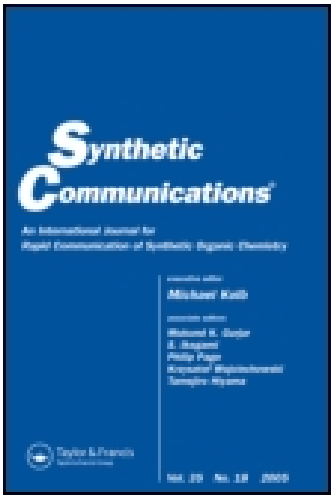

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Novel Route to 2-Arylapomorphines

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Published online: 06 Feb 2007.

To cite this article: Sándor Berényi , Attila Sipos , Ildikó Szabó & Tamás Kálai (2007) Novel Route to 2-Arylapomorphines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:3, 467-471, DOI: 10.1080/00397910601039200

To link to this article: http://dx.doi.org/10.1080/00397910601039200

Synthetic Communications®, 37: 467–471, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910601039200

Novel Route to 2-Arylapomorphines

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Abstract: The synthesis of 2-arylapomorphines (**1**, **2**) has been accomplished using a new method involving a Suzuki-type cross-coupling reaction of 2-bromoapocodeine (**8**) and arylboronic acids.

Keywords: Suzuki-type cross-coupling reaction, synthesis of 2-arylapomorphines

Apomorphine derivatives modified in the 2-position are known to be effective on dopamine receptors.[1,2] The synthesis of some 2-arylapomorphines (**1**, **2**) has been recently reported. These compounds, especially 2-(4-hydroxyphenyl)-apomorphine (**2**), exhibited high affinity for the dopamine D_2 receptor.[3]

The synthesis of compounds **1** and **2** was performed by Suzuki–Miyaura–type reaction of the corresponding triflate-substituted aporphine derivative originating from natural codeine.[3]

In this communication, we describe a new synthesis of 2-arylapomorphines (**1**, **2**) with a Suzuki-type cross-coupling reaction by treatment of 2-bromoapocodeine (**8**) with the appropriate arylboronic acids. The synthesis of 2-bromoapocodeine (**8**) from natural thebaine (**3**) was performed via 14β-chlorocodeinone (**4**),[4] 14β-chlorocodeine (**5**), 6-*O*-tosyl-14β-chlorocodeine

Received in the U.K. April 4, 2006
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(**6**), and 6-bromo-6-demetoxythebaine (**7**) by our previously published procedures[5,6] (Scheme 1).

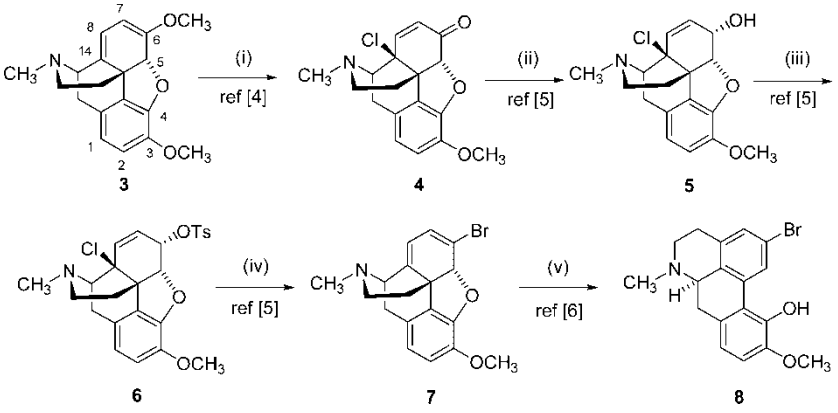
The cross-coupling of 2-bromoapomorphine (**8**) with appropriate arylboronic acids was carried out in the presence of tetrakis (triphenylphosphine) palladium(0) catalyst and $Ba(OH)_2 \cdot 8H_2O$ base in a solvent mixture of 1,4-dioxane–H_2O (4:1). Isolated yields for 2-phenylapocodeine and 2-(4-hydroxyphenyl)-apocodeine were found to be 81% and 79%, respectively.

2-Arylapocodeines (**9**, **10**) were O-demethylated with a reagent mixture of methanesulfonic acid and methionine to prepare the desired 2-phenylapomorphine (**1**) and 2-(4-hydroxyphenyl)-apomorphine (**2**) (Scheme 2) with a yield of 92% and 87%, respectively.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on precoated Merck 5554 Kieselgel 60 F_{254} foils using chloroform—methanol (9 : 1) mobile phase. The spots were visualized with Dragendorff's reagent. ^{1}H NMR spectra were recorded on a Bruker WP 200 SY spectrometer, chemical shifts are reported in parts per million (δ) from internal TMS, and coupling constans (J) are measured in Hertz.

Mass spectral measurements were performed with an Automass Multi (ThermoQuest) instrument in the EI mode (direct inlet). The source temperature was 140 °C; ionization was 70 eV. Optical rotation was determined with a Perkin-Elmer model 241 polarimeter. Elemental analyses (C, H, N, S) were obtained on a Carlo Erba 1106 analyzer.



Scheme 1. (i) *N*-Cl-succinimide, acetone–water 2:1, 0°C; (ii) $NaBH_4$, MeOH, 0°C; (iii) TsCl, abs. pyridine, 0°C; (iv) LiBr, DMF, 100°C; and (v) CH_3SO_2OH, 90°C.

