

SYNTHESIS OF 4-ARYLTETRAHYDROISOQUINOLINES: APPLICATION TO THE SYNTHESIS OF CHERYLLINE

Somsak Ruchirawat^{1-3*}, Sopchok Tontoolarug², and Poolsak Sahakitpichan¹

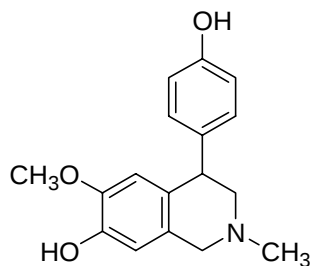
¹Chulabhorn Research Institute, Vipavadee Rangsit Highway, Bangkok 10210, Thailand

²Department of Chemistry, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand

³Programme on Research and Development of Synthetic Drugs, Institute of Science and Technology for Research and Development, Mahidol University, Salaya Campus, Thailand

Abstract- A concise route for the synthesis of 4-aryltetrahydroisoquinolines was developed using the addition of Grignard reagents to nitrostyrene derivatives as the key step. The application to the synthesis of cherylline was described.

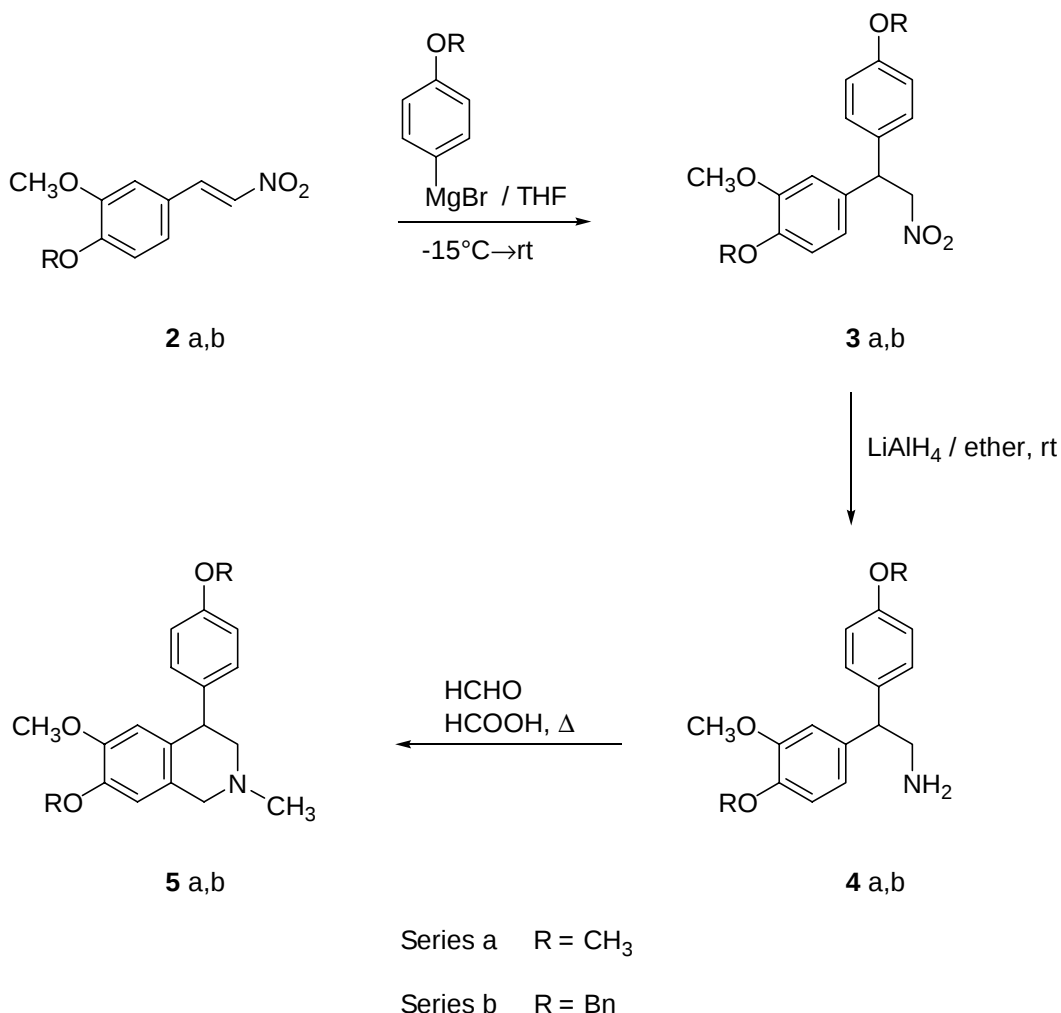
Cherylline has been isolated from *Crinum powellii* var. *alba* and other *Crinum* species.¹ It is a representative of the very rare natural 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloids. Due to the uniqueness of the structure and potential medicinal properties of the 4-arylisoquinoline derivatives,² many synthetic routes for these compounds³ and especially cherylline (**1**)⁴ have been reported. In the course of our synthetic work on alkaloids, we have successfully developed a new approach for the synthesis of cherylline.



