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Syntheses of (−)-hygrine and (−)-norhygrine via Wacker oxidation

Mahesh S. Majik, Santosh G. Tilve *

Department of Chemistry, Goa University, Taleigao-Plateau, Goa 403 206, India

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ABSTRACT

Hygrine is an important biosynthetic intermediate for tropane alkaloids. A synthesis of (−)-hygrine starting from L-proline is described. The acetonyl side chain of hygrine was fashioned through the Wittig reaction followed by regioselective Wacker oxidation. In addition, this Letter provides the first synthesis of (−)-norhygrine.

The tropane alkaloids have attracted considerable interest due to their significant biological properties, hallucinogenic characteristics, and their utility as pharmacological probes.[1] Several members of this class of heterocycles including (−)-hyoscyamine **2**, (−)-scopolamine **3**, and (−)-cocaine **4** (Fig. 1) are used in medicine as antimuscarinic drugs[2] and their biosynthesis has been extensively studied over last few decades.[3] Hygrine **1**, the prototype of pyrrolidine alkaloids has served as a precursor for the tropane skeleton. It was isolated from several plants[4] and it appears to have no detectable optical activity when isolated. Later, (±)-hygrine was resolved with D-(+)-tartarate to give diastereomeric purity of maximum 80% after several recrystallizations and absolute configurations[4a] of (+)-hygrine and (−)-hygrine were determined by the relative correlations with those of D-proline and L-proline, respectively. Recently, Park and co-workers[5] confirmed the absolute configuration of (+)-hygrine as '*R*' by its first asymmetric synthesis.

To the best of our knowledge, the racemic hygrine has been synthesized three times in the 1980's.[6a–c] Recently, Klussmann and co-workers have disclosed a new method toward racemic hygrine using a metal catalyst.[6d] In spite of the apparently simple molecular structure of hygrine **1**, only two asymmetric syntheses are reported. This may be because of its tendency to racemize readily in neutral or basic conditions.[4a,4c] The recent first enantioselective synthesis of (+)-hygrine reported by Park and co-workers[5] is based on asymmetric phase transfer catalytic alkylation, and thereafter a short and direct synthesis of (+)-hygrine is reported by Garcia and Colmenares using D-proline as a starting material.[7]

Although only (+)-hygrine acts as a precursor for the tropane alkaloids, both the enantiomers of the hygrine appeared to serve equally well in the biosynthesis of the cuscohygrine as well as for the incorporation studies of radiolabeled hygrine [^{14}C] into the tropane alkaloids.[3b]

So far, there is no report on the synthesis of (−)-hygrine. Hence, in continuation of our interest in the synthesis of small bioactive molecules,[8] we describe herein an easy access to (−)-hygrine starting from L-proline using Wittig olefination and Wacker oxidation as the key steps. During this study, the synthesis of (−)-norhygrine was also accomplished for the first time.

The requisite (*S*)-*N*-carbobenzyloxyprolinal **7** was prepared from easily available L-proline according to literature procedure.[9] The commercially available ethyltriphenylphosphonium bromide salt **8** was treated with *n*-BuLi to generate in situ the desired ylide. The Wittig reaction of this ylide with (*S*)-*N*-carbobenzyloxyprolinal **7** afforded the corresponding olefin **9** in 56% yield (Scheme 1). The double bond geometry of olefin was assumed to be cis based on ^{13}C NMR peak of allylic methyl carbon which appeared at δ 12.8. The stage was now set up to generate the carbonyl functionality. The

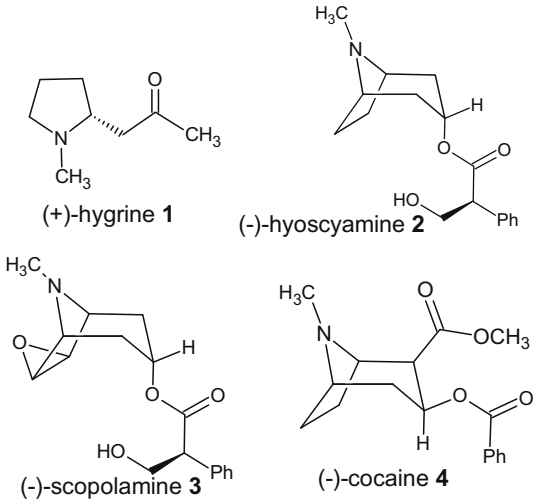

Figure 1. Hygrine and medicinally important tropane alkaloids.

* Corresponding author. Tel.: +91 832 6519317; fax: +91 832 2452886.
E-mail addresses: stilve@unigoa.ac.in, santoshtilve@yahoo.com (S.G. Tilve).

