Tetrahedron Letters 50 (2009) 590–592

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A new synthesis of the benzo[*c*]phenanthridines nornitidine, noravicine, and isodecarine, based on a microwave-assisted electrocyclic reaction of the aza 6π-electron system

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ARTICLE INFO

Article history:
Received 22 October 2008
Revised 18 November 2008
Accepted 20 November 2008
Available online 24 November 2008

ABSTRACT

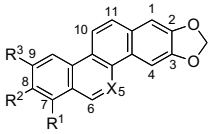
A new and versatile synthetic route to a benzophenanthridine alkaloid was developed by a bond formation between C4b and N5 on the benzo[*c*]phenanthridine nucleus, using a microwave-assisted electrocyclic reaction of the aza 6π-electron system. This strategy was successfully used to synthesize nornitidine (**1b**), noravicine (**1d**), and isodecaline (**1f**).

New and more versatile synthetic routes to benzo[*c*]phenanthridines are in high demand,[1–7] because of their potent anti-tumor activity.[8–17] Among benzo[*c*]phenanthridines, nitidine (**1a**) and 7-hydroxy-8-methoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium hydrogen sulfate (NK109) (**1e**) are the most promising compounds, exhibiting significant anti-tumor activity against drug-resistant human tumor cell lines.[18–21] Nitidine (**1e**) is a potent inhibitor of topoisomerase II.[21]

In our laboratory, we have focused on the construction of fused pyridine ring systems, such as furoisoquinoline,[22] phenanthridine,[23] β-carboline,[24] and azaanthraquinone alkaloids,[25] using a microwave-assisted electrocyclic reaction of the aza 6π-electron system. Here, we describe a new and versatile synthesis of benzo[*c*]phenanthridine alkaloids, using the microwave-assisted electrocyclic reaction of the aza 6π-electron system to induce bond formation between the C4b and N5-positions[13] in the tetracyclic benzo[*c*]phenanthridine nucleus (Fig. 1).

We planned the syntheses of nornitidine (**1b**), noravicine (**1d**), and isodecarine (**1f**), derived from 11,12-dihydrobenzo[*c*]phenanthridines **2** as shown in retro-synthetic Scheme 1. Dihydro-compound **2** would be obtained from a 2-cycloalkenylbenzaldoxime methyl ether **3** through a microwave-assisted electrocyclic reaction. An oxime ether **3** could be prepared from 2-cycloalkenylbenzaldehyde **4**, which would be provided by the Suzuki–Miyaura reaction between 2-bromobenzaldehyde **5** and 2-(6,7-methylenedioxy-3,4-dihydronaphthyl)boronic acid pinacol ester **6**.

Initially, to obtain a required pinacol borate **6**, we attempted an alternative synthesis of 6,7-methylenedioxy-β-tetralone (**7**) (Scheme 2). Treatment of 2-allyl-4,5-methylenedioxyphenol



1a : R^1 = H, R^2 = R^3 = OMe, X = $^+$N-Me (nitidine)
1b : R^1 = H, R^2 = R^3 = OMe, X = N (nornitidine)
1c : R^1 = H, R^2 + R^3 = OCH_2O, X = $^+$N-Me (avicine)
1d : R^1 = H, R^2 + R^3 = OCH_2O, X = N (noravicine)
1e : R^1 = OH, R^2 = OMe, R^3 = H, X = $^+$N-Me (NK109, fagaridine)
1f : R^1 = OH, R^2 = OMe, R^3 = H, X = N (isodecaline)

Figure 1.

(**8**)[26] with trifluoromethanesulfonyl anhydride (Tf_2O) and pyridine afforded the *O*-triflate **9**,[27] which was subjected to the Stille reaction with allyltributyltin in the presence of $PdCl_2(PPh_3)_2$ and LiCl to give the diallylbenzene **10**. Olefin metathesis of diallylbenzene **10** with the Grubbs's I catalyst yielded 1,4-dihydronaphthalene **11**, which was subjected to hydroboration followed by oxidation to afford 2-hydroxytetrahydronaphthalene **12**. The alcohol **12** was subsequently oxidized by pyridinium chlorochromate (PCC) in CH_2Cl_2 to give the known β-tetralone **7**.[28] The unstable tetralone **7** was immediately treated with *N*-phenylbis(trifluoromethanesulfonamide (Tf_2NPh) and LDA to obtain the triflate **13**, via a reaction with bis(pinacolate)diborane and $PdCl_2(dppf)$[29] to afford the expected pinacol borate **6**.

Next, the Suzuki–Miyaura reaction of readily available 2-bromobenzaldehydes (**5b**, **5d**, and **5f**) with the prepared pinacol borate **6** smoothly proceeded in the presence of $PdCl_2(PPh_3)_2$ to give the 2-cycloalkenylbenzaldehydes **4b** and **4d**, or in the presence of $PdCl_2(dppf)$[30] to give **4f**. The reaction of **5f** with **6**, however, yielded the deacetylated product **4f**.

