A VERSATILE APPROACH TO *TRANS*-1,3-DISUBSTITUTED TETRAHYDRO-β-CARBOLINES USING OXAZINANES

Kamajit Singh* and Prasant K. Deb

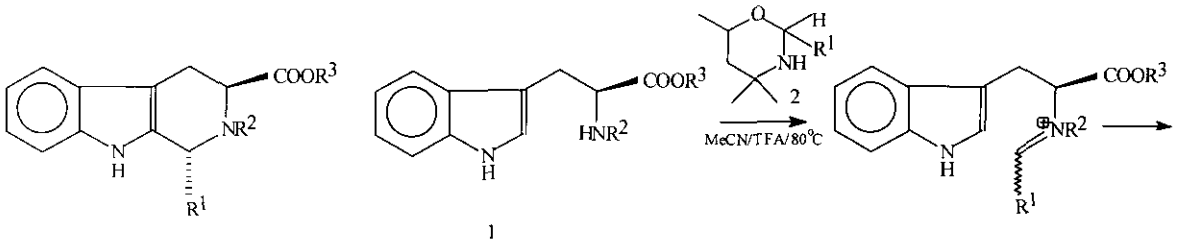
Department of Applied Chemical Sciences & Technology, Guru Nanak Dev University, Amritsar – 143 005, India

Abstract - Under the conditions of thermodynamic control, the diastereoselectivity of the reaction between tryptophan esters and oxazinanes (carbonyl equivalents) can be controlled by incorporating N_b-benzyl substituents; the reaction proceeds in essentially quantitative yield and with *trans*-diastereoselectivity.

The Pictet-Spengler reaction[1] has long been an important reaction for the synthesis of numerous naturally occurring alkaloids, embodying tetrahydro-β-carbolines or tetrahydroisoquinoline framework, mediating pharmacologically useful effects.[2] Therefore, the synthesis of these systems in a synthetically useful manner is of widespread interest to both organic synthesis and medicinal chemistry. Conventional Pictet-Spengler reaction quite often lacks practicability owing to handling and non-availability of desired functionalized aldehydes. Perhydrooxazines (oxazinanes), which have been synthesized from a variety of reagents other than aldehydes,[3] have amply demonstrated synthetic superiority[4] over conventional carbonyl compounds owing to carbonyl character[3] of the C-2. However, a generally applicable methodology for the execution of title protocol is currently not available. We have seen, in accordance with the carbonyl compounds, by using conditions of thermodynamic control, the Pictet-Spengler reaction between (L)-tryptophan ester and appropriately substituted oxazinanes can be controlled to give the title compounds selectively.

The oxazinanes which were used as reagents in the diastereoselective synthesis are readily available from a variety of cheaply available combinations. If the secondary amines **(1)** are treated with oxazinanes **(2)** – existing mainly in tautomeric iminium form,[5] at 80°C in anhydrous acetonitrile as solvent in the

presence of 2 to 3 equivalents of trifluoroacetic acid, the iminium intermediate (Scheme) formed *in situ* cyclises spontaneously by intramolecular attack of C-2 of indole nucleus on iminium functionality to deliver 1,3-disubstituted tetrahydro-β-carbolines **(3)** and **(4)** in excellent yields and with very high diastereomeric ratios (Table). The *trans*-N_b- substituted diastereomers are thermodynamically more stable than their *cis*-congeners especially where the reactions are catalysed by TFA and conversion of *cis*-diastereomer into the more stable *trans*-diastereomers is believed to occur under acidic conditions by cleavage of the carbon (C-1)-nitrogen (N-2) bond with complete retention of configuration at C-3



Scheme. The thermodynamically controlled reaction yields predominantly *trans*-1,3-disubstituted tetrahydro-β-carbolines **(3)**.

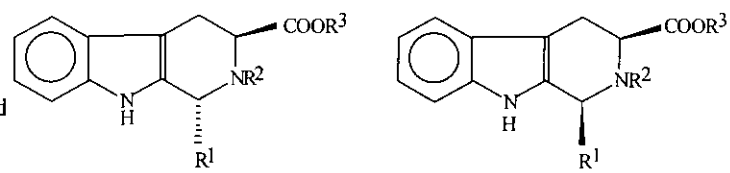


Table : Diastereoselectivity in the Pictet-Spengler reaction between oxazinanes **(2)** and (L)-TrpOR[3].

