygenation of pyrrole derivatives **1**;[2] however, formation of a number of other side products has limited the overall yield of **3**. In spite of the limitations of availability of substrate, singlet-oxygen addition to the furan derivatives following ammonolysis is an alternative method




**Scheme 1** Synthesis of 5-hydroxy-1,5-dihydropyrrol-2-one derivatives **3**.

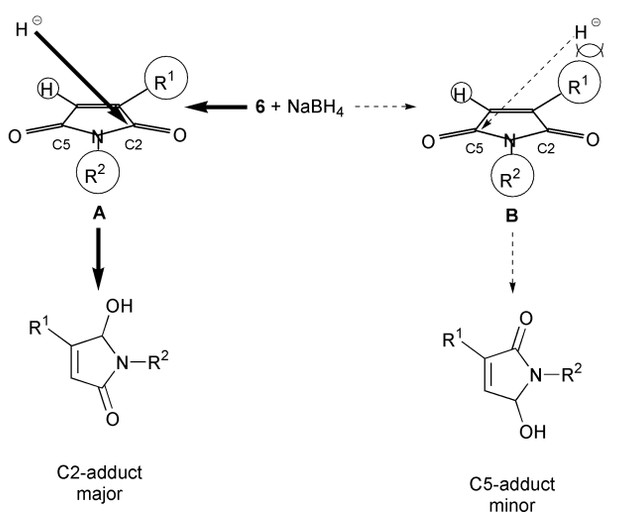
(Scheme 1).[3,4] We describe herein a convenient and direct synthesis of 5-hydroxy-1,5-dihydropyrrol-2-one derivatives **3** by a hydride addition to maleimide derivatives **4**.

## Results and discussion

Results of the reduction of maleimide derivatives **4**[5] are shown in Table 1.[6] Reduction of *N*-benzylmaleimide **4a** with sodium borohydride (1 equiv.) gave the unsaturated hydroxylactam **3a** as well as the saturated hydroxylactam **5a** in 41% and 59% yield, respectively (entry 1).[7] Addition of Lewis acid dramatically changed the chemoselectivity. In the presence of cerium(III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$, commercially available without further purification),[8] the unsaturated hydroxylactam **3a** was obtained in 91% yield (entry 2). No other side product was observed. Samarium(III) chloride was also an effective Lewis acid to give **3a** in 62% yield (entry 3). In the cases of *N*-allyl- and *N*-methylmaleimide **4b**,**c**, the reduction proceeded smoothly under the same reaction conditions, giving excellent yields of the desired unsaturated hydroxylactam **3b**,**c** (entries 4 and 5). The yield of **3** was reduced in the absence of the *N*-protection (entry 6).

We also investigated the reduction of citraconimide derivatives **6**. The reduction was carried out in the same manner mentioned above. Results are shown in Table 2. In all cases of citraconimide derivatives, no formation of the saturated hydroxylactam derivatives was observed. Treatment of *N*-benzylcitraconimide **6a** with $NaBH_4$ gave a mixture of the C2-adduct **7a** and C5-adduct **8a** in a ratio of 88 : 12 (entry 1). On the other hand, reverse regioselectivity was obtained by addition of $CeCl_3 \cdot 7H_2O$ with the **7**–**8** ratio of 29 : 71 (entry 2). Higher regioselectivity up to a **7**–**8** ratio of 9 : 91 was observed when diisobutylaluminium hydride (DIBAL-H) was used as a reducing agent (entry 4). These tendencies were observed in the reduction of *N*-diphenylmethyl, *N*-phenyl, *N*-allyl-, and *N*-H citraconimides **6b**–**e**. Complete reverse regioselectivity was revealed in the reduction of citraconimide **6e** (entries 9–11).

Previously Speckamp *et al.* reported a remarkably regioselective reduction of *gem*-disubstituted succinimides, in which the hydride attacks the hindered carbonyl group.[9] Their pioneering work and interpretation of the regiochemistry may explain our results. The regioselectivity could be ascribed to the depicted models as shown in Scheme 2. The complete coplanarity of the




**Scheme 2** Proposed mechanism of regioselectivity in the reduction of **6** with $NaBH_4$.

carbonyl groups and the double bond moiety in maleimide and citraconimide derivatives is well-established; therefore, a mechanism based on a general proposal for nucleophilic addition to carbonyl groups offers a satisfactory explanation.[10] The hydride anion approaches from the less hindered carbonyl group and attacks the more hindered C2 atom as depicted in model **A** virtually along a straight line through the carbonyl bond (Scheme 2).

On the other hand, in the reduction with $NaBH_4$–$CeCl_3$ or DIBAL-H the regioselectivity is explained by the effect

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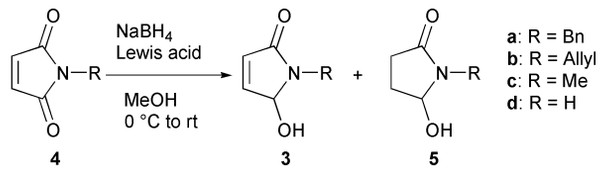
**Table 1** Chemoselective reduction of maleimide derivatives **4**

