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2-ARYLSULFINYLMETHYL OXAZINES: CHIRAL CARBONYL EQUIVALENTS

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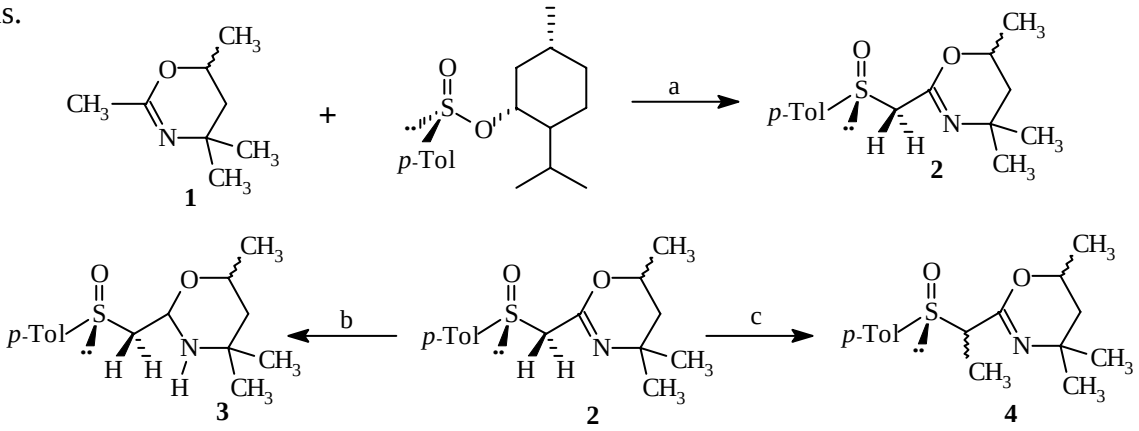
Abstract - A single pot acid catalysed condensation reaction of 2-arylsulfinylmethyloxazinane – a chiral carbonyl equivalent (derived from the title oxazine by BH_4^- reduction) with tryptamine and tryptophan esters, furnishes tetrahydro-β-carbolines and can be subsequently transformed into indole alkaloids.

The Pictet-Spengler reaction[1] belongs to one of the most important and powerful methods used in alkaloid chemistry. It has been applied in numerous cases[1] for the construction of tetrahydroisoquinoline (THIQ) and tetrahydro-β-carboline (THBC) alkaloids as well as more complex classes of natural products derived from these heterocyclic systems. Consequently, the development of variant approaches which allow chemists to carry out this transformation in stereoselective manner is of great interest in organic synthesis. For enantioselective synthesis, chiral formamidines[2] developed by Meyers are particularly worthy of note as these have been extensively employed in the synthesis of THBC and THIQ systems with high enantioselectivity.

The use of a stereogenic sulfur center of a chiral sulfoxide to achieve stereocontrol in asymmetric syntheses has been amply demonstrated.[3] Use of chiral acetylenic sulfoxides in the enantioselective synthesis of THBC and THIQ alkaloids through a tandem Michael addition/acid induced cyclization reaction sequences has also been reported.[4] Chiral vinyl sulfoxides have been implemented,[5] *via* an intramolecular asymmetric conjugate addition of a nitrogen nucleophile to synthesize alkaloidal systems.

Unfortunately not many sulfoxide derivatives of the later type are available, therefore their use in asymmetric synthesis of THBCs and THIQs has been limited. Using an unconventional approach we have been engaged in designing models[6] of the folate cofactor and investigating their use

in the development of strategies for chemical syntheses based on the reactivity pattern of the cofactor. Recently we have reported[7] that simple oxazinanes (carbonyl equivalents) can be convincingly employed to synthesize otherwise inaccessible 1,3-disubstituted THBCs in a highly diastereoselective manner. These findings gave us additional impetus in developing optically active oxazinanes (chiral carbonyl equivalents) with a possibility of C-2 elaboration, for effective use in asymmetric synthesis of THBCs and related systems. Herein we report a convenient extension of Meyer's approach[8] for the synthesis of new, stereochemically homogenous chiral oxazines and their use as two carbon synthons for enantio- and diastereselective synthesis of THBCs, convertible into congeners of yohimbine alkaloids.



