Diastereoselective Synthesis of 2-Monosubstituted and 2,6-Disubstituted Piperidines

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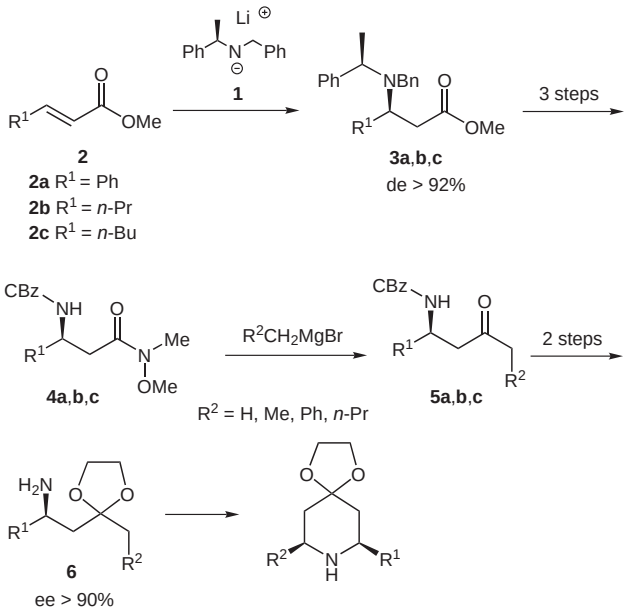
Abstract: An intramolecular Michael-type reaction, involving β′-amino-α,β-unsaturated ketone is used to prepare 2-mono- and 2,6-disusbtituted piperidines in a diastereoselective manner. This strategy allows an easy access to 2,6-*trans*-piperidine, starting from either *E*- or *Z*-olefin configuration.

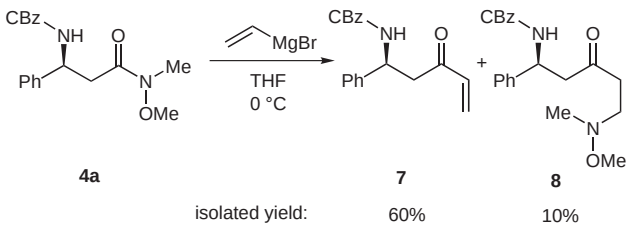
Key words: piperidines, intramolecular Michael reaction, diastereoselectivity

Previous investigations from our laboratory[1] have shown that intramolecular Mannich-type cyclisation[2] between an aldehyde and a β-aminoketal offers an efficient route to the diastereoselective preparation of 2,6-*cis*-disubstituted piperidines, which are very useful synthons for alkaloid synthesis.[3] In order to generalize this strategy, it was essential to work out an efficient preparation of enantiomerically pure 1,3-aminoketals. Last year, our laboratory has developed a successful approach to this target (Scheme 1).[4]



Scheme 1

Conjugate addition of (*R*)-*N*-benzyl-*N*-methylbenzylamide (**1**) to α,β-unsaturated esters **2** led to a wide range of β-aminoesters **3** with high diastereoselectivity.[5] Subsequent transformation of ester function to Weinreb amide[6] followed by changing the nitrogen protective group to a carbamate furnished the key intermediate **4** which could be further alkylated with Grignard reagents to give compounds **5**. The 1,3-aminoketal **6** necessary for the formation of the piperidine is then obtained in a good yield and a high enantiomeric excess after two steps: deprotection of the carbonyl group with ethylene glycol in the presence of *p*-TsOH and trimethyl orthoformate, following by hydrogenolysis of the benzyl carbamate. The deprotection of the nitrogen atom was performed with ammonium formate and palladium on charcoal. Our attention was next focused on the use of unsaturated Grignard reagents in order to generate new Michael acceptors which could allow, in an intra- or intermolecular process,[7] the introduction of a new nucleophile. So, use of vinylmagnesium bromide on Weinreb amide **4a** (R^1 = Ph) gave a mixture of the desired β′-amino-α,β-unsaturated ketone **7** (60% yield) and the β,β′-diaminoketone **8**, byproduct obtained by a sequential transformation–nucleophilic substitution–Michael reaction of *N*,*O*-dimethylhydroxylamine (Scheme 2).[8]



