Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 45 (2004) 4171–4173

A new convenient synthesis of phenanthrene alkaloids from 1-arylmethyl-1,2,3,4-tetrahydroisoquinolines

S. V. Kini and M. M. V. Ramana*

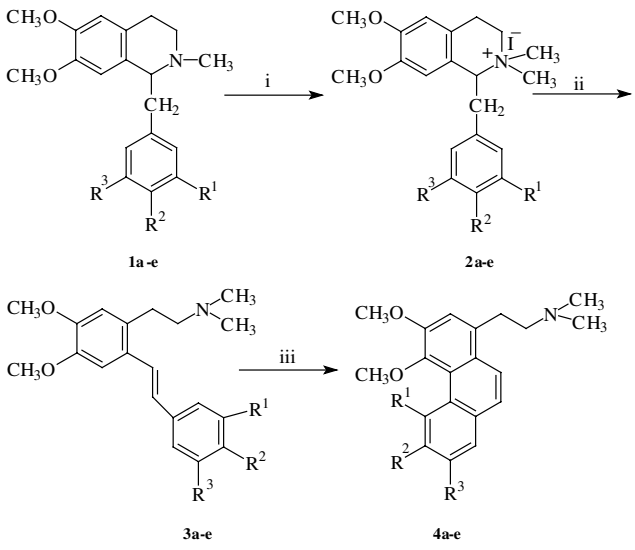
Department of Chemistry, University of Mumbai, Vidyanagari, Kalina, Santacruz (E), Mumbai 400098, India

Received 8 December 2003; revised 14 March 2004; accepted 22 March 2004

Abstract—Hofmann degradation of 1-arylmethyl-1,2,3,4-tetrahydro-2,2-dimethylisoquinolinium iodides with methanolic KOH gave stilbene derivatives, for example, (*E*)-*N*-2{2-[2-(phenyl)ethenyl]-4,5-dimethoxyphenyl}ethyl-*N*,*N*-dimethylamine. Photochemical electrocyclization of these stilbenes afforded the corresponding phenanthrene alkaloids/phenanthrene derivatives.

Phenanthrene alkaloids are derivatives of phenanthrene with a 1-(2-aminoethyl) side chain.[1] Phenanthrene alkaloids exhibit antimicrobial activity,[2] cytotoxicity,[3] dopamine receptor stimulation effects,[4] etc. The majority of these alkaloids have been obtained by degradation of aporphines,[1] which are not easily synthesized. 1-Arylmethyl-1,2,3,4-tetrahydroisoquinolines are important precursors in the biogenesis of aporphine alkaloids[5] that have not, so far, been utilized for the synthesis of phenanthrene alkaloids.

Here we wish to report a new synthesis of the title compounds via 1-arylmethyl-1,2,3,4-tetrahydroisoquinoline derivatives. Compounds **1a**–**e** were converted to the corresponding 1-arylmethyl-1,2,3,4-tetrahydro-2,2-dimethylisoquinolinium iodides[6] **2a**–**e** by refluxing with CH_3I and acetone for 8 h. These quaternary ammonium salts on refluxing with methanolic KOH underwent Hofmann elimination[6] and gave stilbenes **3a**–**e**. Photochemical electrocyclization[7] of these in cyclohexane afforded phenanthrene alkaloids **4a**,**b**,**d** and phenanthrenes **4c** and **4e** (Scheme 1 and Table 1). The starting 1-arylmethyl-1,2,3,4-tetrahydro-2-methylisoquinolines, **1a**–**e** were obtained from the Bischler–Napieralski reactions[8–12] of *N*-(3,4-dimethoxyphenethyl)phenylacetamides followed by $NaBH_4$ reduction of their corresponding dihydro*N*-methylisoquinolinium iodides.[13–15]



Scheme 1. Reagents and conditions: (i) CH_3I, acetone, reflux, 8 h. (ii) 20% methanolic KOH, reflux, 4 h. (iii) *hv*, I_2, O_2, cyclohexane, 5–6 h, 20 °C.

In conclusion, the present method involves the synthesis of phenanthrene alkaloids/phenanthrenes[16,17] in good yields utilizing easily accessible 1-arylmethyl-1,2,3,4-tetrahydroisoquinolines.

