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Tetrahedron Letters 45 (2004) 7487–7489
Tetrahedron Letters

Quinone methide initiated cyclization reaction: synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines

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Received 24 May 2004; revised 30 July 2004; accepted 6 August 2004
Available online 26 August 2004

Abstract—4-Aryl-1,2,3,4-tetrahydroisoquinolines were synthesized in very good yields by in situ generation of *p*-quinone methides resulting in a novel C–C bond formation.

Tetrahydroisoquinolines are an important class of natural and synthetic compounds, which exhibit a vast range of biological activities[1] such as antitumor,[2] antibacterial,[3] antiplasmodial,[4] and β-adrenergic receptor antagonism.[5] Tetrahydroisoquinolines arylated at C-4 display prominent pharmaceutical activities.[6] Cherylline is a naturally occurring optically active, 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloid, isolated from an Amaryllidaceae plant[7] and several synthesis have been reported.[8]

Quinone methides are interesting compounds and play an important role in biosynthesis and in the biological activity of many quinonoid antitumor compounds.[9] However, synthetic methodologies to produce such quinone methides and their applications are limited because in situ generated *o*-quinone methides acting as heterodienes in Diels–Alder reactions.[10] *p*-Quinone methides are involved as transition intermediates in a synthesis of picropodophylline.[11]

We have reported the stereospecific synthesis of dihydroindenyl and tetrahydronaphthalene[12] derivatives by novel C–C bond formation via in situ generated of *p*-quinone methides. Herein, we report[13] the synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines and derivatives of the cherylline alkaloid series, via in situ generated of *p*-quinone methides. 2,6-Disubstitution imparts increased stability to a quinone methide,[14] so a subsequent cyclization would require an internal nucleophile (cyclization terminator) that is stable under the conditions used to generate the quinone methide yet reactive enough to attack the carbon terminus. *N*-(3,5-Dimethyl-4-hydroxyphenethyl)-*N*-tosyl-3,4-dimethoxybenzyl-amine **7a** is required to generate the quinone methide and allow a subsequent cyclization to give the tetrahydroisoquinoline (Scheme 2). Accordingly 4-benzyloxy-3,5-dimethylphenylacetic acid[13a,15] **1** was esterified giving **2**. The ester **2** on reduction with LAH gave alcohol **3** and bromination[16] with CBr_4/PPh_3 gave 4-benzyloxy-3,5-dimethylphenethyl bromide **4** (Scheme 1).

The substituted *N*-tosylated benzylamine **5a** was treated with NaH[17] followed by the addition of phenethyl bromide **4** and gave *N*-(4-benzyloxy-3,5-dimethylphenethyl)-*N*-tosyl-3,4-dimethoxybenzylamine **6a** (Scheme 2). Compound **6a** on debenzylation with palladium charcoal under hydrogen in ethyl acetate gave *N*-(3,5-dimethyl-4-hydroxyphenethyl)-*N*-tosyl-3,4-dimethoxybenzylamine **7a**, which, on oxidation[14] with Ag_2O in dry DCM at room temperature gave quinone methide **8a** as a yellow viscous liquid. The quinone methide was isolated and characterized by its ^1H NMR spectrum, which clearly indicated the formation of quinone methide **8a** by the appearance of methine proton as a triplet at δ 5.78 ($J = 7.8$ Hz) and the disappearance of the singlet at δ 4.40 of the phenolic proton and the triplet at δ 2.42 ($J = 5.6$ Hz) of **7a**. Due to restricted rotation, the two methyl groups resonated as two separate singlets at δ 1.86 and 1.90 in **8a** where as they appeared as a singlet at δ 2.08 in **7a**. The yellow viscous **8a** was dissolved

Keywords: 4-Aryl-1,2,3,4-tetrahydroisoquinolines; *p*-Quinone methides; C–C bond formation; Cherylline analogues.
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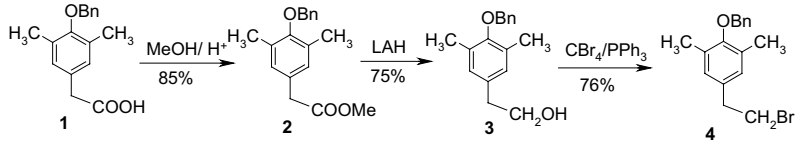
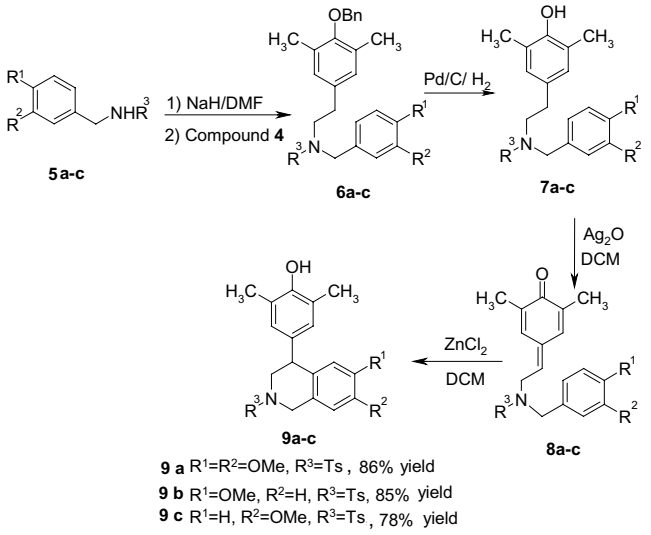
doi:10.1016/j.tetlet.2004.08.053