Scheme 2

This unexpected reaction has already been reported by F. Davis and coworkers[9] who recommended to hydrolyze the reaction mixture under acidic conditions at low temperature, in order to increase the ratio of the Michael acceptor adduct. Unfortunately, even under these conditions, formation of a low amount of byproduct **8** was still observed. However, α,β-unsaturated ketone **7** was a good synthon for the diastereoselective preparation of 2-monosubstituted piperidine, involving an intramolecular Michael reaction. Subsequent treatment of **7** with $BF_3{\cdot}OEt_2$ in anhydrous dichloromethane gave the corre-

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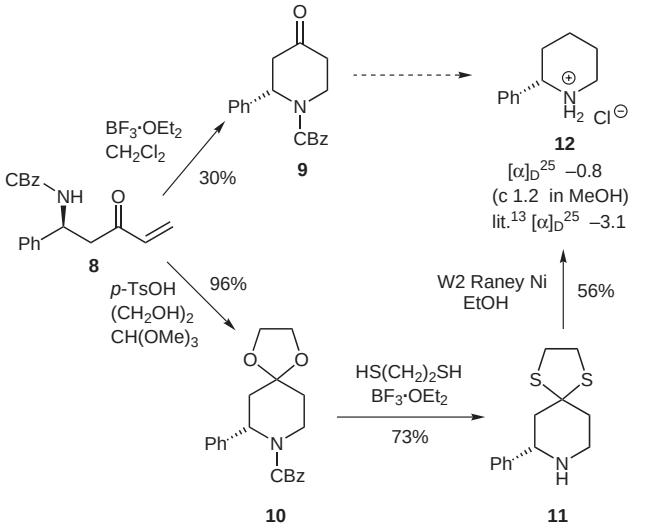
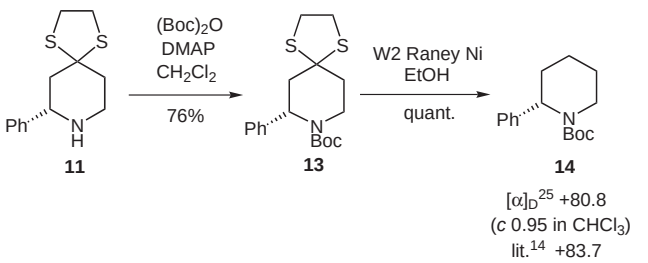
sponding 4-piperidinone **9**, albeit in poor yield. This intramolecular Michael reaction can also be achieved by using ethylene glycol in the presence of trimethylorthoformate as a water scavenger, to give, in a one-pot procedure, excellent conversion into the piperidine **10**, in which the carbonyl function is protected as a ketal (Scheme 3).