Cherylline **1**

The key step of our approach involved conjugate addition of the Grignard reagents to the appropriate nitrostyrene derivative. Nitroalkene chemistry⁵ has been exploited for various synthetic operations, particularly the potential usefulness of the conjugate addition of various organometallic reagents to the nitroalkenes as a means of forming carbon-carbon bonds, which may be followed by further

transformation of the derived nitroalkane products to various nitrogen heterocycles.⁶ Recent application of the nitroalkene chemistry has been extended to the asymmetric synthesis⁷ of various compounds as well as the solid phase synthesis.⁸ The strategy of our approach is illustrated for the synthesis of (±)-dimethylcherylline and cherylline as shown (Scheme 1).



Scheme 1

We have found that by control of the exothermic reaction, 1,4-addition of Grignard reagent to nitrostyrene occurs smoothly at below room temperature in satisfactory yield. The Grignard reagent was prepared by addition of a solution of 4-bromoanisole in dry tetrahydrofuran to a stirred suspension of magnesium turning in dry tetrahydrofuran while maintaining a gentle reflux under nitrogen atmosphere. A solution of 3,4-dimethoxynitrostyrene in dry tetrahydrofuran was then added dropwise to the Grignard reagent which was maintained at -15°C . The product (**3a**) was obtained in 69% yield after purification by column chromatography on silica gel. The nitro compound so obtained could be conveniently reduced by lithium aluminium hydride in ether at room temperature to give the amine (**4a**) in 75% yield. The amine was purified by preparative layer chromatography on silica gel and could be further purified by recrystallization of the derived oxalate salt. Treatment of the amine derivative with 37% formaldehyde

and formic acid at 100 °C for 3 h gave directly (±)-*O,O*-dimethylcherylline (**5a**) in 93% yield according to our previous finding that formaldehyde and formic acid promoted the cyclization and *N*-methylation of activated phenylethylamine in a "one pot" reaction.⁹

The successful preparation of (±)-*O,O*-dimethylcherylline prompted us to further investigate the generality of this method for the preparation of (±)-cherylline. Reaction of nitrostyrene (**2b**) with the Grignard reagent generated from 4-bromo-*O*-benzylphenol furnished nitro compound (**3b**) in 74% yield. Reduction of the addition product (**3b**) with LAH gave amine (**4b**) in 70% yield. The reaction of the amine with formaldehyde and formic acid gave the expected isoquinoline compound (**5b**) in 89% yield. The final step was accomplished by hydrogenolytic removal of the benzyl protecting groups of (±)-*O,O*-dibenzylcherylline in ethyl acetate-ethanol (1:1 by volume) containing 10 % palladium on charcoal at 1 atm. The reaction proceeded in 94 % yield to give (±)-cherylline (**1**). All the spectral data of the synthetic (±)-cherylline exhibited good correlation with those of (±)-cherylline reported in the literature.^{4d} All new compounds exhibit satisfactory analytical and spectroscopic data.¹⁰

In conclusion, we have developed an efficient synthesis of (±)-*O,O*-dimethylcherylline (**5a**) and (±)-cherylline (**1**) from readily available starting materials and the reactions involved are operationally simple which we view as a very attractive process. The key step employed in the synthesis, *i.e.*, the addition of Grignard reagents to the nitrostyrenes works well under the employed conditions. The application of this approach to the synthesis of other alkaloids is under further investigation.

