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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 8166–8169

Manganese(III) acetate mediated oxidation of aporphines: a convenient and useful synthesis of oxoaporphines

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Received 21 February 2006; revised 14 September 2007; accepted 14 September 2007
Available online 20 September 2007

Abstract—Manganese(III) acetate mediated oxidation of aporphines to oxoaporphines is described. The developed methodology was conveniently applied for the synthesis of naturally occurring oxoaporphine alkaloids, oxoglaucine, and atheroline, starting from commercially available boldine.

Oxoaporphines are a subclass of isoquinoline alkaloids and widely distributed in plants of the families: annonaceae, araceae, hernandiaceae, lauraceae, papaveraceae, rannunculaceae, menispermaceae, etc., although in minor amounts.[1] These are most probably derived in the plants by the oxidation of corresponding aporphines. Oxoaporphines are bright yellow or orange colored compounds, which turn pink or red upon the addition of mineral acids.[1b] Oxoaporphines possess a broad range of biological activities such as antimicrobial,[2] antiviral,[3] cytotoxic,[4] and platelet aggregation inhibition.[5] Oxoglaucine and liriodenine (Fig. 1) are the most commonly available among oxoaporphine alkaloids and hence, their pharmaceutical properties have been studied in detail. Oxoglaucine had immunomodulatory activity[6] while liriodenine displayed topoisomerase II inhibitory activity[7] as well as anti-arrhythmic activity[8] by influencing the production of nitric oxide in the cell.

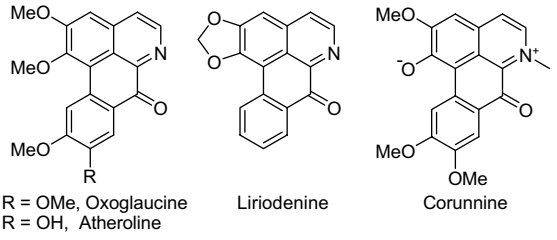

Figure 1. Some of the naturally occurring oxoaporphines alkaloids.

The non-degradative oxidation of aporphines to oxoaporphines has been the subject of a limited number of publications. Thus, treatment of glaucine (1,2,9,10-tetramethoxyaporphine) with chromium trioxide (CrO_3) in pyridine,[9] manganese dioxide,[10] lead(IV) acetate (LTA),[11] ceric ammonium nitrate (CAN),[12] and periodic acid[13] afforded oxoglaucine in varying yields. LTA and periodic acid gave 69%[11] and 70% yield, respectively, while CrO_3 and MnO_2 furnished very poor yields (≈10%). However, the oxidation of glaucine with CAN provided a mixture of 3-nitroglaucine and 3-nitrooxoglaucine along with glaucine by in situ nitration of glaucine with nitric acid generated from CAN followed by oxidation. All these reagents have only been utilized for the oxidation of glaucine and never been applied to the other derivatives of aporphines.

Among all the above reported reagents for the oxidation of glaucine to oxoglaucine, only periodic acid gave good yield and is also non-toxic. Therefore, we decided to study the oxidation of different aporphines with periodic acid. However, the oxidation of diisopropylboldine **1b**[14] in acetic acid afforded a mixture of 2,9-diisopropyloxy-1,10-dimethoxy-7-oxoaporphine **2b** and a characteristic green colored zwitterion compound **3b** in the ratio of 1:2 (Table 1, entry 4). Most probably **3b** might have

Keywords: Isoquinoline alkaloids; Aporphines; Manganese(III) acetate; Iodobenzene diacetate; Oxoaporphine; Oxoglaucine; Atheroline.
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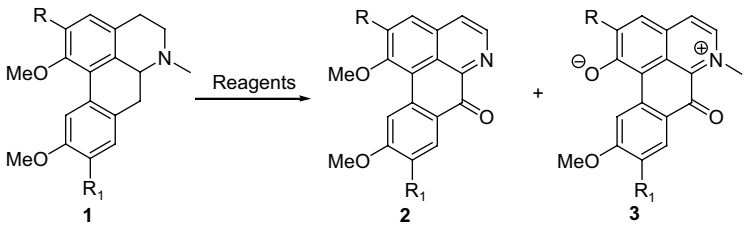
doi:10.1016/j.tetlet.2007.09.096

