



0957-4166(95)00379-7

Indoles from 3-Nitropyridinium Salts¹: A new Route to Chiral Indoles and Indolines

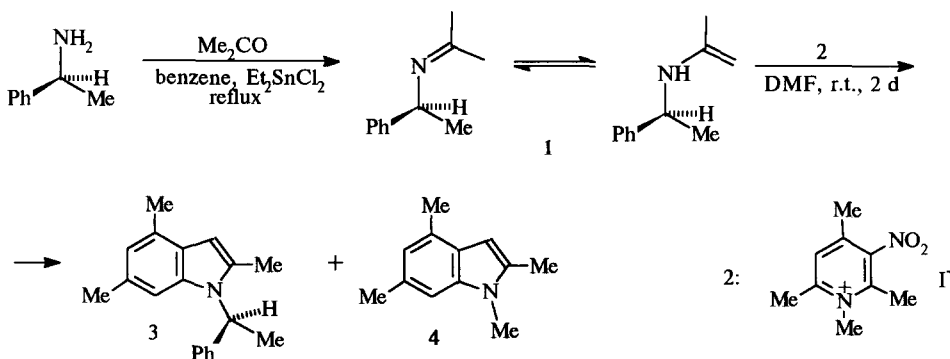
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Abstract: (S)-1-(1-Methylbenzyl)-2,4,6-trimethylindole was prepared by interaction of (S)-isopropyliden(1-methylbenzyl)amine with 1,2,4,6-tetramethyl-3-nitropyridinium iodide. The indoles thus prepared undergo diastereoselective hydride reduction and debenzylation to afford chiral (S)-2,4,6-trimethylindoline with high yield and optical purity up to 76%.

The transformation of 1-methyl-3-nitropyridinium salts by the action of N-alkylketimines under mild reaction conditions has been shown by us to be a very useful method for the preparation of alkylindoles^{2a,b}. As previously reported^{2b}, the source of nitrogen atom in indole is imine, but not the pyridinium salt. This method makes it possible to suggest a new strategy for the introduction of a chiral substituent on to the nitrogen atom of indoles. Thus, the use of (S)-isopropyliden(1-methylbenzyl)amine **1** in the reaction with 3-nitro-1,2,4,6-tetramethylpyridinium iodide **2** leads to the mixture of (S)-1-(1-methylbenzyl)-2,4,6-trimethylindole **3** and 1,2,4,6-tetramethylindole **4**.

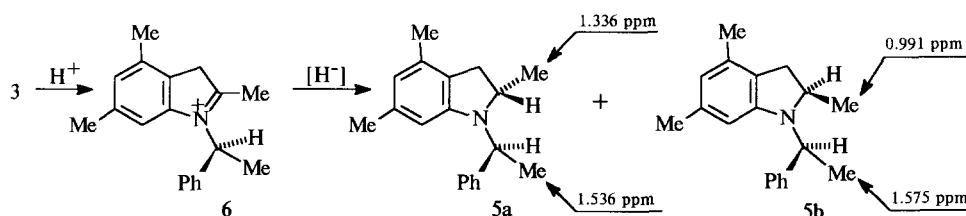


Scheme 1

Earlier (+)-**3** was prepared in only 10% yield from **2** and mixture of acetone with (+)-1-methylbenzylamine⁴.

We wish to describe herein an efficient synthesis of (S)-**3** in 78% yield. Thus, the mixture of (S)-1-methylbenzylamine (2.9 g, 24 mmol, $[\alpha]_D^{23} - 39$ (neat), 96.5% ee), acetone (8.8 mL, 0.12 mol), benzene (50 mL) and catalytic amounts of diethyltin dichloride was refluxed for 2 h in a Soxhlet extractor with molecular sieves 4A. The reaction was monitored by capillary GC analysis. After solvent evaporation in vacuo isopropyliden(1-methylbenzyl)amine **1** (purity > 98%, capillary GC) was obtained as a pale yellow oil. Crude **1** was added to a stirred solution of **2** (0.924 g, 3 mmol) in anhydrous DMF (15 mL). The mixture was stirred at r.t. for 2 d. The solvent was distilled off and the residue was diluted with water and extracted with hexane. The major product **3**⁵ was separated from the by-product **4** by Harwood's flash chromatography technique⁶ (SiO₂, octane-ether, 95:5) as pale yellow oil (0.615 g, 78%).

Treatment of **3** with boron hydride⁷ gave a mixture of diastereomeric indolines **5a** and **b**. The ratio of **5a**:**5b** was determined by ¹H and ¹³C NMR and HPLC (Table). Reduction of **3** by boron hydrides in acid medium proceeds via intermediate formation of chiral indoleninium ion **6**⁸.