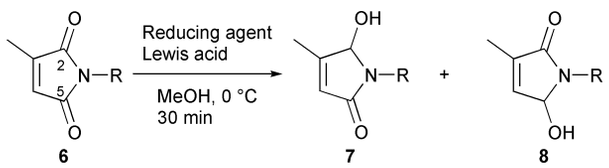



**4** **3** **5**

| Entry | Substrate | Lewis acid[a] | Time/h | **3**/Yield (%) | **5**/Yield (%) |
|---|---|---|---|---|---|
| 1 | **4a** | – | 1 | 41 | 59 |
| 2 | **4a** | $CeCl_3 \cdot 7H_2O$ | 1 | 91 | 0 |
| 3 | **4a** | $SmCl_3$ | 2 | 62 | 0 |
| 4 | **4b** | $CeCl_3 \cdot 7H_2O$ | 1 | 96 | 0 |
| 5 | **4c** | $CeCl_3 \cdot 7H_2O$ | 1.5 | 90 | 0 |
| 6 | **4d** | $CeCl_3 \cdot 7H_2O$ | 0.5 | 62 | 0 |

[a] Lewis acid (1 equiv.) was used.

**Table 2** Regioselective reduction of citraconimide derivatives **6**



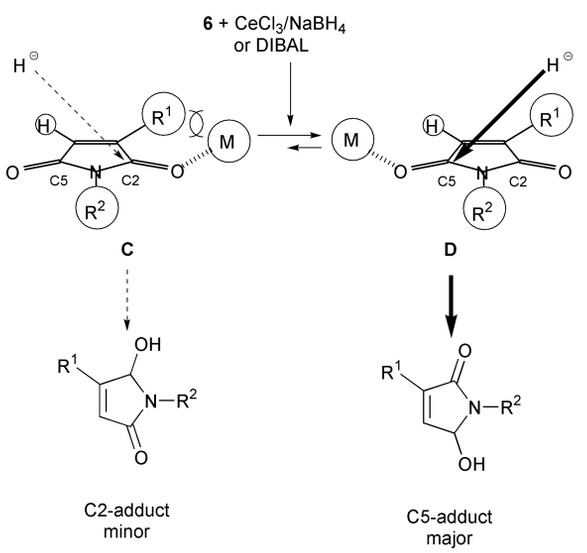

**6** **7** **8**

**a**: R = $CH_2Ph$, **b**: R = $CHPh_2$, **c**: R = Ph, **d**: R = Allyl, **e**: R = H

| Entry | Substrate | Reducing agent | Lewis acid[a] | **7** + **8**/Yield (%) | Ratio[b] **7**–**8** |
|---|---|---|---|---|---|
| 1 | **6a** | $NaBH_4$ | – | 97 | 88 : 12 |
| 2 | **6a** | $NaBH_4$ | $CeCl_3 \cdot 7H_2O$ | 90 | 29 : 71 |
| 3 | **6a** | $NaBH_4$ | $SmCl_3$ | 78 | 35 : 65 |
| 4 | **6a** | DIBAL-H[c] | – | 95 | 9 : 91 |
| 5 | **6b** | $NaBH_4$ | – | 96 | 89 : 11 |
| 6 | **6c** | $NaBH_4$ | – | 73 | 89 : 11 |
| 7 | **6c** | $NaBH_4$ | $CeCl_3 \cdot 7H_2O$ | 87 | 25 : 75 |
| 8 | **6d** | $NaBH_4$ | $CeCl_3 \cdot 7H_2O$ | 95 | 36 : 64 |
| 9 | **6e** | $NaBH_4$ | – | 96 | >99 : <1 |
| 10 | **6e** | $NaBH_4$ | $CeCl_3 \cdot 7H_2O$ | 52 | 18 : 82 |
| 11 | **6e** | DIBAL-H[c] | – | 95 | <1 : >99 |

[a] Lewis acid (1 equiv.) was used. [b] Determined by HPLC using YMC-Pack SIL. [c] The reaction was carried out in THF solution.

of a complexation of the carbonyl group with a cerium or aluminium atom as shown in Scheme 3. The methanol–$Ce^{3+}$ complex[11] or cerium ion preferably coordinated with the less hindered carbonyl group and activated the C5 atom; therefore, the hydride anion approaches from the more hindered carbonyl group and attacks the C5 atom as depicted in model **D** (Scheme 3). Similarly, a complexation of the less hindered carbonyl group with DIBAL-H regioselectively afforded the C5-adduct through an intramolecular hydride anion addition.




**Scheme 3** Proposed mechanism of regioselectivity in the reduction of **6** with $NaBH_4$–$CeCl_3 \cdot 7H_2O$ or DIBAL-H.

In summary, we have demonstrated that convenient synthesis of 5-hydroxy-1,5-dihydropyrrol-2-one derivatives **3** can be accomplished by $NaBH_4$ reduction in the presence of $CeCl_3$. Both regioisomers can be prepared with high regioselectivities in the reduction of citraconimide derivatives with $NaBH_4$, $NaBH_4$–$CeCl_3$, or DIBAL-H. †

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## Notes and references

† Registry Number; **3a**: 323204-69-9, **3b**: 323204-70-2, **3c**: 55260-27-0, **3d**: 34085-09-1, **4a**: 1631-26-1, **4b**: 2973-17-3, **4c**: 930-88-1, **4d**: 541-59-3, **5a**: 41194-02-9, **5c**: 41194-00-7, **5d**: 62312-55-4, **6a**: 73383-82-1, **6b**: 161573-67-7, **6c**: 3120-04-5, **6d**: 17423-10-8, **6e**: 1072-87-3, **7a**: 323204-71-3, **7e**: 79641-88-6, **8a**: 164727-42-8, **8d**: 323204-72-4, **8e**: 37772-60-4.

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