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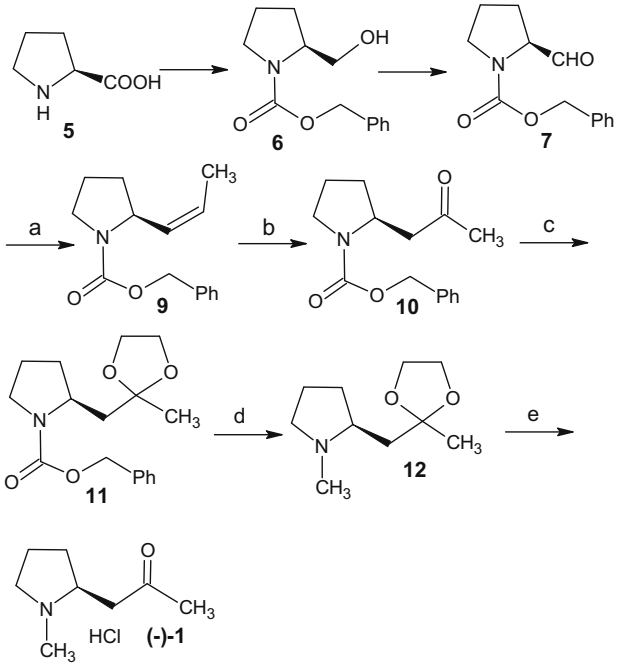
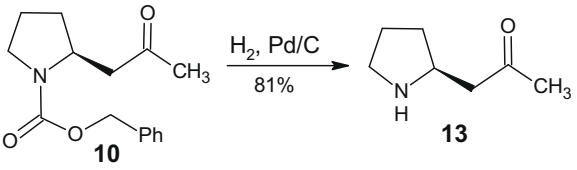


Scheme 1. Synthesis of (−)-hygrine. Reagents and conditions: (a) ethyltriphenylphosphonium bromide **8**, *n*-BuLi, Et_2O, 56%; (b) $PdCl_2$, CuCl, O_2, DMF–H_2O, 76%; (c) $HOCH_2CH_2OH$, *p*TsOH, 82%; (d) LAH, THF, 66%; (e) 6 N HCl, THF, 73%.

Wacker oxidation has served as a versatile reaction that has found broad applications in synthetic chemistry for the functionalization of an alkene.[10] Wacker oxidation is the method of choice for the oxidation of terminal olefin to ketone. However, for its application to internal olefin, the problem of regioselectivity is needed to be considered. It was conjectured that the bulky phenyl group (Cbz) as well as pyrrolidine ring would favor the regioselectivity in Wacker oxidation.[10c] Hence, olefin **9** was treated with $PdCl_2$/CuCl, O_2 in DMF:H_2O at 70 °C for 48 h. The expected acetonyl carbamate **10** was obtained exclusively in good yield. The regioselectivity in Wacker oxidation was also further inveterated by changing the N-protecting group (carboethoxy protected olefin gave 31% yield for Wacker oxidation).

Now, the completion of the total synthesis of (−)-hygrine required the introduction of the methyl group on the nitrogen of the pyrrolidine ring. The most direct route to achieve this transformation would be the use of protection/reduction/deprotection strategy recently applied by Park and co-workers for the synthesis of (+)-hygrine.[5] Thus, the acetonyl carbamate **10** was subjected to ketalization reaction using ethylene glycol, *p*TsOH in refluxing benzene to give corresponding ketal **11**. Further, the reduction of the benzyloxycarbonyl group using LAH provided the corresponding *N*-methyl pyrrolidine ketal **12** having $[\alpha]_D^{29}$ −32.4 (*c* 0.34, $CHCl_3$); [lit.[5] $[\alpha]_D^{30}$ +33.3 (*c* 1.0, $CHCl_3$) for *R*-isomer]. Finally, the deprotection of the ketal **12** with 6 N HCl in THF provided (−)-hygrine·HCl having $[\alpha]_D^{30}$ −32.1 (*c* 0.25, H_2O); [lit.[5] $[\alpha]_D^{29}$ +34.5 (*c* 0.5, H_2O) for *R*-isomer]. The spectral properties of synthetic product **1** matched well with the previous report.[5] Thus, the synthesis of (−)-hygrine·HCl was achieved from carbobenzyloxyprolinal in five steps in 17% overall yield.

The regioselective preparation of the acetonyl carbamate **10** from the olefin **9** was further exploited for the first asymmetric synthesis of (−)-norhygrine **13** (Scheme 2). Norhygrine is found in various plants[4] and so far only one synthesis of its racemate has appeared in the literature.[11] Thus, the deprotection of benzyloxycarbonyl group by hydrogenolysis without affecting the ketone



Scheme 2. Synthesis of (−)-norhygrine.

carbonyl furnished (−)-norhygrine **13** having $[\alpha]_D^{33}$ −29.6 (*c* 0.14, $CHCl_3$).

In conclusion, we have accomplished a brief synthesis of (−)-hygrine·HCl in five steps from carbobenzyloxyprolinal. The key feature of the present synthesis is the use of Wacker oxidation for the generation of carbonyl functionality in a regioselective manner. Moreover, we have demonstrated the utility of this approach for the first asymmetric synthesis of (−)-norhygrine.

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Supplementary data

Supplementary data (experimental procedures and spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.098.

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