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10. All compounds have been fully characterized : Compound (**3a**), oil, IR (neat) 1605, 1590, 1545, 1510, 1460, 1375, 1250, 1140, 1025 cm^{-1} . NMR (400 MHz, CDCl_3) δ 3.78 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 4.80 (br t, 2H), 4.915 (d, 1H, $J = 7.2$ Hz), 4.918 (d, 1H, $J = 9.4$ Hz), 6.70 (d, 1H, $J = 2.0$ Hz), 6.77 (dd, 1H, $J = 8.0, 2.0$ Hz), 6.82 (d, 1H, $J = 8.0$ Hz), 6.86, 7.15 (AA'BB', 2H each, $J = 8.7$ Hz). ^{13}C (100 MHz) δ 47.83, 55.22, 55.86, 79.61, 111.14, 111.34, 114.33, 119.27, 128.58, 131.35, 131.92, 148.35, 149.23, 158.86. MS 317(M^+ , 55.43), 271(22.44), 270(100), 257(53.92), 239(15.35). Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{NO}_5$: C, 64.34; H, 6.03; N, 4.41. Found : C, 64.21; H, 6.17; N, 4.29. Compound (**3b**), oil, IR (neat) 1600, 1580, 1545, 1510, 1500, 1450, 1375, 1235, 1140, 1020 cm^{-1} . NMR (400 MHz, CDCl_3) δ 3.83 (s, 3H), 4.78 (br t, 1H), 4.888 (d, 1H, $J = 7.5$ Hz), 4.890 (d, 1H, $J = 8.7$ Hz), 5.02 (s, 2H), 5.11 (s, 2H), 6.69 (dd, 1H, $J = 8.0, 2.0$ Hz), 6.72 (d, 1H, $J = 2.0$ Hz), 6.82 (d, 1H, $J = 8.0$ Hz), 6.92, 7.13 (AA'BB', 2H each, $J = 8.7$ Hz), 7.26-7.43 (m, 10H). ^{13}C (100 MHz) δ 47.86, 56.03, 70.02, 70.99, 79.57, 111.72, 114.02, 115.24, 119.30, 127.21, 127.45, 127.86, 128.02, 128.54, 128.59, 128.65, 131.58, 132.41, 136.76, 136.98, 147.57, 149.86, 158.10. MS 469(M^+ , 5.90), 422(2.20), 331(6.13), 92(8.67), 91(100). Anal. Calcd for $\text{C}_{29}\text{H}_{27}\text{NO}_5$: C, 74.18; H, 5.80; N, 2.98. Found : C, 74.01; H, 6.10; N, 2.65. Compound (**4a**), m.p. (oxalate salt, MeOH-ether) 108-109 $^{\circ}\text{C}$. IR (KBr) 2930(br), 1610, 1590, 1515, 1250, 1150, 1025 cm^{-1} . NMR (400 MHz, CDCl_3) δ 1.56 (br s, 2H), 3.27 (br s, 2H), 3.77 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (t, 2H, $J = 7.5$ Hz), 6.73 (d, 1H, $J = 1.6$ Hz), 6.79 (dd, 1H, $J = 8.0, 1.7$ Hz), 6.82 (d, 1H, $J = 8.3$ Hz), 6.85, 7.16 (AA'BB', 2H each, $J = 8.7$ Hz). ^{13}C (100 MHz) δ 7.16, 53.77, 55.19, 55.81, 55.84, 111.24, 111.53, 113.97, 119.67, 128.84, 135.01, 135.59, 147.59, 148.99, 158.14. MS 287(M^+ , 4.49), 258(26.96), 257(100). Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_7 \cdot 1/2 \text{H}_2\text{O}$: C, 59.06; H, 6.26; N, 3.62. Found : C, 59.40; H, 6.18; N, 3.61. Compound (**4b**), m.p. (oxalate salt, MeOH-ether) 114-116 $^{\circ}\text{C}$. IR (KBr) 3050-2950(br), 1605, 1580, 1505, 1250, 1225, 1140, 1020 cm^{-1} . NMR (400 MHz, CDCl_3) δ 1.4 (br s, 2H), 3.23 (d, 2H, $J = 7.7$ Hz), 3.86 (t, 1H, $J = 7.6$ Hz), 3.84 (s, 3H), 5.03 (s, 2H), 5.12 (s, 2H), 6.72 (dd, 1H, $J = 8.0, 2.0$ Hz), 6.75 (d, 1H, $J = 2.0$ Hz), 6.82 (d, 1H, $J = 8.0$ Hz), 6.92, 7.15 (AA'BB', 2H each, $J = 8.7$ Hz), 7.26-7.44 (m, 10H). ^{13}C (100 MHz) δ 7.26, 53.85, 55.99, 69.99, 71.16, 112.13, 114.03, 114.89, 119.72, 127.21, 127.44, 127.74, 127.91, 128.48, 128.54, 128.90, 135.29, 136.17, 137.28, 146.81, 149.63, 157.39. MS 439(M^+ , 1.47), 410(15.02), 409(38.12), 92(8.33), 91(100), 44(11.28). Anal. Calcd for $\text{C}_{31}\text{H}_{31}\text{NO}_7 \cdot 1/2 \text{H}_2\text{O}$: C, 69.13; H, 5.99; N, 2.60. Found : C, 68.73; H, 5.90; N, 2.82. Compound (**5a**), m.p. (ether-hexane) 97-99 $^{\circ}\text{C}$ (lit.,^{4d} 97-99 $^{\circ}\text{C}$). IR (CHCl_3) 1610, 1580, 1515, 1460, 1250, 1140, 1035 cm^{-1} . NMR (400 MHz, CDCl_3) δ 2.41 (s, 3H), 2.48 (dd, 1H, $J = 8.0, 11.4$ Hz), 2.97 (ddd, 1H, $J = 11.6, 5.5, 1.0$ Hz), 3.54 (d, 1H, $J = 14.3$ Hz), 3.66 (d, 1H, $J = 14.3$ Hz), 3.64 (s, 3H), 3.79 (s, 3H), 3.85 (s, 3H), 4.16 (br t, 1H),