Keywords: Hofmann elimination; Stilbenes; Phenanthrene alkaloids; Phenanthrenes; Photochemical electrocyclization.
* Corresponding author. Tel.: +91-2512-496332; fax: 91-2226-145722; e-mail: mmvramana@indiatimes.com

0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.03.127

Table 1

Compound	R^1	R^2	R^3	R^2R^3	Mp[a] (°C)	Yield[b] (%)
2a	H	H	H		222	93
2b	H	OCH_3	OCH_3		217	94
2c	H	OCH_3	H		122	92
2d	H			$-OCH_2O-$	120	93
2e	OCH_3	OCH_3	OCH_3		129	97
3a	H	H	H		112	90
3b	H	OCH_3	OCH_3		94	92
3c	H	OCH_3	H		85	89
3d	H			$-OCH_2O-$	118	95
3e	OCH_3	OCH_3	OCH_3		134	88
4a	H	H	H		199	33
4b	H	OCH_3	OCH_3		118	36
4c	H	OCH_3	H		78	34
4d	H			$-OCH_2O-$	126	36
4e	OCH_3	OCH_3	OCH_3		156	31

[a] Melting points are uncorrected.
[b] Yields refer to purified product.

References and notes

1. Castedo, L.; Tojo, G. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1990; Vol. 39, pp 99–138.
2. Wu, W. N.; Beal, J. L.; Doskotch, R. W. *J. Nat. Prod.* **1980**, *43*, 143–148.
3. Gupta, R. S.; Skrepinsky, J. L.; Shiminovitch, L. *J. Mol. Pharmacol.* **1980**, *18*, 136–138.
4. Bhattacharya, S. K.; Bose, R.; Ghosh, P.; Tripati, V. J.; Ray, A. B.; Dasgupta, B. *PsychoPharmacol. (Berlin)* **1978**, *59*, 29–41.
5. Blaschke, G. *Arch. Pharm.* **1968**, *301*, 432–435.
6. Mndzhoyan, A. L.; Mnatsakanyan, V. A.; Arutyunyan, L. S. *Arm. Khim. Zh.* **1969**, *22*, 842–847; *Chem. Abstr.* **1970**, *72*, 21808w.
7. Estevez, J. C.; Vellavarde, M. C.; Estevez, R. J.; Seuas, J. A.; Castedo, L. *Can. J. Chem.* **1990**, *68*, 964–968.
8. Robinson, R. A. *J. Org. Chem.* **1951**, *16*, 1911–1920.
9. Tsatsas, G. *Ann. Pharma Frang.* **1952**, *10*, 61–71; *Chem. Abstr.* **1952**, *46*, 11209b.
10. Kundo, H.; Kundo, T. *J. Pharm. Soc. Jpn.* **1928**, *48*, 324–337; *Chem. Abstr.* **1928**, *22*, 3414.
11. Dyke, S. F.; Sainsbury, M. *Tetrahedron* **1965**, *21*, 1907–1915.
12. Becker, D.; Hughes, L. R.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1674–1681.
13. Albonico, S. M.; Kuck, A. M.; Dealofeu, V. *Ann. Chem.* **1965**, *685*, 200–206; *Chem. Abstr.* **1965**, *63*, 11634f.
14. Kitasato, Z. *Acta Phytochim.* **1927**, *3*, 175–258; *Chem. Abstr.* **1928**, *22*, 1779.
15. El-Sayed, H. A.; Swaringen, R. A.; David, A.; Yeowell; Crouch, R. C.; Hurlbort, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2067–2077.
16. General procedure for the Hofmann degradation of 1-arylmethyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2,2-dimethylisoquinolinium iodides **2a**–**e**.
    A stirred solution of **2a** (2.2 g, 0.005 mol) and 20% methanolic KOH (25 mL) was refluxed for 4 h. After removal of the solvent under reduced pressure, the residue was decomposed with chilled water (50 mL) and extracted with chloroform (3 × 25 mL). The combined chloroform extract was washed with water (2 × 50 mL) and dried over anhydrous sodium sulfate. After removal of the solvent, the residue obtained was purified by column chromatography [neutral alumina, petroleum ether–$CHCl_3$, 95:5] to afford (*E*)-*N*-2{2-[2-(phenyl)ethenyl]-4,5-dimethoxyphenyl}ethyl-*N*,*N*-dimethylamine **3a**, as a white crystalline solid (90%), mp 111–112 °C.
