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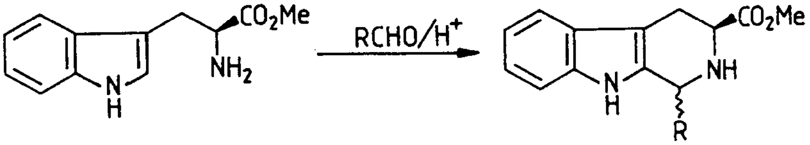
EXCEPTIONAL STEREOCHEMICAL CONTROL IN THE PICTET-SPENGLER REACTION

Patrick D Bailey,* Sean P Hollinshead and Neil R McLay

Department of Chemistry, University of York,
Heslington, York YO1 5DD, U.K.

Summary. Cis-1,3-disubstituted tetrahydro-β-carbolines can be formed with high stereo- and enantio-selectivity by conducting the Pictet-Spengler reaction at low temperature.

Several recently published syntheses of indole alkaloid precursors have used L-tryptophan derivatives in the stereo-selective and enantio-specific preparation of cis-1,3-disubstituted tetrahydro-β-carbolines.[1] The common feature of these reports is that the pivotal Pictet-Spengler reaction (Scheme) was conducted at room temperature (CH_2Cl_2/TFA/r.t.) rather than under the standard conditions[2] of refluxing benzene or toluene. It was quite possible that the cis-selectivity was a consequence of the particular substrates used, rather than being a feature of the reaction conditions. Nevertheless, it is perhaps surprising that no systematic exploration into the effects of solvent/temperature on the stereo- and enantio-selectivity of the reaction has been reported until now.



Scheme

Initially, we chose to investigate the well documented condensation of tryptophan methyl ester with phenylmethanal,[3] using the range of conditions outlined in Table 1. The results show that in refluxing benzene, the trans-isomer is favoured by a ratio of about 2:1, whereas at 0°C in CH_2Cl_2, the cis-isomer predominates to the extent of >4:1;[4] a further reaction in PhH at room temperature indicated that this reversal of stereo-selectivity was primarily due to the temperature, rather than to the solvent. Even more significantly, it was discovered that the reaction in refluxing benzene has led to almost complete racemisation ($[\alpha]_D^{20}$ +1.0°, c = 1.0 in pyridine - cis-isomer), whilst the reaction in CH_2Cl_2 at 0°C had retained optical integrity ($[\alpha]_D^{20}$ +33.1°, c = 1.0 in pyridine - cis-isomer).[5]

Temp. (°C)	Solvent	Cis:Trans Ratio	Yield (%)[6]
110	PhMe	40:60	62
80	PhH	37:63	76[a]
40	CH_2Cl_2	45:55	72
r.t.	CH_2Cl_2	80:20	74
r.t.	PhH	78:22	65
0	CH_2Cl_2	82:18	74[b]
-70	CH_2Cl_2	83:17	62

Table 1. The reaction of phenylmethanal with L-tryptophan methyl ester.[4] *Cis* and *trans* isomers were identified by ^{13}C NMR using the method of Cook *et al*,[8] and *cis*:*trans* ratios were determined from the ^1H NMR areas of the methyl ester peaks. Enantiomeric excesses (e.e.) of a) 11% and b) 90% were estimated by the addition of chiral shift reagent, tris[3-heptafluoropropylhydroxymethylene--(+)-camphorato] europium(III).

To see whether the stereochemical control could be extended to other substrates, a series of condensations were conducted in CH_2Cl_2 at 0°C or in PhH at reflux. From the results summarised in Table 2, it is clear that little selectivity is afforded in refluxing benzene. In contrast, the cis-isomers predominate by ratios of about 4:1 when the reactions are carried out in CH_2Cl_2 at 0°C.

Aldehyde	$CH_2Cl_2/0^oC$		PhH/Reflux	
	C:T ratio	Yield (%)[6]	C:T ratio	Yield (%)[6]
PhCHO	82:18	74	37:63	76
$C_6H_{11}CHO$	71:29	71	59:41	85
$MeCH_2CH_2CHO$	80:20	72	47:53	88
$PhCH_2CH_2CHO$	83:17	75	51:49	83
Me_2CHCHO	83:17	82	43:57	76

Table 2. The reaction of aldehydes with tryptophan methyl ester in CH_2Cl_2 at 0^oC and in PhH at reflux.[4] *Cis* and *trans* isomers were identified by ^{13}C NMR using the method of Cook *et al*,[8] and *cis*:*trans* ratios were determined from the relative peak heights of diastereotopic carbons (average of at least 5 peak ratios) in the ^{13}C NMR spectra.

Thus, we have shown that high *cis*-selectivity can be achieved if the Pictet-Spengler reaction is conducted at lower temperatures than are commonly used. Moreover, in all cases where the e.e. has been recorded, high optical purity has been observed for reactions conducted in CH_2Cl_2 at (or below) room temperature. It would seem certain that this procedure should be adopted routinely for the chiral synthesis of *cis*-1,3-disubstituted tetrahydro-β-carbolines.

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4 Typical experimental procedures were as follows:
Method A. The aldehyde and *L*-Trp-OMe were stirred at 0°C in CH_2Cl_2 with a trace of TFA over molecular sieves, until imine formation was complete (24h). Cyclisation was initiated by the addition of excess TFA (2 mol. eq.), and the mixture was stirred until reaction was complete by TLC (3 - 4h).
Method B. The aldehyde and *L*-Trp-OMe in PhH were brought to reflux over molecular sieves, and a trace of TFA was then added. After 1h, an excess of TFA (2 mol. eq.) was added, and refluxing was continued for 3h. Although spontaneous cyclisation in refluxing PhH was occasionally observed (c.f. Ref. 3), acid catalysis gave much more reliable results. However, the *amount* of acid present did not affect the *cis*:*trans* ratios.

5 This reaction in refluxing benzene (Dean-Stark water extraction) was catalysed by p-TsOH; the reaction in CH_2Cl_2 used *Method A*.[4] For both reactions, the *cis*-isomers were isolated by flash chromatography.[7]

6 Yields are quoted for the pure isolated *cis*/*trans* mixture of diastereoisomers, obtained after purification by flash chromatography;[7] all products gave the expected ^{1}H NMR, ^{13}C NMR, IR and MS. Care was taken to avoid separation of the diastereoisomers at this stage, to ensure that NMR would give accurate values for the *cis*:*trans* ratios.

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