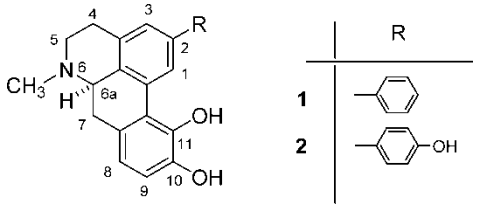


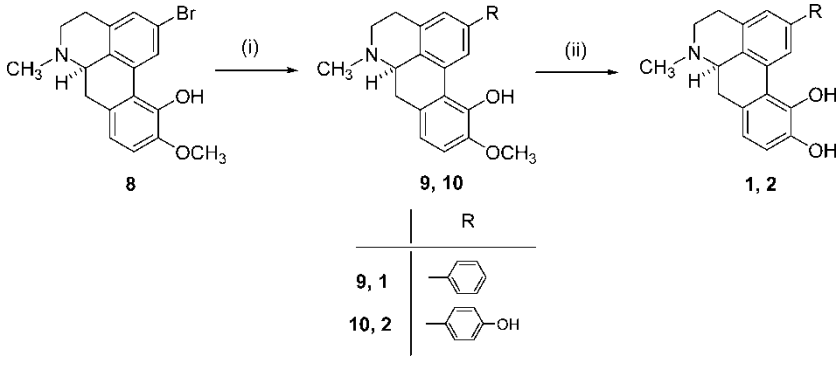
Figure 1.

Cross-Coupling of 2-Bromoapocodeine (8) with Arylboronic Acids (General Procedure)

A mixture of 2-bromoapocodeine (1130 mg, 3.137 mmol), arylboronic acid (3.137 mmol), $Pd(PPh_3)_4$ (184 mg, 0.159 mmol), and $Ba(OH)_2 \cdot 8H_2O$ (990 mg, 3.137 mmol) was boiled in 1,4-dioxane–H_2O (4:1) under reflux for 30 min. After evaporation at reduced pressure, the residue was dissolved in chloroform (20 ml) and filtered. The filtrate was evaporated, and the residue was purified by flash chromatography (silica, chloroform–methanol 1:1) to yield compounds **9** or **10**.

2-Phenylapocodeine (9)

White crystalline solid; mp 85–88°C; yield: 910 mg (81.2%); anal. calc. for $C_{24}H_{23}NO_2$ (%): C, 78.88; H, 6.34; N, 3.84; O, 10.94; found (%): C, 78.62; H, 6.30; N, 3.99; O, 11.09; $[\alpha]_D^{25}$ −145.7 (c 0.5, chloroform); MS m/z (%) 357 (M^+, 8), 356 (10), 312 (22), 277 (35), 154 (100); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 8.55$ [d, 1H, H1, $J(1,3) = 4.8$], 7.81–7.51 (m, 2H, 2-Ar),



Scheme 2. (i) Arylboronic acid, $Pd(PPh_3)_4$, $Ba(OH)_2 \cdot 8H_2O$, 1,4-dioxane–H_2O 4:1, 100°C, 30 min; (ii) CH_3SO_2OH, methionine, 90°C, 4 h.

7.50–7.19 (m, 4H, 2-Ar, H3), 6.80 (dd, 2H, H8-9), 6.32 (s, 1H, OH), 4.02 (s, 1H, $H6_a$), 3.91 (s, 3H, OCH_3), 3.45–3.08 (m, 4H, $H4_a$, $H5_a$, $H5_b$, $H7_a$), 2.90–2.52 (m, 5H, $H4_b$, $H7_b$, NCH_3).

2-(4-Hydroxyphenyl)-apocodeine (10)

White crystalline solid; mp 130–131°C; yield: 922 mg (78.7%); anal. calc. for $C_{24}H_{23}NO_3$ (%): C, 77.19; H, 6.21; N, 3.75; O, 12.85; found (%): C, 77.51; H, 6.22; N, 3.61; O, 12.66; $[\alpha]_D^{25}$ −101.4 (*c* 0.75, chloroform); MS m/z (%) 373 (M^+, 68), 372 (100), 312 (27), 304 (31), 280 (75); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 8.50$ [d, 1H, H1, $J(1,3) = 3.9$], 7.75 (s, 1H, OH), 7.51 (d, 2H, 2-Ar, $J_{ortho} = 9.8$), 7.23 (s, 1H, H3), 6.87–6.69 (m, 4H, H8-9, 2-Ar), 6.25 (s, 1H, OH), 4.15 (s, 1H, $H6_a$), 3.95 (s, 3H, OCH_3), 3.72 (s, 1H, $H5_a$), 3.40–3.05 (m, 4H, $H4_a$, $H5_b$, $H7_a$, $H7_b$), 2.82–2.52 (m, 4H, $H4_b$, NCH_3).

O-Demethylation of 2-Arylapocodeins (9 and 10) to Yield Corresponding 2-Arylapomorphines (1 and 2) (General Procedure)

A mixture of 2-arylapocodeine (1000 mg), methionine (1000 mg, 6.702 mmol), and CH_3SO_2OH (4 ml) was boiled at 90°C for 4 h. After cooling, the pH of the mixture was set to 10 by concentrated NH_3 solution and extracted with chloroform (3 × 15 ml). The organic layers were collected, washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, and evaporated. The residue was subjected to silica-gel column chromatography. Elution with chloroform–methanol (1:1) gave **1** and **2**.

2-Phenylapomorphine Hydrochloride (1)

Yield: 818 mg (92.2%); mp >230°C (HCl salt); spectral data were in agreement with previously published results.[3]

2-(4-Hydroxyphenyl)-apomorphine Hydrochloride (2)

Yield: 762 mg (87.2%); mp >230°C (HCl salt); spectral data were in agreement with previously published results.[3]

ACKNOWLEDGMENT

The authors thank the National Science Foundation for financial support of this work (Grant OTKA Reg. No. T049436).

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