    IR (KBr): [ν 1620, Ar (C=C)]; ^{1}H NMR ($CDCl_3$, 60 MHz): $\delta = 2.3$ [s, 6H, N–$(CH_3)_2$], 2.45–3.55 (m, 4H, $-CH_2-CH_2$), 3.95 (s, 6H, $-OCH_3$), 7.6–6.5 [m, 9H, (ArH and CH=CH)]; UV (methanol) λ_{max} nm ($\log\varepsilon$): 207 (4.16), 294 (4.15), 322 (4.16); GC–MS *m*/*z*: 311 (M^+) (54), 296 (22), 80 (17), 267 (15), 222 (35),178 (12), 152 (29), 91 (33), 58 (100); Analysis $C_{20}H_{25}NO_2$ requires: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.21; H, 8.19; N, 4.46.
    Compounds **3b**–**e** were synthesized in a similar manner.
    (*E*)-*N*-2{2-[2-(4,5-Dimethoxyphenyl)ethenyl]-4,5-dimethoxyphenyl}ethyl-*N*,*N*-dimethylamine **3b**, white crystals (92%), mp 94 °C, (lit.,[6] mp 94 °C).
    (*E*)-*N*-2{2-[2-(4-Methoxyphenyl)ethenyl]-4,5-dimethoxyphenyl}ethyl-*N*,*N*-dimethylamine **3c**, white crystals (89%), mp 85 °C, (lit.,[6] mp 85 °C).
    (*E*)-*N*-2{2-[2-(4,5-Methylenedioxyphenyl)ethenyl]-4,5-dimethoxyphenyl}ethyl-*N*,*N*-dimethylamine **3d**, white crystals (95%), mp 118–120 °C.
    IR (KBr): [ν 1620, Ar (C=C)]; ^{1}H NMR ($CDCl_3$, 60 MHz): $\delta = 2.4$ [s, 6H, N–$(CH_3)_2$], 2.6–3.8 (m, 4H, $-CH_2-CH_2$), 4.0 (s, 6H, $-OCH_3$), 5.7 (s, 2H, $-O-CH_2-O$), 6.25–7.35 [m, 7H, (Ar and CH=CH)]; UV (methanol) λ_{max} nm ($\log\varepsilon$): 223 (3.96), 295 (3.73), 35 (3.88); Analysis $C_{21}H_{25}NO_4$ requires: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.92; H, 7.13; N, 3.99.
    (*E*)-*N*-2{2-[2-(3,4,5-Trimethoxyphenyl)ethenyl]-4,5-dimethoxyphenyl}ethyl-*N*,*N*-dimethylamine **3e**, white crystals (88%), mp 132–134 °C.
    IR (KBr): [ν 1610, Ar (C=C)]; ^{1}H NMR ($CDCl_3$, 60 MHz): $\delta = 2.45$ [s, 6H, N–$(CH_3)_2$], 2.6–3.7 (m, 4H, $-CH_2-CH_2$), 4.0 (s, 9H, $-OCH_3$), 3.8 (s, 6H, $-OCH_3$), 6.4–6.8 [s, 6H, (ArH and CH=CH)]; UV (methanol) λ_{max} nm ($\log\varepsilon$): 221 (4.04), 328 (4.08); GC–MS *m*/*z*: 401 (M^+) (23), 385 (24), 356 (20), 342 (26), 221 (28), 180 (33), 163 (23), 87 (25), 74 (21), 58 (100); Analysis $C_{23}H_{31}NO_5$ requires: C, 68.80; H, 7.78; N, 3.49. Found: C, 68.86; H, 7.76; N, 3.42.
17. General procedure for the photochemical electrocyclization of stilbene derivatives **3a**–**e**.
    A stirred solution of **3a** (200 mg, 0.00064 mol), cyclohexane (300 mL) and iodine (10 mg) was irradiated using a high pressure mercury lamp [USHIO-UM-452 (450 W)] at 20 °C for 5 h. The reaction mass was washed with 1% aqueous sodium thiosulfate solution (100 mL) followed by water (100 mL). The cyclohexane solution was dried over

