Pergamon

Tetrahedron Letters 42 (2001) 1359–1361

TETRAHEDRON LETTERS

An efficient synthesis of argemonine, a pavine alkaloid†

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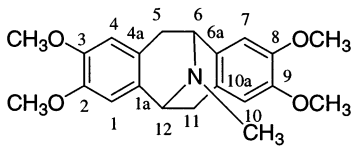
Received 30 November 2000; accepted 5 December 2000

Abstract—A method for the synthesis of 1,2-dihydroisoquinoline derivatives is described and the conversion of the 1,2-dihydroisoquinoline intermediate to a pavine alkaloid via palladium-induced intramolecular hydroarylation reaction and radical cyclization is presented.

Argemonine is a prototypical member of the pavine alkaloids, a small group of tetracyclic natural products, and contains the tetrahydroisoquinoline core embedded in its skeleton.[1] Recent findings of biological activities of the pavine alkaloids include inhibition of *herpes simplex* virus type 1[2] and inhibitory activity against tumor necrosis factor-α (TNF-α) production.[3]



Argemonine

There are a number of syntheses[1,4] of pavine alkaloids reported, but most involve an acid-catalyzed intramolecular cyclization of the activated aromatic ring with an iminium salt as in the Pictet–Spengler reaction. The drawback of such a procedure is the failure with nonactivated aromatic compounds and the lack of chemoselectivity in the cyclization of unsymmetrical compounds.

We have developed a new synthesis of pavine alkaloids based on the retrosynthetic analysis shown in Scheme 1. The key steps involve a palladium-induced intramolecular hydroarylation[5] and a radical cyclization[6] of the key halo derivatives of 1-benzyl-*N*-carboethoxy-1,2-dihydroisoquinolines. The intramolecular hydroarylation involves the reduction of the organopalladium complex formed during the carbon–carbon bond formation in the much exploited Heck reaction.[7] We have also developed a new method for the synthesis of the key 1,2-dihydroisoquinoline derivatives. During our investigation a method for the synthesis[8] of this type of compound was reported involving the addition of a benzylstannane to an isoquinoline in the presence of methyl chloroformate in dichloromethane. We found that 1-benzyl-*N*-carboethoxy-1,2-dihydroisoquinolines could be conveniently obtained by the reaction of 1-benzylisoquinoline derivatives with tributyltin hydride. For example, treatment of papaverine **4a** with tributyltin hydride in dichloromethane at room temperature under a nitrogen atmosphere, followed by addition of ethyl chloroformate at −78°C and warming to room temperature gave a white solid which, after recrystallization from methanol–dichloromethane, provided compound **3a** in 79% yield. Having found a method for the synthesis of 1-benzyl-*N*-carboethoxy-1,2-dihydroisoquinolines, we then began the synthesis of our key intermediate. The synthesis started with bromination of commercially available papaverine **4a** with a solution of bromine in acetic acid at room temperature for 2 h to give 2′-bromopapaverine[9] **4b** in 75% yield.

Application of the tin hydride reduction gave the required product which was recrystallized from methanol–dichloromethane to give compound **3b** as a white solid in 85% yield. It is interesting to note the

Keywords: pavine alkaloid; intramolecular hydroarylation reaction; radical cyclization reaction.

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† This work has been taken in part from Namsa-aid, A., M.Sc. Thesis, Mahidol University 1997, and was presented at the 8th Belgian Organic Synthesis Symposium, July 10–14, 2000, Gent, Belgium.