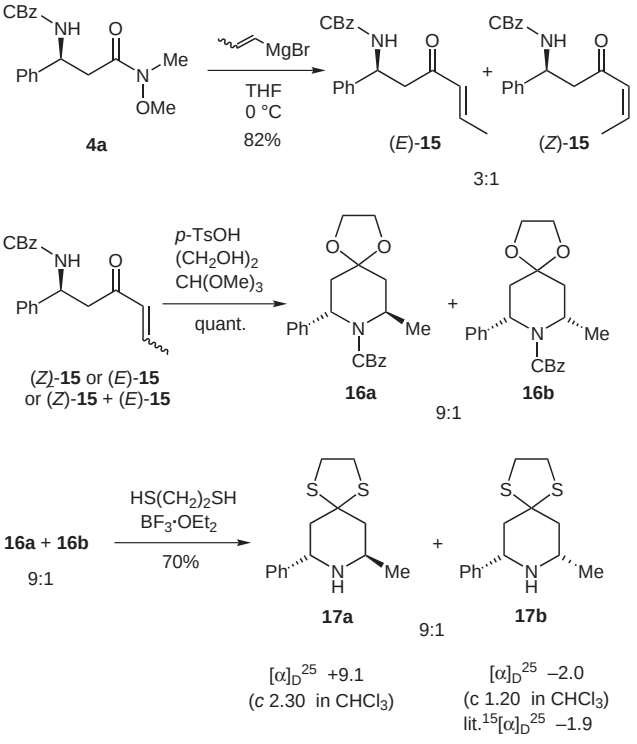
Scheme 3

Finally, the treatment of piperidine **10** with an excess of ethanedithiol in dichloromethane in the presence of $BF_3{\cdot}OEt_2$ allowed the deprotection of the nitrogen group[10] and gave the corresponding dithiolane derivative **11** in 73% yield. Thioketal **11** was converted into 2-phenylpiperidine hydrochloride **12** after hydrogenolysis realized in the presence of freshly prepared W2 Raney nickel[11] in refluxing ethanol, followed by a treatment with hydrochloric acid in diethyl ether.[12] Comparison of the specific rotation of **12** with those reported in the literature[13] showed that partial racemization occurs during the desulfurization step, probably due to a retro-Mannich-type reaction. In order to circumvent this problem, we decided to protect the nitrogen atom with a *tert*-butoxycarbonyl group to decrease its nucleophilicity (Scheme 4). Thus, treatment of piperidine **11** with di-*tert*-butyl dicarbonate in dichloromethane and cleavage of the thioketal group (W2 Raney nickel) led to the N-protected piperidine **14** in 76% yield. The specific rotation of this protected piperidine **14** was in agrement with those reported in the literature.[14]



Scheme 4

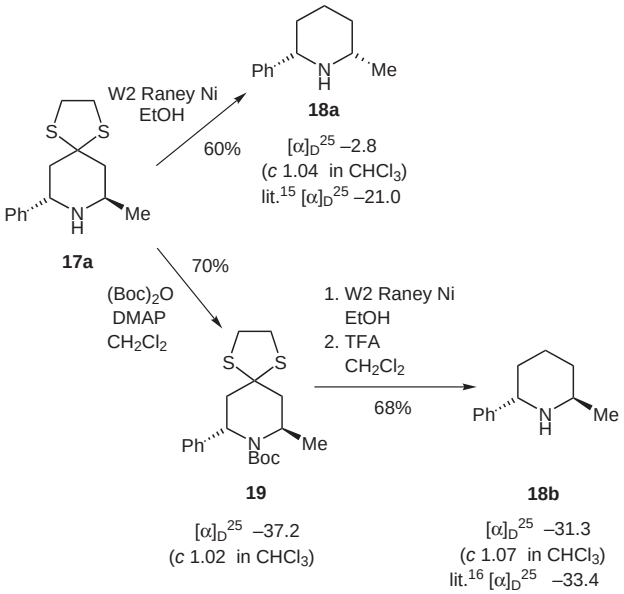
This result showed that no racemization occurred during the entire sequence, and this prompted us to test the addition of crotylmagnesium bromide on amide **4a** in order to prepare 2,6-disubstituted piperidines. The same protocol (vide supra) was used to carry out a separable mixture of diastereoisomers (*E*)-**15** and (*Z*)-**15** in 62% and 20%, respectively (Scheme 5). Subsequent reactions could be conducted either separately on each isomer or on the mixture of the two diastereoisomers. Treatment of (*E*)-**15** with ethylene glycol and trimethylorthoformate gave quantitatively a mixture of *trans*- and *cis*-N-protected 2,6-disubstituted piperidines **16a** and **16b** in a 9:1 ratio. The same ratio was obtained when (*Z*)-**15** was used. To prevent any deprotection, more stable compounds were required. This mixture of two diastereoisomers **16a** and **16b** were converted into the corresponding N-deprotected thioketals **17a** and **17b** by action of ethanedithiol in the presence of $BF_3{\cdot}OEt_2$. Careful separation of each isomer by silica gel chromatography led to **17a** and **17b** in, respectively, 60% and 10% yield. The relative configuration of methyl and phenyl group in the two diastereoisomers have been assigned by NMR particularly with the signals corresponding to H-5 and H-3 (axial and equatorial) on the piperidine ring, showing typical coupling constants for a 2,6-*trans*- or a 2,6-*cis*-conformation.



Scheme 5

Effectively, on the 2,6-*cis*-diastereoisomer **17b**, the phenyl and the methyl group were both in equatorial position and subsequently the signal of axial H-5 was a doublet of doublet with two coupling constants of 13Hz ($J_{H5a–H5e}$) and 11 Hz ($J_{H5a–H6a}$). In the case of **17a**, axial H-5 also appeared as a doublet of doublet with two coupling constant

of 14 Hz ($J_{H5a–H5e}$) and 5 Hz ($J_{H5a–H6e}$). This small value of the coupling constant between axial H-5 and H-6 clearly proved the equatorial position of H-6 and consequently the axial position of the methyl group. The specific rotation and spectral data of **17b** were consistent with those reported.[15]