anhydrous sodium sulfate. After evaporation of the solvent, the residue obtained was purified by column chromatography [neutral alumina, petroleum ether–$CHCl_3$, 95:5] to afford the corresponding 1-[2-(*N*,*N*-dimethylaminoethyl)]-3,4-dimethoxyphenanthrene **4a**, as a white crystalline solid (33%), mp 199 °C, (lit.,[18,19] mp 199–200 °C), a naturally occurring phenanthrene alkaloid, [*Atherosperminine*].

IR (KBr): [ν 1600, Ar (C=C)]; ^{1}H NMR ($CDCl_3$, 60 MHz): $\delta = 2.25$ [s, 6H, N–$(CH_3)_2$], 2.3–3.85 (m, 4H, –CH_2–CH_2), 3.88 (s, 3H, –OCH_3), 3.90 (s, 3H, –OCH_3), 7.20–7.5 (m, 3H, ArH), 7.65 (m, 3H, ArH), 9.67 (m, 1H, ArH); UV (methanol) λ_{max} nm ($\log \varepsilon$): 212 (4.20), 234 (4.33), 258 (4.63), 304 (4.04), 346 (3.21); Analysis calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53; Found: C, 77.61; H, 7.38; N, 4.60.

Compounds **4b**–**e** were synthesized in a similar manner.

1-[2-(*N*,*N*-Dimethylaminoethyl)]-3,4,6,7-tetramethoxyphenanthrene **4b**, white crystals (36%), mp 118 °C, (lit.,[20] mp 118–120 °C), a naturally occurring phenanthrene alkaloid, [*N-methylsecoglaucine*].

IR (KBr): [ν 1600, Ar (C=C)]; ^{1}H NMR ($CDCl_3$, 60 MHz): $\delta = 2.4$ [s, 6H, N–$(CH_3)_2$], 2.45–3.3 (m, 4H, –CH_2–CH_2), 3.95 (s, 6H, –OCH_3), 4.10 (s, 6H, –OCH_3), 7.22–7.8 (m, 4H, ArH), 9.3 (m, 1H, ArH); UV (methanol) λ_{max} nm ($\log \varepsilon$): 268 (4.40), 323 (3.68), 348 (2.55), 368 (2.55); Analysis calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79; Found: C, 71.58; H, 7.42; N, 3.83.

1-[2-(*N*,*N*-Dimethylaminoethyl)]-3,4,6-Trimethoxyphenanthrene **4c**, white crystals (34%), mp 78–80 °C.

IR (KBr): [ν 1600, Ar (C=C)]; ^{1}H NMR ($CDCl_3$, 60 MHz): $\delta = 2.40$ [s, 6H, N–$(CH_3)_2$], 2.55–3.7 (m, 4H, –CH_2–CH_2), 3.85 (br, 9H, –OCH_3), 6.45–7.55 (m, 5H, ArH), 9.3 (m, 1H, ArH); UV (methanol) λ_{max} nm ($\log \varepsilon$): 216 (4.50), 256 (4.73), 325 (4.03), 370 (3.27); Analysis $C_{21}H_{25}NO_3$ requires: C, 74.30; H, 7.42; N, 4.13. Found: C, 74.38; H, 7.33; N, 4.22.

1-[2-(*N*,*N*-Dimethylaminoethyl)]-3,4-dimethoxy-6,7-methylenedioxyphenanthrene **4d**, white crystals (36%), mp 126–127 °C, (lit.,[21] mp 126–127 °C), a naturally occurring phenanthrene alkaloid, [*Thalictuberine*].

IR (KBr): [ν 1600, Ar (C=C)]; ^{1}H NMR ($CDCl_3$, 60 MHz): $\delta = 2.40$ [s, 6H, N–$(CH_3)_2$], 2.45–3.7 (m, 4H, –CH_2–CH_2), 3.9 (s, 6H, –OCH_3), 5.85 (s, 2H, -O–CH_2–O-), 7.1–7.8 (m, 5H, ArH), 9.25 (m, 1H, ArH); UV (methanol) λ_{max} nm ($\log \varepsilon$): 261 (4.84), 285 (4.05), 310 (4.32), 345 (3.50); Analysis calcd for $C_{21}H_{23}NO_4$: C, 71.38; H, 6.56; N, 3.96; Found: C, 71.33; H, 6.40; N, 4.04.

1-[2-(*N*,*N*-Dimethylaminoethyl)]-3,4,5,6,7-pentamethoxyphenanthrene **4e**, white crystals (31%), mp 154–156 °C.

IR (KBr): [ν 1600, Ar (C=C)]; ^{1} H NMR ($CDCl_3$, 60 MHz): $\delta = 2.7$ [s, 6H, N–$(CH_3)_2$], 2.85–3.7 [m, 4H, –CH_2–CH_2], 3.8 (s, 6H, –OCH_3), 3.95 (s, 9H, –OCH_3), 6.3–7.0 (m, 4H, ArH); UV (methanol) λ_{max} nm ($\log \varepsilon$): 211 (4.32), 296 (3.71), 326 (3.59); GC–MS m/z: 399 (M^+) (25), 384 (21), 355 (28), 341 (14), 327 (10), 296 (14), 179 (29), 169 (28), 101 (15), 86 (17), 58 (100). Analysis requires $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.23; H, 7.39; N, 3.57.

18. Ramana, M. M. V.; Potnis, P. V. *Nat. Prod. Lett.* **1996**, *8*, 317–320.
19. Bick, I. R. C.; Douglas, G. K. *Aust. J. Chem.* **1965**, *18*, 1997–2001.
20. Lu, S. T.; Tsai, L. *Heterocycles* **1988**, *27*, 751–754.
21. Herath, W.; Hussain, F.; Guinaudeu, H.; Shamma, M. *J. Nat. Prod.* **1987**, *50*, 757–761.