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C₂ Symmetric Amines. III. An Asymmetric Synthesis of (S,S)-1,3-Dialkyl Isoindolines by Sequential Formamidine Alkylation

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Summary: Metalation-alkylation of isoindoline **5** in the form of its chiral formamidine, **6** leads to C_2 -dialkylated derivatives in high ee's.

Asymmetric synthetic methods have benefited from a variety of chiral auxiliaries not the least of which are those possessing C_2 symmetry.¹ In our continuing program to evaluate the synthetic versatility of chiral formamidines to mediate asymmetric C-C bond forming reactions,² we have investigated the suitability of sequential alkylations in the isoindoline system to give 1,3-dialkyl products, **1**. In contrast to the isoquinolines **2a**,³ we felt secure that the sequential metalation-alkylation would not lead to the 1,1-dialkyl product **2b**, but rather to the 1,3-dialkyl product, **1**. This is based on the relative kinetic acidity of both benzylic carbons present in isoindoline. If this indeed occurs, then the possibility of reaching C_2 symmetrical isoindolines and other novel and interesting chiral systems will be realized. Gawley has described⁴ an oxazoline-mediated route to (R,R)-1,3-dibenzylisoindoline, **4** (R = benzyl) while the mono-alkylation of isoindoline **3** has been reported.⁵ Dialkylation in the latter instance led to a 1:1 mixture of *cistrans* **3** (R = Me).



We now wish to describe an efficient asymmetric double alkylation of indolines mediated by chiral formamidines. Our first task was to provide ready access to the starting indoline, **5**. Previous procedures^{4,6} involved corrosive or potentially hazardous reagents, so we adapted our earlier preparation of 2,5-dihydropyrrole.⁷ The use of o-xylenyldichloride and hexamethylene tetramine gave, after acidic and basic workup (Delepine reaction), a 40-45% yield of **5** on a 15-20



g scale.⁸ The isoindoline **5** was transformed into the achiral and chiral formamidines **6b** and **6a** (80-95%) respectively, by heating with the dimethylamino formamidines **7b**^{3a} and **7a**.^{3c} The racemic material **6b** was prepared to provide a stereochemical standard for determining the enantiomeric purity of the products derived from (+)-**6a**.

Metalation of **6a** with *n*-butyllithium (THF, -78 °C) gave a deep blue anion solution after 25 min which was cooled to -100 °C and treated with 1.05 equiv of electrophile, slowly added (25 min) as a THF solution. After 30 min, the mixture was quenched (H₂O) and extracted with EtOAc. Chromatography (EtOAc-Hexane) gave pure monoalkylated **8a-8c** which was remetalated and alkylated as above, to furnish **9a-9c**. Hydrazinolysis^{3c} gave the free chiral C_2 amines **10a-10c** in good overall yields (Table 1). Due to the two adjacent substituents on **9**, hydrazinolysis was slower than usual requiring 24 h at 65-70 °C. In sharp contrast, the hydrazinolysis of **11** and **12** was complete in 5-10 min at room temperature furnishing the novel chiral tricyclic amines **13** and **14**. The latter were prepared by alkylation of the lithio anion of **6a** with the appropriate bromochloroalkanes.⁹



Table 1		Chiral	C2	Amines	and	1-Azabicy	clo	Amines
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isoindoline	yield (% from 6a) ^a	%eeb	[α]	<u>con</u> f'n
10a	63	97	+16.7° (CH ₂ Cl ₂)	S,S
10b	64	>99	+6.1 (EtOH)	S,S ^c
10c	61	95	-26.3(CH ₂ Cl ₂)	S,S
13	68	94	-40.1 (CH ₂ Cl ₂)	S
14	62	94	+7.5 (CH ₂ Cl ₂)	S

a) Purities of diastereomers 8 and 9 were determined by capillary GC and were >95:5, the minor product identified (NMR) as the *cis* dialkyl isomer. b) Determined by hplc (Diacel, OJ) on the naphthoyl amide of 10 and 11, 12. c) The R,R enantiomer was reported as -5.4° (CH₂Cl₂), see ref. 4.

The absolute configurations assigned to **10a-c** and **13**, **14** are based upon our earlier studies using S-valinol which gave exclusively the S-configuration (as in 8). This was also supported by the R,R-1,3-dibenzylisoindoline reached *via* chiral oxazolines which has, on numerous occasions, led to the opposite configuration⁴ than that observed with the chiral formamidines (Table 1).

Further studies using these C_2 amines are in progress and will be reported in the future.

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References and Notes

- For an excellent and recent review, see Yamamoto, Y.; Hoshino, J.; Fujmoto, Y.; Ohmoto, J.; Sawada, S. Synthesis 1993, 298. See the previous Letter (Part II) for additional references on C₂-symmetric systems.
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- 8. Preparation of 5. Ortho-xylenyldichloride (50 g), hexamethylene tetramine (40.7 g) was heated at reflux in 500 mL CHCl₃ for 4 h. On cooling, the solution was filtered and the collected solid washed with CHCl₃, and dried *in vacuo* overnight. The solid was dissolved in 500 mL EtOH and treated with (slowly!) 92 mL 12 M HCl and allowed to stir for 24 h. All the volatiles were removed under aspirator and the remaining solid dried (0.25 mm, 12 h). The solid was dissolved in 500 mL EtOH and extracted with EtOAc (10 x 100 mL), dried (K₂CO₃), concentrated and distilled; bp 113 °C (25 torr) to give 14.66 g (44%). Distillation was best when the receiving flask contained a shiny piece of copper metal to avoid oxidation of the product.
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