Table 1. Oxidation of aporphines with different reagents



1 2 3

Entry	Compounds	Substituents	Reagent	Temperature (°C)	Time (h)	Products	Yield[a] (%)
1	**1a**	$R = R_1 = OMe$	$Pb(OAc)_4$	25	12	**2a**	50
2	**1b**	$R = R_1 = OPr^i$	$Pb(OAc)_4$	25	12	**2b**	50
3	**1a**	$R = R_1 = OMe$	HIO_4	70	1.5	**2a**	70
4	**1b**	$R = R_1 = OPr^i$	HIO_4	70	1.5	**2b**	25
						3b	50
5	**1a**	$R = R_1 = OMe$	$PhI(OAc)_2$	115[b]	1	**2a**	50
						3a	5
6	**1a**	$R = R_1 = OMe$	$PhI(OAc)_2$	115[b]	18	**2a**	10
						3a	60
7	**1b**	$R = R_1 = OPr^i$	$PhI(OAc)_2$	115[b]	1	**2b**	15
						3b	40
8	**1a**	$R = R_1 = OMe$	$Mn(OAc)_3$	70	2	**2a**	75
9	**1b**	$R = R_1 = OPr^i$	$Mn(OAc)_3$	70	5	**2b**	68
10	**1c**	$R = R_1 = H$	$Mn(OAc)_3$	70	3	**2c**	80
11	**1d**	$R = OMe$; $R_1 = OTf$	$Mn(OAc)_3$	70	5	**2d**	75
12	**1e**	$R = OTf$; $R_1 = OMe$	$Mn(OAc)_3$	70	2	**2e**	70

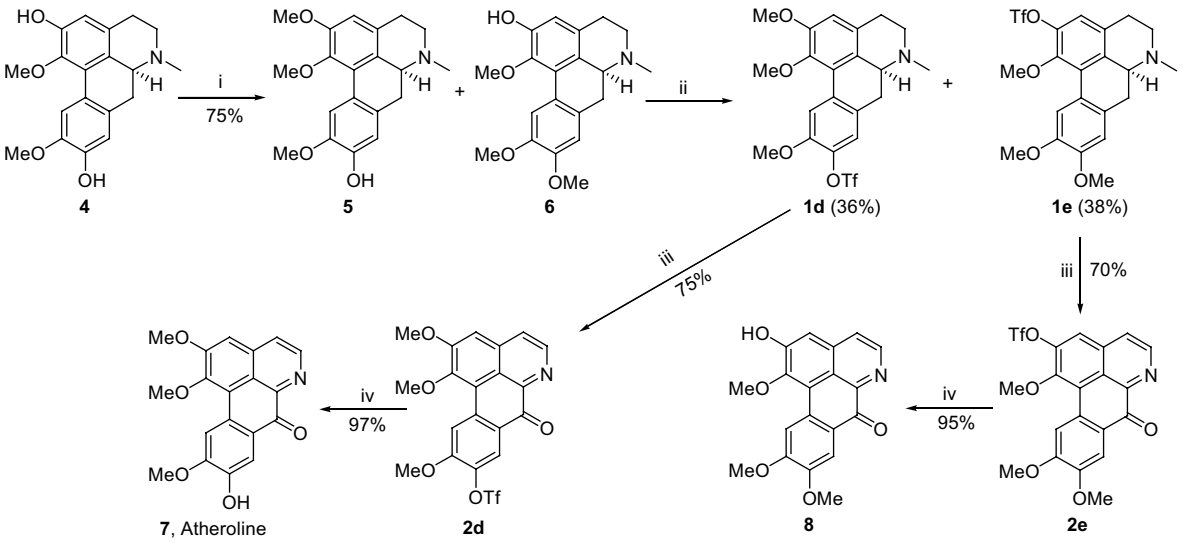
[a] Yields are based upon isolated crystalline solid products.
[b] Reflux temperature of acetic acid.

