A NEW POTENTIAL ACYL IMINIUM ION FOR THE ASYMMETRIC SYNTHESIS OF PIPERIDINE DERIVATIVES

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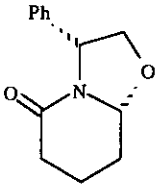
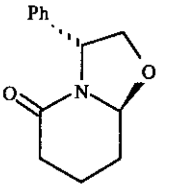
Abstract - Epimeric oxazolopiperidones (**1a**) and (**1b**) were prepared independently, both from *R*-(-)-phenylglycinol as starting material. They represent chiral potential iminium ions.

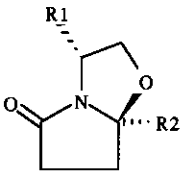
Acyl iminium ions are known as strong electrophiles widely used in C-C bond formation α to nitrogen.[1] The preparation, reactivity and application of these derivatives in the synthesis of nitrogen containing compounds have been thoroughly studied, particularly by Speckamp and co-workers.[1] In the course of our research of new starting materials for the asymmetric synthesis of piperidine derivatives,[2] we designed compound (**1**) as a chiral potential acyl iminium ion. Chiral bicyclic lactams (e.g. γ-lactams of type **2**), analogous to **1** have already been reported by Meyers' group for the asymmetric synthesis of quaternary carbon compounds.[3] More recently, Naito and Ninomiya [4] have described the synthesis and use of acyl lactam (**3**) for the synthesis of simple piperidine alkaloids while Meyers [5] has reported the usefulness of lactam (**2**) for the synthesis of pyrrolidine alkaloids. These reports prompt us to disclose our preliminary results in the synthesis of **1**.



1 a



1 b



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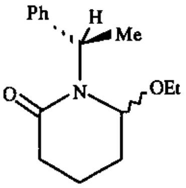
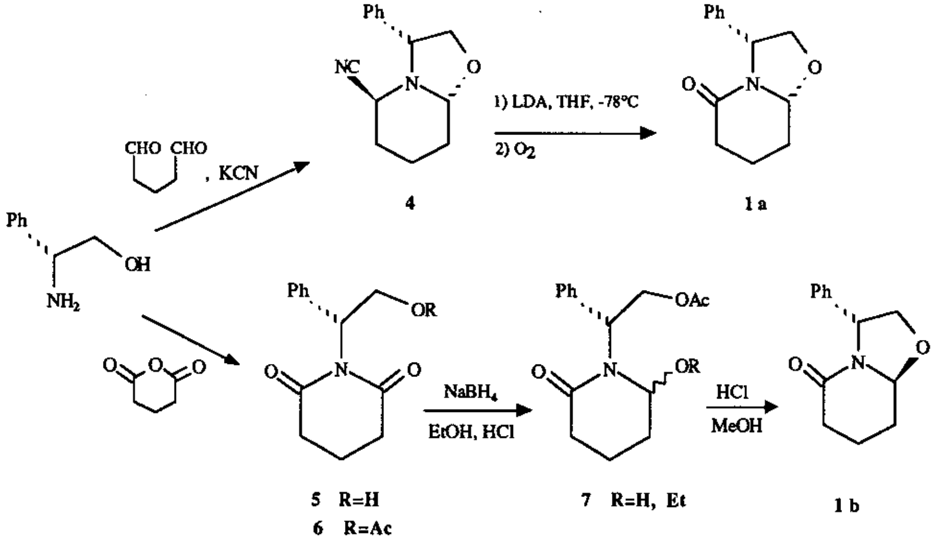


3

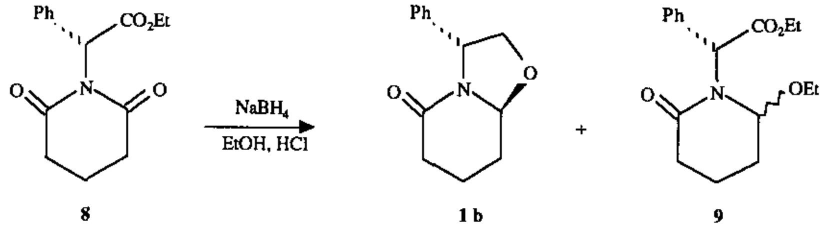
We first planned to synthesize compound (**1**) starting from the chiral 2-cyano-6-oxazolopiperidine (**4**) which was easily prepared in one step by condensation of *R*-(-)-phenylglycinol, glutaraldehyde and KCN [2] (Scheme 1). The