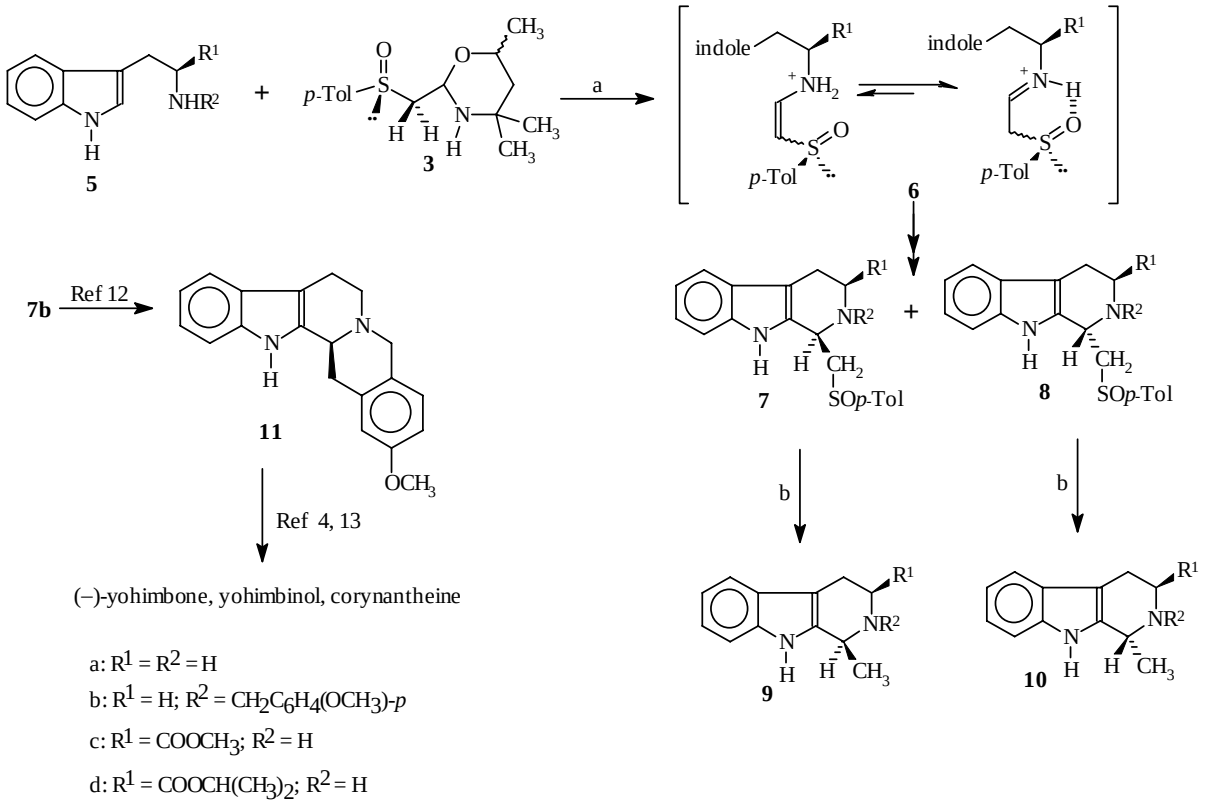
Scheme 1. a) n-BuLi, -78°C, THF, 85%. b) $NaBH_4$, THF : EtOH (1 : 1), [8] -45°C, quantitative. c) NaH, MeI, THF , 0°C, 68%.

Reaction of metallated (n-BuLi/THF) 2,4,4,6-tetramethyl-5,6-dihydro-(4*H*)-1,3-oxazine (**1**)[9] with (–)-(*S*)-menthyl *p*-toluenesulfinate[10] at -78°C (Scheme 1) afforded the title compound (**2**) as a diastereomeric mixture[11] in 85% overall yield, after crystallization from hot hexane. On the basis of the fact that such Anderson type reactions proceed with inversion[10] at the sulfinyl sulfur atom, the absolute configuration (*R*) can be assigned at the sulfinyl sulfur of compound (**2**). The assignments of all the protons have been made on the basis of NOE connectivity while the carbons have been distinguished by the HMQC spectrum. The ^{1}H NMR ($CDCl_3$) of **2** exhibits signals at δ 1.02 (s, 3H, Me), 1.05 (s, 3H, Me), 1.09 (s, 3H, Me), 1.12 (s, 3H, Me), 1.19 (m, 8H, 2×Me and 2×C(5)H), 1.64 (m, 2H, C(5)H), 2.39 (s, 6H, 2 × Me), 3.42 (d, J = 12.69, 2H, -CH_2SO-*p*Tol), 3.80 (m, 2H, -CH_2SO*p*-Tol), 4.05 (m, 2H, C(6)H), 7.29 (d, J = 8.00, 4H, ArH), 7.57 (d, J = 8.15, 4H, ArH). The characteristic feature of

