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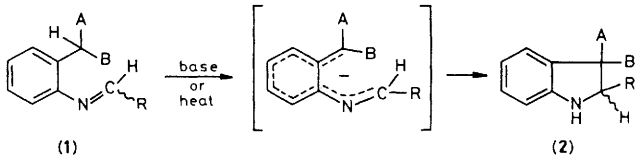
Enantioselective 1,5-Electrocyclization. Synthesis of Optically Active Indolines

Siem J. Veenstra and W. Nico Speckamp*

Laboratory of Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

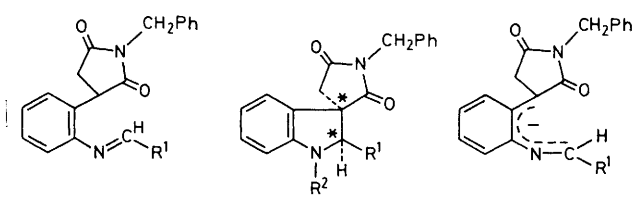
Intramolecular base-catalysed 1,5-electrocyclization of aldehyde imines derived from *o*-aminophenyl succinimide (**3**) in the presence of a chiral alcohol yields chiral indolines (**4**) with optical purities ranging from 17 to 31%.

Intermolecular enantioselective additions of nucleophiles to electrophilic alkenes sometimes give impressive results in terms of optical yields.[1] The corresponding intramolecular variant, although only occasionally studied, has also been shown to afford appreciable asymmetric induction.[2] Recently a novel intramolecular addition of a carbanionic species on to an imine was reported[3] which could be represented in a general way by the reaction (**1**) → (**2**) (Scheme 1). While enantioselective intermolecular imine additions have been studied before[4] the reaction which we report now differs essentially in mechanism and is termed more accurately as a 1,5-electrocyclization.[5] For the latter type of reaction no examples of asymmetric induction have been reported so far.



(1) (2)

Scheme 1



(3) a; R^1 = Bu^t
b; R^1 = Pr^n
c; R^1 = Ph
d; R^1 = CH=CHPh

(4) R^2 = H
(6) R^2 = Ac

(5)

The intramolecular imine cyclization is exemplified by the base-catalysed conversion of the imine (**3a**) into the indoline (**4a**) which proceeds in a stereocontrolled fashion in a bulky alcoholic solvent. The compounds (**4**) are of value in a short and general synthesis of indole alkaloids.[6] Since the origin of the stereoselective effect was assumed to reside in a particularly strong association between the hydroxy-moiety of the alcohol and the reactive intermediate,[7] most probably the anion (**5**), the use of a chiral alcohol could profoundly influence the stereochemical outcome. We now report that addition of a chiral co-solvent in the 1,5-electrocyclization of (**3a—d**) leads to the optically active indolines (**4a—d**), thereby in principle allowing the enantioselective synthesis of Aspidosperma alkaloids.

In a typical reaction (−)-menthol {0.500 g; $[\alpha]_{578}$ (room temp.) −42 °, *c* = 6.3, $CHCl_3$} was dissolved in tetrahydrofuran (THF) (10 ml) and Bu^nLi (0.5 mmol; 20% soln. in hexane) followed by a solution of (**3a**) (0.5 mmol) in toluene (1 ml) added. The mixture was stirred for 3 h at 0 °C, and the menthol was removed by column chromatography on silica gel with EtOAc–cyclohexane (1:10) as eluant affording chemically pure (**4a**) (139 mg; 62%) as an oil {$[\alpha]_{578}$ (room temp.) −55°, *c* = 1.0, $CHCl_3$} structurally identical with the product, m.p. 159—160 °C, formed upon treatment of (**3a**) with $NaOBu^t$. The enantiomeric purity of (**4a**) was determined *via* 250 MHz ^1H n.m.r. analysis of the benzylic AB pattern using the shift reagent Eu(hfc)$_3$,† and this indicated an enantiomeric excess (e.e.) value of 31% (±2). Upon fractional crystallization of (**4a**) from EtOAc–hexane the pure enantiomer was obtained; m.p. 137—138 °C {$[\alpha]_{578}$ (room temp.) −152°, *c* = 0.92, $CHCl_3$}. Since the type of cation and/or the reaction

† Eu(hfc)$_3$: tris-[3-(heptafluoropropylhydroxymethylene)-(−)-camphorato]europium(III), >99%, Gold Label, Aldrich.

Table 1. Enantioselective synthesis of the indolines (**4**) from the imines (**3**).

Entry	R^1	Alcohol	T/°C	Cation	Product	t/min	e.e. (±2%) of (**4**)	Chemical yield (%)	$[\alpha]_{578}$ (room temp.) ($CHCl_3$)
1	Bu^t	(−)-Menthol	0	Li	(**4a**)	180	31[a]	62	−55° (*c* 1.0)
2	,,	(−)-Menthol	Room temp.	Li	(**4a**)	90	27[b]	65	−44° (*c* 1.7)
3	,,	(−)-Menthol	,,	Na	(**4a**)	90	28[b]	52	−43° (*c* 9.3)
4	,,	(−)-Borneol	0	Li	(**4a**)	180	17[b]	73	−25° (*c* 4.0)
5	Pr^n	(−)-Borneol	0	Li	(**4b**)	15	18[a]	70	−10° (*c* 3.9)
6	,,	(−)-Menthol	0	Li	(**4b**)	15	18[b]	40	−10° (*c* 13.9)
7	Ph	(−)-Menthol	−40	Li	(**6c**)	120	29[a]	64	+4.7 (*c* 14.0)
8	$PhCH{=}CH_2$ (*E*)	(−)-Menthol	0	Li	(**6d**)	15	22[a]	85	+44° (*c* 7.0)

[a] e.e. determined by ^1H n.m.r. spectroscopy with $Eu(hfc)_3$. [b] e.e. calculated from $[\alpha]_{578}$ (room temp.).