O_2 oxidation[6] of the anion of **4** (generated by LDA at -78°C in THF) easily gave the expected lactam (**1a**) in a 46% yield (73% based on recovered starting material)). It was interesting to notice that this reaction gave lactam (**1a**)[7] as a unique stereoisomer. The stereochemistry of oxazolopiperidone (**1a**) was difficult to be proved by nmr and it was expected according to its preparation that the configuration at the oxazolidine center of **1a** remained the same as that of the starting material. It then appeared that the relative strereochemistry of **1a** was reverse as that one found by Meyers for similar lactams in both pyrrolidine and piperidine series.[3] To confirm this assumption, we decided to synthesize lactam (**1**) through the reduction of imide (**5**) following the procedure described by Speckamp.[8] Some difficulties were encountered in the preparation of imide (**5**); attempts to condense glutaric anhydride with *R*-(-)-phenylglycinol, produced uncyclized products or polymeric materials under a variety of experimental conditions.[9] Good results were finally obtained using acetyl chloride as a dehydrating reagent and acylated imide (**6**) was obtained in 65% yield. The $NaBH_4$ reduction of **6** in EtOH with added dilute HCl gave a mixture of epimeric ethoxy- and hydroxylactams (**7**) which upon treatment with 1M HCl in MeOH (15h, room temperature) gave rise to the clean formation of **1b**[7] in 50% yield from **6**.(Scheme 1)



Scheme 1

Another approach was also tested for the preparation of **1**. Imide (**8**) was easily prepared (95% yield) from *R*-(-)-ethyl phenylglycinate and glutaric anhydride in the presence of AcCl and was reduced ($NaBH_4$, added HCl) to a mixture of **1b** (37%) and ethoxylactam (**9**) (19%) (Scheme 2)



Scheme 2

The stereochemical assignment of each isomer (**1a**) and (**1b**) was based on the stereochemical course of their formation: Lactam (**1a**) possesses the configuration of the starting material (**4**), while lactam (**1b**) has the configuration of the more stable oxazolidine, as observed by Meyers.[3] The nmr data showed that the oxazolidine proton H-2 was shifted to lower field in **1b** (δ H-2: 5.02 ppm) than in **1a** (δ H-2: 4.82 ppm) due to the anisotropic effect of the phenyl group.

Oxazolopiperidinones (**1a**) and (**1b**) represent an extension of the chemistry of the 2-cyano-6-oxazolopiperidine system previously studied in our laboratory.[2]

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5. A. I. Meyers and L. E. Burgess, *J. Org. Chem.*, 1991, **56**, 2294.

6. Only one related reaction has been reported: D. S. Grierson, M. Urrea, and H.-P. Husson, *Heterocycles*, 1985, **23**, 2493.; for similar oxidation of nitriles, see: H. Yamanaka and S. Ohba, *Heterocycles*, 1990, **31**, 895; R. W. Freerksen, S. J. Selikson, and R. R. Wroble, *J. Org. Chem.*, 1983, **48**, 4087.

7. **1a**: mp 71°C (ether); $[\alpha]_D$ -51° (CH_2Cl_2, *c* 2.2); ^1H nmr ($CDCl_3$, 400 MHz): 1.75 (m, 2H), 1.97 (m, 1H), 2.35 (m, 3H), 3.98 (d, *J*=9 Hz, 1H), 4.12 (dd, *J*=9, 7 Hz, 1H), 4.82 (dd, *J*=9.5, 3.5 Hz, 1H), 4.90 (d,

J= 7Hz, 1H), 7.30 (m, 5H); ir (neat): 1640 cm^{-1}; ms (EI) m/z: 217(M$^{+\cdot}$, 70), 187(29), 159(20), 148(23), 120(39), 104(100); Hrms calcd for $C_{13}H_{15}NO_2$: 217.1103, found: 217.1109.

1b: oil; $[\alpha]_D$ -88° (CH_2Cl_2, *c* 0.6); ^1H nmr ($CDCl_3$, 400 MHz): 1.50-2.05 ppm (m, 4H), 2.35 (dt, J=18, 6 Hz, 1H), 2.52 (dd, J=18, 6 Hz, 1H), 3.75 (dd, J=8, 7.5 Hz, 1H), 4.51 (dd, J=8, 7.5 Hz, 1H), 5.02 (dd, J=8, 4 Hz, 1H), 5.25 (t, J=7.5 Hz, 1H), 7.25 (m, 5H); ^{13}C nmr ($CDCl_3$, 50 MHz): 17.1, 28.5, 31.4, 58.2, 72.5, 88.9, 126.3, 127.8, 129.0, 139.9, 169.0; ir (neat): 1670 cm^{-1}; ms (EI) m/z: 217(M$^{+\cdot}$, 100), 187(26), 120(48), 104(79), 91(27); Hrms calcd for $C_{13}H_{15}NO_2$: 217.1103, found: 217.1108.

8. J. C. Hubert, J. B. P. A. Wijnberg, and W.N. Speckamp, *Tetrahedron*, 1975, **31**, 1437.

9. Meyers reported (ref. 3c) that condensation of *S*-valinol with glutaric anhydride gave only a moderate yield of maleimide (22%) and that the reaction was accompanied by extensive polymerization.

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