Scheme 1.



Scheme 2.

in dry DCM and $ZnCl_2$ was added with stirring at room temperature affording 4-(3,5-dimethyl-4-hydroxyphenyl)-*N*-tosyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **9a** as a thick viscous liquid in 86% yield (Scheme 2).[18] The cyclization was indicated by the appearance of a methine proton (C-4) as a triplet at δ 4.10 ($J = 6.2$ Hz) in the ^{1}H NMR spectrum. Similarly, the compounds 4-(3,5-dimethyl-4-hydroxyphenyl)-*N*-tosyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline **9b** and 4-(3,5-dimethyl-4-hydroxyphenyl)-*N*-tosyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline **9c** were also prepared and all the new products were characterized by ^{1}H NMR, IR, MS, and CHN analysis. The results confirm the novel C–C bond formation in this synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines, in very good yields, with simple and mild procedures. We are currently exploring the application of this methodology to the synthesis of natural products.

In conclusion, we have demonstrated a new and convenient synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines via a novel C–C bond formation by in situ generation of *p*-quinone methides in very good yields.

Acknowledgements

One of the authors B.C.R. thanks the Director, IICT and Dr. V. Jayathirtha Rao for their constant encouragement.

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18. *Typical experimental procedure*. *4-(3,5-Dimethyl-4-hydroxyphenyl)-N-tosyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* **9a**: to a solution of *N*-(3,5-dimethyl-4-hydroxyphenethyl)-*N*-tosyl-3,4-dimethoxybenzylamine **7a** (0.15 g, 0.3 mmol) in dry DCM (6 mL), Ag_2O (0.37 g, 1.6 mmol) was added and the mixture stirred at room temperature for 6 h. The contents were filtered using Celite as filter aid and the solvent was removed under reduced pressure below 40 °C to give the quinone methide **8a** as a yellow viscous liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.86 (s, 3H, CH_3), 1.90 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.02 (d, 2H, CH_2, J = 6.2 Hz), 4.18 (s, 2H, CH_2), 5.78 (t, 1H, methine, J = 7.8 Hz), 6.58 (s, 2H, dienone), 6.62–6.8 (m, 2H, aromatic), 6.75 (s, 1H, aromatic), 7.29 (d, 2H, aromatic, J = 7.6 Hz), 7.69 (d, 2H, aromatic, J = 7.6 Hz).
To the quinone methide **8a** in dry DCM (5 mL), $ZnCl_2$ (0.22 g, 1.6 mmol) was added and the mixture stirred for 30 min at room temperature. The organic layer was washed with water, dried over sodium sulfate, the solvent removed under reduced pressure and the residue purified by column chromatography using silica gel giving 4-(3,5-dimethyl-4-hydroxyphenyl)-*N*-tosyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **9a** (0.12 g, 86%) as a thick viscous liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.20 (s, 6H, $2CH_3$), 2.42 (s, 3H, CH_3), 2.84, 2.92 (dd, 1H, C3–H, J = 7.2 and 11.2 Hz), 3.66 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.72, 3.78 (dd, 1H, C3–H, J = 6.4 and 11.2 Hz), 4.02 (d, 1H, C1–H, J = 5.8 Hz), 4.10 (t, 1H, C–4H, J = 6.2 Hz), 4.42 (d, 1H, C–1H, J = 5.8 Hz), 4.61 (s, 1H, OH, D_2O exchangeable), 6.35 (s, 1H, aromatic), 6.56 (s, 1H, aromatic), 6.68 (s, 1H, aromatic), 7.29 (d, 2H, aromatic, J = 7.4 Hz), 7.64 (d, 2H, aromatic, J = 7.4 Hz). IR (KBr): 3475, 2940, 1590, 1510, 1265, 1220, 1150 and 1125 cm^{-1}. Mass (EI): *m/e* 467 (M^+), 311, 309, 284, 269, 253, 190, 166, 135, 92, 83, 43. Anal. Calcd for $C_{26}H_{29}NSO_5$: C, 66.80; H; 6.20; N, 2.99. Found: C, 66.82; H; 6.24; N, 2.96.