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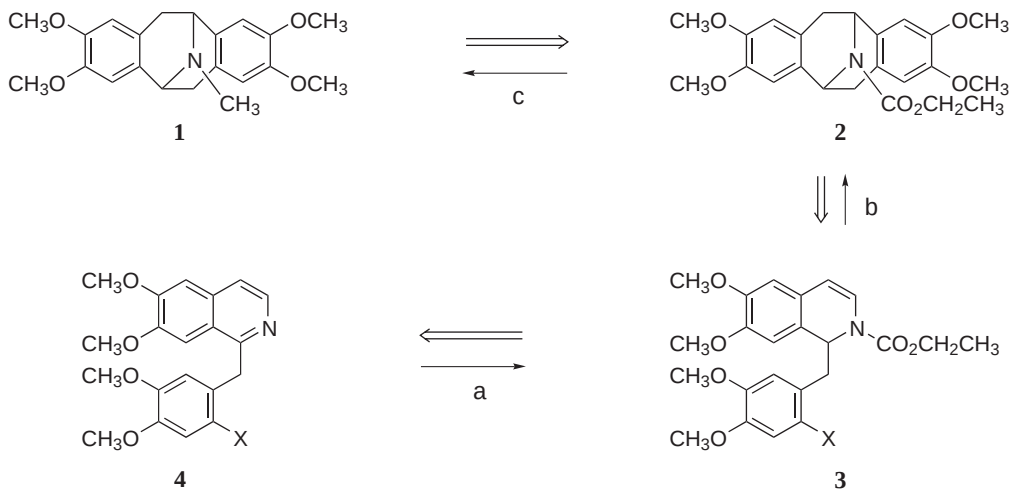
PII: S0040-4039(00)02233-4



a) X = H, b) X = Br, c) X = I

Scheme 1. *Reagents and conditions*: (a) i. Bu_3SnH/CH_2Cl_2, ii. $EtOCOCl/CH_2Cl_2$, −78°C→rt (**3a**, 79%; **3b**, 85%; **3c**, 85%); (b) See Table 1; (c) LAH/THF, reflux 4 h (**1**, 87%).

chemoselective reduction of the iminium intermediate with tributyltin hydride in the presence of the aryl bromide group. Once the key compound **3b** was obtained, we applied the intramolecular hydroarylation cyclization to effect pavine ring formation. The cyclization of **3b** was accomplished using 10–20 mol% of a reactive catalyst formed from $Pd(PPh)_4$ in DMF at 80–90°C in the presence of sodium formate as a reducing agent. After purification by PLC, *N*-ethoxycarbonylpavine **2**[10] was obtained in 44% yield together with the corresponding reduction product **3a** in 34% yield as shown in entry 1 of Table 1. The yield of the *N*-ethoxycarbonylpavine **2** was increased to 56% when the starting iodo compound **3c** was used instead of the bromo compound **3b** under similar conditions (entry 3, Table 1). The 2′-iodopapaverine **4c** could be conveniently obtained by the reaction of papaverine with iodine and silver trifluoroacetate.[11] The appearance of four aromatic protons as singlets in the NMR spectrum indicated that 2′-iodopapaverine was obtained.

In addition, the radical cyclization using tributyltin hydride and AIBN of compounds **3b** and **3c** was investigated. It was found that the yield of *N*-ethoxycarbonylpavine **2** was only 30% from the cyclization of the bromo compound **3b** under the tributyltin hydride/AIBN conditions. The corresponding reduction product **3a** was obtained from the reaction in 5% yield. Similarly, the iodo compound **3b** underwent cyclization with tributyltin hydride to afford the pavine **2** in 42% yield together with 10% of the reduction product **6**. The *N*-ethoxycarbonylpavine **2** was reduced by LAH to form the *N*-methylpavine in 87% yield. The physical and spectroscopic data of our synthetic compound are in full agreement with those of argemonine **1**.[4b]

In conclusion, we have devised a new method for the synthesis of pavine alkaloids as illustrated in the synthesis of natural (±)-argemonine. With appropriate introduction of the iodo group, the approach could be used to synthesize both symmetrical and unsymmetrical pavine alkaloids. We found that the palladium-catalyzed reductive intramolecular arylation reaction is very useful and gives better yields than radical cyclization.

Acknowledgements

We are grateful to the Thailand Research Fund (TRF) for the generous financial support. We acknowledge the facilities in the Department of Chemistry provided by the PERCH programme.

