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Enantioselective α-Alkylation of Piperidine *via* Chiral Perhydropyrido [2,1-b] [1,3,4]-oxadiazinone: An Easy Route for the Synthesis of Both Enantiomers Of Coniine

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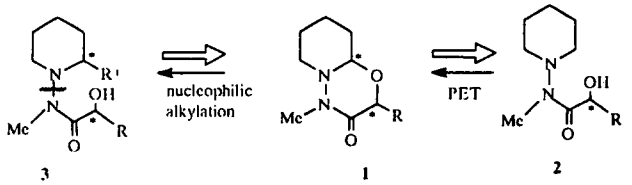
Abstract: Enantioselective direct alkylation of piperidine involving chiral perhydropyrido [2,1-b] [1,3,4]-oxadiazinone using either form of mandelic acid as chiral auxiliary is reported. The application of the strategy is demonstrated by the synthesis of (R)- as well as (S)- coniine. © 1997 Elsevier Science Ltd.

Due to wide occurrence of optically active 2-substituted piperidine moiety in a large number of ubiquitous natural products of biological importance, developing synthetic strategies for the preparation of this heterocyclic derivative constitutes an area of current research interest[1]. In this context, various chiral derivatives derived using phenyl glycinol as chiral auxiliary[2,3], have been utilised. Many other strategies employing 2-substituted pyrrolidines[4], 8-phenyl menthol[5], α-methyl benzyl amine[6], a sultam[7], α-amino acids[8] and *p*-tolyl sulphoxides[9] as chiral auxiliaries are also reported. Although varying degree of successes are claimed in these reports, none of them have used piperidine moiety as such for the alkylation purposes. Moreover, the chiral auxiliaries in most of these strategies are sacrificed at the end of the reaction process. In order to develop a new methodology for direct alkylation of piperidine employing a recyclable chiral auxiliary, our attention was drawn to a precursor of type **1** considering its reactive cyclic N-O acetal functionality suitable for nucleophilic alkylations. The synthesis of **1** was envisaged by the photosensitised electron transfer (PET) cyclisation of an *in situ* generated iminium cation from a chiral precursor of type **2** by following the experimental protocol as reported earlier[10] (**Scheme I**). In this communication, we wish to disclose the success of our concept by demonstrating the enantioselective synthesis of (R)-as well as (S)-coniine from **1** (R=Ph) using either form of chiral mandelic acid as recyclable auxiliary.

Scheme I

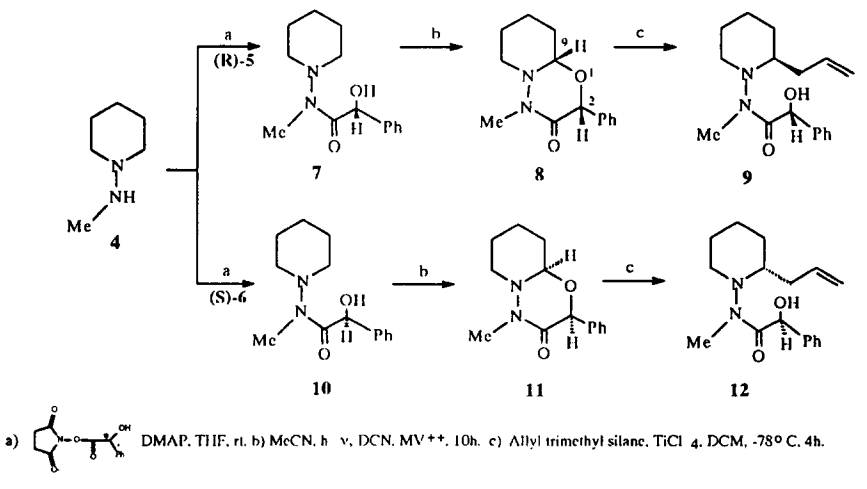


3 **1** **2**

To realize the above concept, we began our effort by synthesising compound **7** as precursor suitable for preparing compound of type **1**. It was obtained in 80% yield by the reaction of N-hydroxy succinimide

activated ester of (R)-mandelic acid [(R)-**5**, obtained by the condensation of (R)-mandelic acid with N-hydroxy succinimide in the presence of DCC] with N-methylamino piperidine (**4**). Amine (**4**) was prepared (75 %) by the LAH reduction of the corresponding ethyl carbamate of 1-amino piperidine, obtainable either commercially or derivable easily from piperidine[11]. PET cyclisation of **7** essentially employed the experimental details as described in our earlier report[10]. It consisted the irradiation of **7** (1 g, 4.03 mmol), 1,4-dicyanonaphthalene (DCN, 0.16 g, 0.89 mmol) and methyl viologen (MV^{++}, 0.05 g, 0.194 mmol) in CH_3CN through a pyrex filtered light (>280 nm) using 450W-Hanovia medium pressure lamp for 10 h without removing dissolved air from the solution. All the light under this setup was absorbed by DCN only. Usual workup and purification of the crude photolysate by silica gel flash chromatography gave **8** in 70% yield (**Scheme II**) along with the quantitative recovery[12] of DCN. Based on the appearance of two N-Me peaks [δ 3.15(major), δ3.2 (minor)] in the ^1H NMR spectrum of **8**, this product was suggested to be the mixture of diastereomers in the ratio of 7:1 (confirmed by HPLC analysis, reverse phase column C_{18}. CH_3CN : H_2O as eluent). The *cis*-stereochemistry between H_2 and H_9 of major isomer **8** was established through proton NOE difference experiment . The observed diastereoselectivity in **8** was expected to emerge due to the front side attack of the nucleophile to the iminium cation intermediate, generated during photoirradiation as observed in our earlier studies[13]. Diastereomers could not be isolated in pure form, therefore, crude mixture of **8** was planned to be utilized as such for further reaction. It may be mentioned that a small amount of **8** (6-8%) was found gettting transformed into starting **7** during chromatographic purification.