Scheme 2

Table. Reduction of indole **3** with boron hydrides

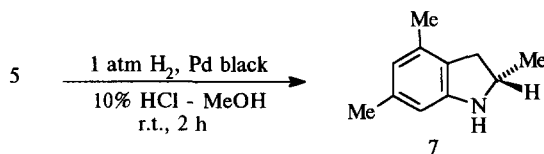
entry	boron hydride (BH)	Conditions				5a:5b	de, %	yield, % ^{a)}
		molar ratio of BH to 3	solvent	temp, °C	time, h			
1	NaBH(OAc) ₃	2	AcOH	r.t.	1	2.6:1	44	85
2	NaBH ₃ CN	2.5	MeOH-HCl	-50	1	5:1	67	90
3	NaBH ₃ CN	2	MeOH-HCl	-80	1	9:1	80	88
4	Bu ₄ NBH ₄	3	CH ₂ Cl ₂	reflux	20			b)
5	NaBH ₄	4	MeOH-HCl	-80	2	6:1	71	83
6	C ₅ H ₅ NBH ₃	3	MeOH-HCl	-50	1.5	2:1	33	80
7	<i>t</i> -BuNH ₂ BH ₃	8	MeOH-HCl	-80	1.5	2.3:1	39	75

a) Yields were referred to isolated mixture of **5a** and **5b**.

b) Only indole **3** was isolated in 70% yield.

As shown in the table, moderate to good diastereoselectivity was observed for all entries. It can be seen from the table that when complex boron hydrides are used the reaction diastereoselection increases. In this case it is probably the stereocontrolled formation of an indoleninium ion-borohydride ion pair prior to hydride reduction. The borane-amine complexes displayed only poor stereoselectivity ($de < 40\%$).

The configuration of newly generated asymmetric centre in **5a** was assigned by correlation with (S)-2-methylindoline ($[\alpha]_D -7.8$, c 1.05, EtOH)⁹. The hydrogenolysis of mixture indolines **5a** and **b** leads to (S)-2,4,6-trimethylindoline (**7**, $[\alpha]_D -0.5$, c 1.29, EtOH)¹⁰ in 85% yield and optical purity of 76% ee (determined by HPLC on a chiral column).



Scheme 3

The nucleophilic addition reaction of a hydride-ion to carbon-nitrogen double bond of **6** presents an example of 1,3-asymmetric induction. At this point in time, we do not have enough data, neither experimental nor computational, to describe the transition state topology of this reaction.

Acknowledgements: This work was financially supported by International Science Foundation (Grant No NBD300) and Russian Fundamental Investigation Foundation (Grant No 93-03-4593).

References and Notes

- Part 11. For part 10, see: Yurovskaya M.A., Karchava A.V., Bundel' Yu.G. *Khim.Geterotsikl.Soed.* **1992**, 1187.
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- For explanation of indole **4** formation see: Afanasyev A.Z., Yurovskaya M.A., Bundel' Yu. G. *Khim.Geterotsikl.Soed.* **1987**, 134.
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- 1-(S)-(1-methylbenzyl)-2,4,6-trimethylindole (**3**): pale yellow oil $[\alpha]_D^{28} +8.38$ (c 0.78, hexane). ^1H NMR (CDCl_3 , 400 MHz) δ : 1.92 (3H, d, $J = 7.1$, CHCH_3), 2.30 (3H, s, 2- CH_3), 2.31 (3H, s, 4- CH_3), 2.47 (3H, s, 6- CH_3), 5.72 (1H, q, $J = 7.1$, CHCH_3), 6.24 (1H, bs, 3-H), 6.67 (1H, bs, 5-H), 6.70 (1H, bs, 7-H), 7.13-7.35 (5H, m, Ph). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz) δ : 14.14, 18.61, 21.84, 22.70, 52.32, 99.45, 108.44, 121.33, 125.95, 126.22 (2C), 126.97, 128.50 (2C), 128.63, 129.98, 135.29, 136.26, 141.68. MS (EI, 70 eV) m/z (I): 263 (60, M^+), 159 (100, $\text{M}^+ - \text{PhCH}=\text{CH}_2$).

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10. (S)-(-)-2,4,6-Trimethylindoline (7), pale yellow oil, C₁₁H₁₅N.HCl, mp 161-163°C (dec) [α]_D -0.5 (c 1.29, EtOH). ¹H NMR (CDCl₃, 400MHz) δ : 1.28 (3H, d, J = 6.82, 2-CH₃), 1.91 (1H, bs, NH), 2.15 (3H, s, CH₃), 2.21 (3H, s, CH₃), 2.49 and 3.04 (each 1H, each m, CH₂), 3.98 (1H, m, CHCH₃), 6.28 (1H, bs, H_{ar}), 6.35 (1H, bs, H_{ar}) MS (EI 70eV) m/z 161 (M⁺).

(Received in UK 7 August 1995; accepted 11 October 1995)