^{1}H NMR spectrum is that it shows a multiplet at δ 3.80 and a doublet at δ 3.42. The appearance of an apparent multiplet at δ 3.80 shows the presence of two diastereomers having very close chemical shifts which is further corroborated by duplication of signals in the aliphatic region. Its ^{13}C NMR ($CDCl_3$) depicted signals at δ 21.0, 21.3, 29.2, 29.3, 31.2, 41.3, 41.4, 50.3, 62.4, 62.6, 68.6, 124.7, 129.6, 139.2, 139.3, 141.9, 152.0. The appearance of parent ion peak in its mass spectrum at *m*/*z* 279 (M^+) and other fragmentation pattern along with the microanalytical data [Anal. Calcd for $C_{15}H_{21}NO_2S$: C 64.51, H 7.52, N 5.01. Found: C 64.54, H 7.58, N 4.98] corroborate the assigned structure. Oxazine (**2**) was reduced[8] to oxazinane (**3**) using $NaBH_4$ at -45°C. Acid catalysed reactions of **3** were performed with tryptamine and tryptophan derivatives (**5c**, **d)** to obtain THBCs convertible into the title targets (Scheme 2). The chemical yields and the extent of stereoselectivity were comparable with the known syntheses.[4] To further widen the synthetic scope, compound (**2)** was metallated and quenched with MeI to obtain further elaborated oxazine (**4**).

If a stoichiometric mixture of tryptamine and **3** in anhydrous MeCN : AcOH (10 : 1) solution is combined at ambient temperature, the sequence: formation of iminium intermediate (**6**) (hydrogen bonded), its spontaneous *in situ* conversion into a spiroindolenine,[7a] through acid induced intramolecular electrophilic attack of the iminium carbon at C-2 or at C-3 of the indole moiety and subsequent rearrangement-deprotonation yields THBCs (**7a** and **8a**) in 70 : 30 (1*R* : 1*S*) diastereomeric ratio (^{1}H NMR correlation),[11] out of which **7a** could be isolated in 40% yield. This sequence depicts the crucial carbon-nitrogen and carbon-carbon bond formations in a one pot reaction and points to the creation of a new chiral center at C-1 of the alkaloidal system.

Similarly secondary amine (**5b**)**,** which was prepared from tryptamine through reductive amination with *p*-methoxybenzaldehyde, reacts with **3** in MeCN : AcOH (10 : 1) at reflux temperature, yielding **7b** and **8b** respectively in 80% isolated yield and in 30 : 70 (1*R* : 1*S*) diastereomeric ratio. The THBC (**7b**) has been converted into the homochiral pentacyclic intermediate (**11**) which is a known precursor[13] of pentacyclic yohimbine alkaloids - yohimbinol and corynantheine.



Scheme 2. a) CH_3CN : AcOH (10 : 1) , 76-78%. b) Raney Ni, MeOH, 0° C, 88-90%.

Reaction of a stoichiometric mixture of (*L*)-tryptophan methyl esters with **3** in anhydrous MeCN : AcOH (10 : 1) at ambient temperature furnished a mixture of THBCs, (**7c** and **8c**) (*cis* : *trans* :: 33 : 66) in 76% isolated yield. Likewise reaction of tryptophan isopropyl ester with **3** under similar set of conditions, yielded THBCs (**7d** and **8d**) *cis* : *trans* diastereomers in 78% yield and similar diastereomeric ratio.

THBCs (**7 c/d** and **8 c/d**) upon desulphurization by Raney Ni led to the formation of C-1 methyl-1,3-disubstituted THBCs (**9 b/c** and **10 b/c**), respectively. In view of the facile removal of the C-3 ester function, following the method of Yamada,[14] the formation of optically pure eleagnine[11] - a harman alkaloid with *known absolute configuration* can be sought.

One interesting outcome of this methodology is the reversal[15] of stereochemical bias in comparison with chiral acetylenic sulfoxide approach. The transformations depicted in the Scheme-2 showed a fair degree of diastereoselectivity comparable with the reported methods,[4] when the chiral oxazines are employed as inductors. In addition this strategy has a scope for asymmetric synthesis of many more C-1 substituted THBCs and the related compounds.

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9. Except for its easy availability, there is no specific reason for choosing a chiral oxazine (**1**) as its chirality does not effect the stereochemical outcome of the reaction depicted in Scheme 2.

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15. The complexities of this process are currently outside the realm of our complete understanding, however switching from the chiral acetylenic sulfoxides to the oxazinane (**3**), we have been successful in altering the stereochemical outcome of the reaction from **7a/8a** (30 : 70) and **7b/8b** (70 : 30) in the former method to **7a/8a** (70 : 30) and **7b/8b** (30 : 70) in the later.