Scheme II

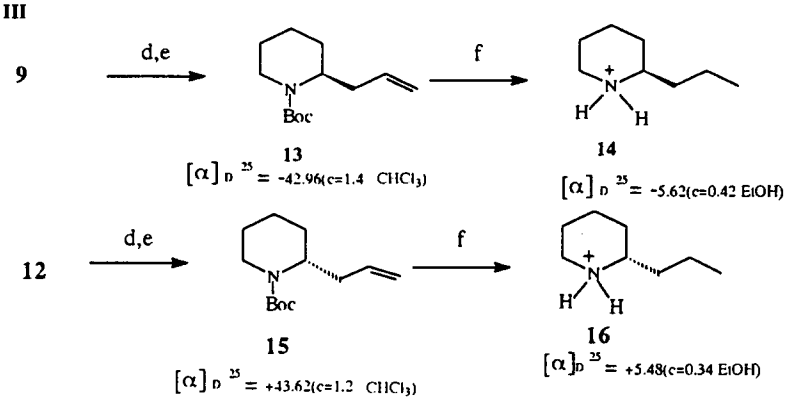


The high reactivity profile of cyclic N-O acetal moiety of **8** gave us an opportunity to subject this compound for the stereoselective nucleophilic alkylation reaction. Towards this end, **8** (0.6 g, 2.44 mmol) was reacted with allyltrimethyl silane (0.33 g, 2.92 mmol) in the presence of $TiCl_4$ (0.55 g, 2.92 mmol) in

dry DCM at -78^0 C which afforded **9** in 95% yield (dr = 6.7:1). The diastereomeric ratio of **9** was estimated by comparing the integration values of the two distinct N-methyl peaks appearing [δ2.92 (major) δ2.90 (minor)] in its ^{1}H NMR spectra. The observed diastereomeric ratio indicated that there is no racemisation during the alkylation reaction. Pure **9** could be obtained by silica gel chromatography using hexane : acetone (4:1) as eluent and characterised by detailed ^{1}H NMR, ^{13}C NMR and mass spectral data[14]

The absolute stereochemistry as shown in structure **9** was determined by transforming this compound into **13** and comparing its optical rotation ($[\alpha]^{25}_D$= - 42.96 c=1.4, $CHCl_3$) with the reported value[15] ($[\alpha]^{25}_D$-39.96, c= 1.2, $CHCl_3$). This transformation was achieved by the reductive cleavage[16] of N-N bond by the Li/NH_3 at - 33^0 C followed by the protection of the resultant amine using $(BOC)_2O$. The mandelic acid chiral auxiliary was recovered in the corresponding amide form. The assignment of the stereochemistry of **13** was further confirmed by converting it into hemlock alkaloid (R)-coniine (**14**), through the steps as shown in **Scheme III** and comparing the m.p. and optical rotation of its hydrochloride salt with literature values (m.p. 218^0 C, Lit.[6h] m.p. 221° C) {$[\alpha]^{25}_D$ -5.62, c=0.46 EtOH; Lit.[2a] $[\alpha]^{20}_D$ -5.8, c=1, EtOH}. Rationalization of the stereochemistry as observed in **9** can be made from the analogy as seen on nucleophilic alkylation of cyclic N-O acetals where Lewis acid initiated ring opening has proceded in an SN_2-like fashion[17].

Scheme III



d) Li/NH_3 (liq.), THF, -33^{0}C, 1h, NH_4Cl (82%) e) $(Boc)_2O$,THF/H_2O, K_2CO_3 f) H_2, Pd/C (10%), EtOH, 10 h, HCl

Since both forms of optically active mandelic acid are cheaply available, the same sequence of reaction, as described in **Scheme II**, was extended using (S)-mandelic acid as auxiliary. PET cyclization of **10** gave **11** (72% dr = 6.8:1) which on usual allylation reaction followed by the sequences as mentioned for **7** (**Scheme II** and **Scheme III**) furnished (S)-conine (**16**), characterized by comparing the physical constants

of its hydrochloride salt with the known values {$[\alpha]^{25}_D$ +5.48, c=0.34, EtOH), Lit.[2a] $[\alpha]^{20}_D$ +5.2 c=1 EtOH}. (m.p. 217-218^{0}C, Lit[6b] m.p. 221^{0}C).

In summary, we have developed a new strategy for the enantioselective alkylation of piperidine using mandelic acid as recyclable chiral auxiliary. The application of this methodology for the alkylations of pyrrolidine and isoquinoline is in progress and the details will be revealed in a full paper.

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14. Spectral data of **9**: ^{1}H NMR ($CDCl_3$) δ 1.25 (4H, m) ,1.6 (2H, m), 1.92 (2H, m), 2.45(3H, m) ,2.92 (3H, S) 4.55 (1H, br s),5.1(2H, m) 5.55 (1H, s)5.72 (1H, m) 7.32 (5H, m) .^{13}CNMR ($CDCl_3$) δ 23.55, 24.03, 24.82, 31.19, 37.01, 52.30, 60.02, 71.77, 117.52, 127.57, 127.64, 128.16, 133.97, 140.26, 174.80. Mass (m/z) 287(M-1),247,172,153,124,113,107,84,79.
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