Entry	R^1	R^2	R^3	Diastereomeric ratio **3 : 4**	Yield (%)[6]
1.	Ph	benzyl	Me	99 : 1	88
2.	4-$MeOC_6H_4$	benzyl	Me	98 : 2	91
3.	3,4,5-tri-$MeOC_6H_2$	benzyl	Me	99 : 1	90
4.	Ph	4-MeO-benzyl	Pr^i	97 : 3	86
5.	4-$MeOC_6H_4$	4-MeO-benzyl	Pr^i	98 : 2	88
6.	3,4,5-tri-$MeOC_6H_2$	4-MeO-benzyl	Pr^i	99 : 1	92

stereocentre.[2] However, like the conventional Pictet-Spengler reaction[7] the diastereoselectivity is not controlled by varying the size of the ester group where N_b-benzyl substituents[8] are present. The

predominantly formed stereoisomer can be isolated in a straightfoward way using simple chromatography and recrystallisation. The diastereomers were identified by analysing 200 MHz- ^{1}H NMR and 50.3 MHz-^{13}C NMR and the stereochemistry was unambiguously assigned by comparison with the literature NMR data.[9]

This method of preparation of the title compounds may be considered a variant of the classical Pictet-Spengler reaction in that the same iminium intermediate is deemed to be involved in the reaction. This approach will be preferred in those cases where the aldehydes required for a Pictet-Spengler reaction are unstable or difficult to access as the oxazinanes can be readily functionalized at C-2.[3] The utility of this approach using oxazinanes bearing aliphatic substituents (equivalents of aliphatic aldehydes) at C-2 to effect synthesis of some target alkaloids is in progress.

ACKNOWLEDGEMENTS

We thank CSIR, New Delhi for the grant 01(1441)/97-EMR-II, the university for a research fellowship to PKD and Professor Harjit Singh for helpful discussions.

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6. Using our standard conditions of reflux at 80°C, the yields refer to that of isolated compounds.

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8. The (L)-tryptophan methyl or iso-propyl esters lacking N_b-benzyl substituents yielded equilibrated mixtures of corresponding **3** and **4** .

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Spectroscopic data of selected **3**

Entry 1: IR (KBr) 3337 (s, NH), 1722 (s, ester) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.22 (d, J=4.5 Hz, 2H, CH_2), 3.62 (s, 3H, OCH_3), 3.86 (d, J=2.3 Hz, 2H, CH_2), 3.92-3.96 (m, 1H, CH), 5.46 (s, 1H, CH), 7.07-7.52 (m, 15H, Ar-H & NH); ^{13}C NMR ($CDCl_3$) δ 24.36 (CH_2), 51.31(OCH_3)*, 54.32 ($\underline{C}H_2C_6H_5$), 56.06 (C-3)*, 60.84 (C-1)*, 106.31, 110.83, 118.16, 119.24, 121.54, 127.05, 127.53, 128.00, 128.31, 128.55, 128.67, 128.89, 134.88, 136.50, 139.41, 142.17, 173.56 (CO).

Entry 4: IR ($CHCl_3$) 3310 (s, NH), 1714 (s, ester) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (d, J=6.3 Hz, 3H, CH_3), 1.21 (d, J=6.2 Hz, 3H, CH_3), 3.17 (d, J=4.2 Hz, 2H, CH_2), 3.79 (m, 3H, OCH_3, merged with multiplet of $C\underline{H}_2Ph$), 3.78-3.82 (m, 2H, CH_2Ph), 3.86-3.91 (m, 1H, CH), 4.91-5.00 (heptet, J=6.2 Hz, 1H, CH), 5.43 (s, 1H, C-1 H), 6.83-7.52 (m, 14H, Ar-H & NH). ^{13}C NMR ($CDCl_3$) δ 21.78 (CH_3), 21.90 (CH_3), 24.35 (CH_2), 53.72 (CH), 55.92 (C-3)*, 60.95 (C-1)*, 67.59 (OCH_3), 106.40, 110.73, 113.72, 118.11, 119.22, 121.45, 127.12, 127.93, 128.65, 128.84, 129.77, 131.44, 134.94, 136.50, 142.42, 158.76, 172.69 (CO).

* characteristic signals

Received, 7th April, 1999