6.35 (s, 1H), 6.56 (s, 1H), 6.83, 7.10 (AA'BB', 2H each, $J = 8.7$ Hz). ^{13}C (100 MHz) δ 44.64, 45.86, 55.14, 55.78, 58.07, 62.10, 108.70, 111.89, 113.65, 127.27, 129.15, 129.81, 136.82, 147.40, 147.49, 158.11. MS 313(M^+ , 35.43), 270(52.86), 269(20.66), 240(19.76), 239(100), 135(11.42). Compound (**5b**), m.p. (ethyl acetate) 141-142 °C(lit.,^{4c,4g} 144-145 °C). IR (CHCl_3) 1610, 1580, 1505, 1255, 1240, 1140 cm^{-1} . NMR (400 MHz, CDCl_3) δ 2.38 (s, 3H), 2.47 (dd, 1H, $J = 11.0, 8.0$ Hz), 2.96 (dd, 1H, $J = 11.0, 5.0$ Hz), 3.48 (d, 1H, $J = 14.5$ Hz), 3.59 (d, 1H, $J = 14.5$ Hz), 3.65 (s, 3H), 4.15 (dd, 1H, $J = 8, 6$ Hz), 5.04 (s, 2H), 5.11 (s, 2H), 6.37 (s, 1H), 6.58 (s, 1H), 6.91, 7.10 (AA'BB', $J = 8.7$ Hz), 7.27-7.46 (m, 10H). ^{13}C (100 MHz) δ 44.69, 45.84, 55.99, 57.99, 62.04, 70.01, 71.06, 111.58, 112.59, 114.64, 127.27, 127.50, 127.74, 127.91, 128.48, 128.53, 129.82, 129.90, 137.12, 137.25, 146.66, 148.23, 157.42. MS 465(M^+ , 7.28), 422(10.06), 331(15.52), 91(100).