formed from **2b** by the migration of methyl group from C_1–O to N_6 atom of oxoaporphine under the reaction conditions. This phenomenon is precedence in the literature and corunnine **3a** was synthesized[11] by heating of oxoglaucine at 180 °C for 24 h. The structure of **3b** was determined by 1D NMR (^1H, ^{13}C) and 2D NMR (COSY, NOESY, HMQC, and HMBC) analysis.[15] Hence, due to the lack of general applicability of periodic acid and the toxicity of LTA, the search for environment friendly reagents for the above transformation, which is widely applicable and amenable to different functional groups, is highly desirable.

Thus, glaucine **1a** and diisopropylboldine **1b** were subjected to the oxidation with different reagents such as LTA, HIO_4, iodobenzene diacetate (IBD) and manganese(III) acetate (MTA) under different reaction conditions and the results are summarized in Table 1. IBD[16] and MTA[17] have similar chemical properties, as LTA except MTA is a single-electron oxidant while IBD and LTA are two-electron oxidants. Moreover, IBD and MTA are also considered environment friendly reagents due to their non-toxic property. The oxidation of **1a** and **1b** with LTA in acetic acid afforded the respective oxoaporphines **2a** and **2b** in 50% yield (entries 1 and 2). Similarly, the oxidation of **1a** with HIO_4 in acetic acid at 70 °C gave only **2a** (entry 3) while **1b** provided a mixture of **2b** and **3b** in the ratio of 1:2 under similar reaction conditions (entry 4). The oxidation of **1a** with IBD in refluxing acetic acid for 1 h furnished **2a** as the major product along with a small amount of corunnine (**3a**) as minor product (5%). Upon prolonged heating of reaction mixture for 18 h (entry 6), **3a** was obtained as the major product, which has been isolated from the species of *Glaucium*[18] and *Thallictrum*.[19] This is the first direct conversion of glaucine to corunnine in a single step. Similarly, the oxidation of **1b** with IBD gave a mixture of **2b** and **3b** and the latter being a major one (entry 7). Surprisingly, oxidation of **1a**–**b** with MTA in acetic acid furnished only the respective oxoaporphines **2a**–**b** even after heating at 70 °C for 5 h and no trace of other products **3a**–**b** could be detected via TLC.

The generality of the above transformation was checked by treating different aporphines (**1a**–**e**) with MTA and the respective oxoaporphines (**2a**–**e**)[20] were obtained as the sole products in 68–80% yields (Table 1). The identities of all the oxoaporphines **2a**–**e** were confirmed by analyses of their ^1H and ^{13}C NMR and high-resolution mass spectra.

The developed methodology was applied for the synthesis of atheroline (**7**),[21] a phenolic oxoaporphine alkaloid starting from commercially available (+)-boldine (**4**) as depicted in Scheme 1. Monomethylation of boldine with trimethylphenylammonium chloride[22] in DMF under high dilution afforded an inseparable mixture of 2- and 9-boldine methyl ether (**5** and **6**) which were separated by converting them to their respective triflate derivatives (*N*-methyllaurotetanine triflate **1d** and predicentrine triflate **1e**) by treatment with *N*-phenyl-bis(trifluromethylsulfonimide).[23] The oxidation of **1d** with MTA in acetic acid furnished oxoaporphine, atheroline triflate **2d**, which on deprotection of triflate group by treatment with KOH–MeOH produced atheroline (**7**) in four steps and overall 20% yield starting from boldine. Similarly, **1e** yielded 2-hydroxy-1,9,10-trimethoxy-7-oxoaporphine (oxopredicentrine, **8**)[24] by oxidation with MTA followed



Scheme 1. Reagents and conditions: (i) Trimethylphenylammonium chloride, *t*-BuOK, DMF, 90 °C, 12 h; (ii) *N*-phenyl-bis(trifluoromethylsulfonimide, K_2CO_3, TEA, CH_2Cl_2, 72 h; (iii) MTA, AcOH, 70 °C; (iv) KOH–MeOH, rt, 2 h.

by hydrolysis, a hitherto unknown oxoaporphine alkaloid, which may be isolated in the near future.