Scheme 6

Treatment of **17a** with W2 Raney nickel in ethanol led to the 2,6-*cis*-disubstituted piperidine **18a** with extensive racemization (Scheme 6). This epimerization process seemed to confirm the retro-Mannich-type reaction observed in the synthesis of 2-monosubstituted piperidine. Additional control experiments are currently in progress to prove this assertion. On the other hand, treatment of piperidine **17a** with di-*tert*-butyl dicarbonate in dichloromethane in the presence of DMAP led to compound **19** in 70% yield. To provide the desired *trans*-disubstituted piperidine **18b**, the thioketal was next cleaved by W2 Raney nickel followed by deprotection of the nitrogen atom using trifluoroacetic acid with a good yield. Spectral data and specific rotation of **18b** were in all agreement with those reported in the literature.[16]

In summary, a new protocol for diastereoselective formation of 2-substituted and 2,6-disubstituted piperidines is reported. Work is currently in progress to determine the mechanism of cyclization process in order to explain the diastereoselective formation of *trans* adduct starting from either *E*- or *Z*-olefins. Our attention is also turned, on the extension of this strategy, to the preparation of more complex structures starting from β′-amino-α,β-unsaturated ketone using intermolecular hetero-Michael addition. This approach is currently in progress and will be proposed in due course.

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References

(1) Ciblat, S.; Calinaud, P.; Canet, J.-L.; Troin, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 353.
(2) (a) Rougnon Glasson, S.; Tratrat, C.; Canet, J.-L.; Chalard, P.; Troin, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 1561. (b) Rougnon Glasson, S.; Canet, J.-L.; Troin, Y. *Tetrahedron Lett.* **2000**, *41*, 9797.
(3) For successful application of our methodology in indolizidine alkaloid enantioselective synthesis, see: Davis, F. A.; Yang, B. *Org. Lett.* **2003**, *5*, 5011.
(4) Bariau, A.; Canet, J.-L.; Chalard, P.; Troin, Y. *Tetrahedron: Asymmetry* **2005**, *16*, 3650.
(5) Davies, S. G.; Brackenridge, I.; Fenwick, D. R.; Ichihara, O.; Polywka, M. E. C. *Tetrahedron* **1999**, *55*, 533; and references cited therein.
(6) (a) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15. (b) Singh, J.; Satyamurthi, N.; Aidhen, I. S. *J. Prakt. Chem.* **2000**, *342*, 340.
(7) (a) Bartoli, G.; Bartolacci, M.; Giulani, A.; Marcantoni, E.; Massaccesi, M.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 169. (b) Rubiralta, M.; Diez, A.; Vila, C.; Castells, J.; Lopez, I. *Heterocycles* **1992**, *34*, 643.
(8) Gomtsyan, A. *Org. Lett.* **2000**, *2*, 11.
(9) Davis, F. A.; Nolt, M. B.; Wu, Y.; Prasad, K. R.; Li, D.; Yang, B.; Bowen, K.; Lee, S. H.; Eardley, J. H. *J. Org. Chem.* **2005**, *70*, 2184.
(10) Bose, D. S.; Thurston, D. E. *Tetrahedron Lett.* **1990**, *31*, 6903.
(11) Augustine, R. L. In *Catalytic Hydrogenation*; M. Dekker, Inc.: New York, **1965**, 23.
(12) Ciblat, S.; Besse, P.; Papastergiou, V.; Veschambre, H.; Canet, J.-L.; Troin, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 2221.
(13) Burke, A. J.; Davies, S. G.; Garner, A. C.; McCarthy, T. D.; Roberts, P. M.; Smith, A. D.; Rodriguez-Sola, H.; Vickers, R. *Org. Biomol. Chem.* **2004**, *2*, 1387; and references cited therein.
(14) Hunt, J. C. A.; Laurent, P.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2378.
(15) (a) Katritzky, A. R.; Qiu, G.; Yang, B.; Steel, P. *J. Org. Chem.* **1998**, *63*, 6699. (b) Ciblat, S.; Besse, P.; Canet, J.-L.; Troin, Y.; Veschambre, H.; Gelas, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2225.
(16) Poerwono, H.; Higashimaya, K.; Yamauchi, T.; Kubo, H.; Ohmiya, S.; Takahashi, H. *Tetrahedron* **1998**, *54*, 13955.