Table 2. C.d. data for (**4a**), (**6d**), and (**7**).

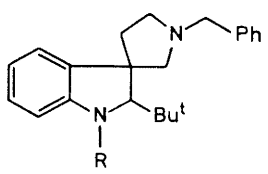
Compound	$[\alpha]_{578}$ (room temp.) ($CHCl_3$)	U.v. (95% EtOH) λ_{max}/nm (ϵ)	C.d. (95% EtOH) λ/nm ($\Delta\epsilon$)
(**4a**)	−152° (*c* 0.35)	246 (3.84), 302 (3.38)	243 (−0.747), 277 (+0.173), 312 (−0.180)
(**6d**)	−67° (*c* 0.9)	247 (3.84), 279 (3.08), 286 (3.02)	246 (−2.72)
(**7**)[a]	+24° (*c* 0.5)	264 (3.74), 306 (3.36)	260 (−0.513), 317 (+0.231)

[a] Inseparable mixture of compounds with R = H and Et.

temperature may be expected to influence the results different conditions were also investigated. As is evident from Table 1 (entries 2 and 3) no major variation in e.e. values was found.

It is interesting that replacement of (−)-menthol by (−)-borneol {$[\alpha]_{578}$ (room temp.) −36.7°, *c* = 4.3, $CHCl_3$} also induced chirality, albeit to a smaller degree (entry 4). Other imines (**3b—d**) were also examined. The e.e. value for the propionyl derivative (**3b**) appeared almost the same in both menthol and borneol (entries 5 and 6) although in menthol the chemical yield was considerably lower. For the phenylindoline (**3c**) as well as the styryl analogue (**3d**)‡ e.e. values of 29 and 22%, respectively, were determined. In view of the low solubility of both compounds the $[\alpha]_{578}$ (room temp.) values were taken after *N*-acetylation (entries 7 and 8).

The present 1,5-electrocyclization results are of great mechanistic interest since formally a simple solvent effect suffices to induce molecular asymmetry.[8] Moreover to the best of our knowledge the reported cases are the first examples of enantioselective electrocyclic reactions and in principle allow the asymmetric synthesis of indole alkaloids *via* this novel route.[6] In the latter respect it seemed of general interest to determine the absolute configuration of the indolines (**4**) by comparison of their c.d. spectra with the corresponding o.r.d. data for the aspidospermidines.[9] Since the u.v. behaviour of these compounds and of the newly synthesized spiroimides is primarily determined by the aniline chromophore, a comparison between both types of indoline derivatives is justified and may give direct information on the configuration at the spiro carbon atom. As follows from Table 2 the imide (**4a**) exhibits a negative Cotton effect at 243 nm which is intensified after *N*-acetylation. In the alkaloid series a similar observation indicates an 11α-configuration for aspidospermidine.[10] A 2,3-*cis*-α-configuration therefore is assigned to the indoline (**4a**). Moreover upon reduction of (**6c**) with $LiAlH_4$ a mixture of *N*-unsubstituted and *N*-ethyl indolines (**7**) was obtained[11] which also showed analogous c.d. behaviour (Table 2).



(7)

‡ Satisfactory analytical and spectral data were obtained for all new compounds.

We conclude that the use of chiral secondary alcohols as co-solvents in base-catalysed 1,5-electrocyclizations gives rise to enantioselective formation of indolines.

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References

1 D. J. Cram and G. D. Y. Sogah, *J. Chem. Soc., Chem. Commun.*, 1981, 625; H. Hiemstra and H. Wijnberg, *J. Am. Chem. Soc.*, 1981, **103**, 417.
2 W. ten Hoeve and H. Wijnberg, *J. Org. Chem.*, 1979, **44**, 1508; K. Herrmann and H. Wijnberg, *ibid.*, 1979, **44**, 2238; B. M. Trost, C. D. Shuey, and F. DiNinno, *J. Am. Chem. Soc.*, 1979, **101**, 1284.
3 W. N. Speckamp, S. J. Veenstra, and H. P. Fortgens, *J. Am. Chem. Soc.*, 1981, **103**, 4643.
4 D. Valentine, Jr., and J. W. Scott, *Synthesis*, 1978, 329.
5 E. C. Taylor and I. J. Turchi, *Chem. Rev.*, 1979, **79**, 181; R. Huisgen, *Angew. Chem.*, 1980, **92**, 979.
6 S. J. Veenstra and W. N. Speckamp, *J. Am. Chem. Soc.*, 1981, **103**, 4645.
7 J. Bjorgo, D. R. Boyd, C. G. Watson, W. B. Jennings, and D. M. Jerina, *J. Chem. Soc., Perkin Trans.*, 1, 1974, 1081; M. Bucciarelli, A. Forni, I. Moretti, and G. Torre, *ibid.*, 1980, 2152.
8 Y. Izumi and A. Tai, 'Stereo-differentiating Reactions,' Academic Press, New York, 1979, p. 82.
9 W. Klyne, R. J. Swan, B. W. Bycroft, D. Schumann, and H. Schmid, *Helv. Chim. Acta*, 1965, **48**, 443.
10 W. Klyne, R. J. Swan, B. W. Bycroft, and H. Schmid, *Helv. Chim. Acta*, 1966, **49**, 837.
11 A. Hajós, 'Complex Hydrides,' Elsevier, Amsterdam–Oxford–New York, 1979, p. 95.