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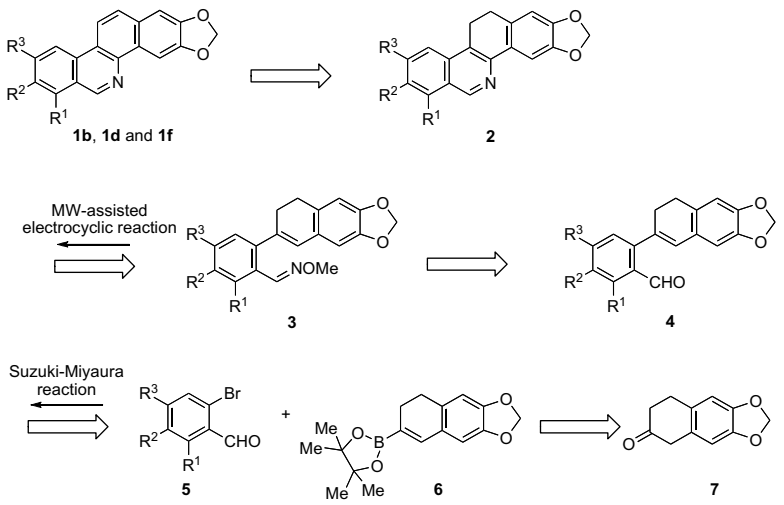
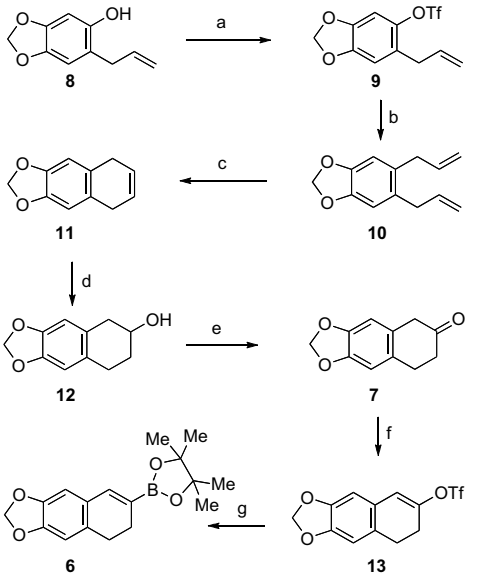
doi:10.1016/j.tetlet.2008.11.076



Scheme 1.

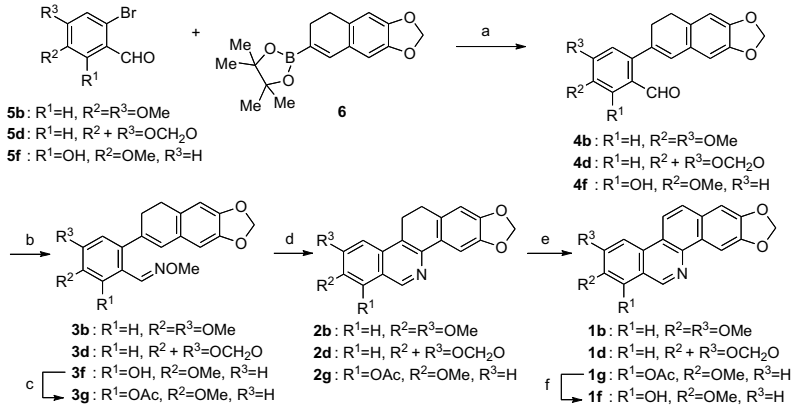


Scheme 2. Reagents and conditions: (a) Tf_2O, pyridine, CH_2Cl_2, rt, 2 h, 93%; (b) allyltributyltin, LiCl, $PdCl_2(PPh_3)^2$, dppf, DMF, 180 °C, 2 h, 99%; (c) Grubbs's I catalyst, CH_2Cl_2, 50 °C, 1 h, 99%; (d) (i) BH_3, THF, 0 °C, 1 h, (ii) 28% H_2O_2, 3 M NaOH, 50 °C, 1 h, 86%; (e) PCC, CH_2Cl_2, rt, 1.5 h, 74%; (f) LDA, Tf_2NPh, THF, −78 °C to rt, 4 h, 84%; (g) bis(pinacolate)diborane, AcOK, $PdCl_2$(dppf), DMSO, 70 °C, 1 h, 86%.

Subsequent treatment of **4** with hydroxylamine methyl ether afforded oximes (**3b**, **3d**, and **3f**). The oxime ether **3f** was converted to the acetyl compound **3g**, and then oximes **3b**, **3d**, and **3g** were subjected to a microwave-assisted electrocyclic reaction at 180 °C to give the tetracyclic 11,12-dihydrobenzo[*c*]phenanthridines (**2b**, **2d**, and **2g**) in good to excellent yield (Scheme 3).[31,32]

Finally, the dihydrobenzophenanthridines **2b**, **2d**, and **2g** were oxidized by refluxing with 10% Pd–C in 1,2-dichlorobenzene to give norniitidine (**1b**), noravicine (**1d**), and *O*-acetylisodecaline (**1g**), respectively. Hydrolysis of the acetyl group of **1g** with $KHCO_3$ afforded isodecaline (**1f**). The physical and spectroscopic data of **1b**,[32–34] **1d**,[32–34] and **1f**[34,35] were identified by comparing them with those previously reported.[36]