Table 1. Intramolecular arylation of 3,4-dihydroisoquinoline derivatives **3a** and **3b** to pavine (**2**)

Entry	Starting material	Conditions	Yield%	Yield%
			Comp. **2**	Comp. **3a**
1	Compound **3b**	$Pd(PPh_3)_4/DMF/HCO_2Na$/reflux 24 h	44	34
2	Compound **3b**	Bu_3SnH/AIBN, benzene, reflux 10 h	30	5
3	Compound **3c**	$Pd(PPh_3)_4/DMF/HCO_2Na$/reflux 24 h	56	15
4	Compound **3c**	Bu_3SnH/AIBN, benzene reflux 10 h	42	10

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All compounds have been fully characterized. Spectroscopic data of some selected compounds, 1-(2-iodo-4,5-dimethoxybenzyl)-2-ethoxycarbonyl-6,7-dimethoxy-1,2-dihydroisoquinoline **3c**: mp 154–156°C; FT-IR (Nujol) 2926, 1708, 1633, 1227 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, 3H, $J=7.1$ Hz), 1.25 (t, 3H, $J=7.1$ Hz), 2.82–3.06 (m, 4H), 3.66 (s, 3H), 3.72 (s, 3H), 3.73 (s, 3H), 3.77 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 4.02 (m, 2H), 4.17 (q, 2H, $J=7.1$ Hz), 5.45 (dd, 1H, $J=8.4$, 5.6 Hz), 5.55 (t, 1H, $J=7.1$ Hz), 5.79, 6.79 (AB q, 2H, $Jab=7.1$ Hz), 5.94, 6.96 (AB q, 2H, $Jab=7.1$ Hz), 6.23 (s, 1H), 6.34 (s, 1H), 6.40 (s, 1H), 6.48 (s, 1H), 6.60 (s, 1H), 6.64 (s, 1H), 7.17 (s, 1H), 7.23 (s, 1H). ^{13}C NMR (100 MHz) δ 14.28, 14.53, 43.78, 44.23, 55.20, 55.71, 55.82, 55.92, 55.97, 56.05, 56.24, 61.99, 62.19, 88.89, 89.60, 107.90, 108.03, 108.39, 108.95, 109.85, 110.23, 113.42, 113.69, 121.24, 121.34, 122.70, 123.15, 123.53, 123.56, 123.75, 124.30, 132.51, 132.61, 147.70, 147.78, 148.07, 148.52, 148.75, 148.96, 152.81, 153.54. FABMS 540 (M^++1, 2.24), 413 (8.16), 262 (100.00). Anal. calcd for $C_{23}H_{26}NO_6I$: C, 51.19; H, 4.86; N, 2.63; Found: C, 50.99: H, 4.82; N, 2.41. *N*-Ethoxycarbonylpavine **2**: mp 190–192°C (lit.[10] mp 183–184°C); FT-IR (KBr) 1686, 1519, 1463, 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, 3H, $J=7.1$ Hz), 2.76 (d, 2H, $J=15.9$ Hz), 3.38 (dd, 1H, $J=15.9$, 5.6 Hz), 3.42 (dd, 1H, $J=15.9$, 5.6 Hz), 3.77 (s, 3H), 3.78 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 4.11–4.25 (m, 2H), 5.42 (d, 1H, $J=5.6$ Hz), 5.52 (d, 1H, $J=5.6$ Hz), 6.45 (s, 1H), 6.48 (s, 1H), 6.66 (s, 1H), 6.67 (s, 1H). ^{13}C NMR (100 MHz) δ 14.65, 35.78, 36.04, 48.97, 49.70, 55.64, 55.89, 61.38, 108.97, 109.20, 111.47, 111.65, 123.95, 124.48, 128.78, 129.08, 147.45, 147.96, 148.05, 154.21. EI-MS 413 (M^+, 17.50), 412 (4.89), 340 (8.25), 278 (6.84), 262 (52.36), 28 (100.00). Anal. calcd for $C_{26}H_{22}N_2O_3$: C, 66.40; H, 6.59; N, 3.48. Found: C, 66.24; H, 6.46; N, 3.73.