In conclusion, an alternative synthesis of 6,7-methylenedioxy-β-tetralone (**7**) was achieved in a five-step sequence, and the desired reagent of the Suzuki–Miyaura reaction, pinacol borate **6**, was derived in two steps. After the C–C bond connection between C9a and C9b by the Suzuki–Miyaura reaction, a new synthetic strategy for anti-tumor benzo[*c*]phenanthridines was established by inducing a bond formation between C4b and N5 using a microwave-assisted electrocyclic reaction of the aza 6π-electron system. Formal total syntheses of nitidine (**1a**) and avicine (**1c**) were achieved. In addition, the total synthesis of isodecaline (**1f**) was completed. This new synthetic strategy will be an useful procedure for the synthesis of other benzo[*c*]phenanthridine alkaloids.



Scheme 3. Reagents and conditions: (a) $PdCl_2(PPh_3)_2$, or $PdCl_2$(dppf) in the case of **4f**, K_2CO_3, MeOH, DMF, 80 °C, 0.5–1 h, 98% (**4b**), 78% (**4d**), 97% (**4f**); (b) $MeONH_2 \cdot HCl$, AcONa, EtOH, 80 °C, 1 h, 95% (**3b**), 98% (**3d**), 95% (**3f**); (c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 80 °C, 1 h, 94%; (d) microwave, 1,2-dichlorobenzene, 180 °C, 84%(**2b**), 94%(**2d**),77%(**2g**); (e) 10% Pd–C, 1,2-dichlorobenzene, 180 °C, 97% (**1b**), 74% (**1d**), 93% (**1g**); (f) $KHCO_3$, MeOH, H2O, rt, 4 h, 74%.

Acknowledgments

This work was supported in part by Grant-in Aid for Scientific Research (C) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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31. Yields of **2b**, **2d** and **2g** by the conventional method were 45% (12 h), 45% (12 h) and 49% (3 h), respectively.
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36. Nornitidine (**1b**) mp 278–281 °C (EtOAc–hexane) (Lit.,[33] mp 281–282 °C); ^{1}H NMR (DMSO-d_6) δ: 3.97 (3H, s), 4.07 (3H, s), 6.20(2H, s), 7.50 (1H, s), 7.69 (1H, s), 7.95 (1H, d, J = 8.7 Hz), 8.15 (1H, s), 8.54 (1H, s), 8.62 (1H, d, J = 8.7 Hz), 9.29 (1H, s); ^{13}C NMR (DMSO-d_6) δ: 55.7, 56.1, 101.0, 101.4, 102.4, 104.5, 107.7, 119.2, 119.7, 121.9, 126.3, 128.2, 128.3, 129.2, 139.5, 147.9, 148.0, 149.7, 149.9, 153.1; MS m/z: 333 (M^+). HR-MS m/z: 333.1031 (Calcd for $C_{20}H_{15}NO_4$: 333.1001).Noravicine (**1d**) mp 312 °C (EtOAc–hexane) (Lit.,[33] mp 325 °C (decomp.)); ^{1}H NMR (DMSO-d_6) δ: 6.20 (2H, s), 6.27 (2H, s), 7.50 (1H, s), 7.67 (1H, s), 7.93 (1H, d, J = 8.8 Hz), 8.31 (1H, s), 8.52 (1H, d, J = 8.8 Hz), 8.53 (1H, s), 9.25 (1H, s); ^{13}C NMR (DMSO-d_6) δ: 100.1, 101.1, 101.5, 102.1, 104.5, 104.8, 119.2, 120.2, 123.2, 126.5, 128.1, 129.3, 130.2, 139.9, 147.8, 148.0, 150.0, 151.5; MS m/z: 317 (M^+). HR-MS m/z: 317.0674 (Calcd for $C_{19}H_{11}NO_4$: 317.0688).Isodecarine (**1f**) mp 239–241 °C ($CHCl_3$–hexane) (Lit.,[34] mp 225–227 °C, Lit.,[35] mp 265–268 °C); ^{1}H NMR (DMSO-d_6) δ: 3.98 (3H, s), 6.20 (2H, s), 7.50 (1H, s), 7.74 (1H, d, J = 8.9 Hz), 7.95 (1H, d, J = 8.9 Hz), 8.27 (1H, d, J = 8.9 Hz), 8.52 (1H, s), 8.53 (1H, d, J = 8.9 Hz), 9.65 (1H, s), 9.98 (1H, s); ^{13}C NMR (DMSO-d_6) δ: 56.8, 101.0, 101.4, 104.4, 113.2, 117.3, 118.6, 118.9, 119.7, 126.8, 127.1, 128.3, 129.3, 138.9, 142.7, 144.2, 146.6, 147.9, 148.1; MS m/z: 319 (M^+). HR-MS m/z: 319.0819 (Calcd for $C_{19}H_{13}NO_4$: 319.0845).