In summary, a highly efficient and general method for the synthesis of oxoaporphines from aporphines has been developed by oxidation of latter with manganese(III) acetate under mild reaction conditions in high yield, which is devoid of any other side-products. The manganese(III) acetate is a much superior reagent for the present transformation than the other reported reagents in terms of general applicability, yields, and environmental friendliness since it also replaces toxic reagents such as lead(IV) acetate.

Acknowledgment

We gratefully acknowledge the National Science Council, Taiwan, ROC, for the financial support of this work under the Grants NSC89-2320-B-002-272 and NSC89-2811-B-002-0137.

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14. Diisopropylboldine (**1b**) and 1,10-dimethoxyaporphine (**1c**) were synthesized from boldine by isopropylation and deoxygenation of hydroxyl groups, respectively (Huang, W. J.; Singh, O. V.; Chen, C. H.; Lee, S. S. unpublished results).
15. The characterization data of compound **3b**: ^{1}H NMR (400 MHz, MeOH-d_4) δ 1.41 (d, 6H, $J = 5.9$ Hz), 1.49 (d, 6H, $J = 5.8$ Hz), 3.99 (s, 3H, OCH_3), 4.45 (s, 3H, N–CH_3), 4.56 (m, 1H, C_2–OC*H*), 4.62 (m, 1H, C_9–OC*H*), 6.67 (s, 1H, C_3–*H*), 7.33 (d, 1H, $J = 5.9$ Hz, C_4–*H*), 7.46 (s, 1H, C_8–*H*), 7.84 (d, 1H, $J = 5.8$ Hz, C_4–*H*), 9.37 (s, 1H, C_8–*H*); ^{13}C NMR (100 MHz, MeOH-d_4) δ 22.03, 22.39, 51,14, 56.36, 72.23, 72.73, 105.39 (C_3), 106.78 (C_{11}), 108.86 (C_8), 111.34 (C_{11b}), 121.77 (C_4), 124.81 (C_{3b}), 125.92 (C_{7a}), 128.74 (C_{6a}), 133.89 (C_{11a}), 138.60 (C_5), 140.50 (C_{3a}), 146.78 (C_9), 157.10 (C_{10}), 161.03 (C_2), 172.42 (C_1), 175.82 (C_7); EI-HRMS: $m/z = 407.1732$ (calcd for $C_{24}H_{25}NO_5$: 407.1733).

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20. *General procedure*: To a solution of glaucine (118 mg, 0.33 mmol) in acetic acid (5 mL) was added manganese(III) acetate dihydrate (730 mg, 2.72 mmol) and the mixture was stirred at 70 °C for 2 h. After the completion of the reaction (TLC), acetic acid was distilled off under high vacuo, residue was dissolved in chloroform (100 mL) and washed with saturated sodium bicarbonate solution (50 mL) followed by water (3 × 50 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was chromatographed over silica gel (10 g) using chloroform as eluent to afford oxoglaucine **2a** as yellow fine needles, yield 88 mg (75%); mp = 196–198 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.94 (s, 3H, OCH_3), 4.02 (s, 6H, 2 × OCH_3), 4.05 (s, 3H, OCH_3), 7.11 (s, 1H, C_3–*H*), 7.69 (d, 1H, J = 5.1 Hz, C_4–*H*), 7.94 (s, 1H, C_8–*H*), 8.71 (s, 1H, C_{11}–*H*), 8.81 (d, 1H, J = 5.1 Hz, C_5–*H*). Characterization data: compound **2b**, mp = 172–174 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44 (d, 6H, J = 6.1 Hz), 1.53 (d, 6H, J = 6.1 Hz), 4.01 (s, 6H, 2 × OCH_3), 4.87 (m, 2H), 7.18 (s, 1H, C_3–*H*), 7.79 (d, 1H, J = 5.4 Hz, C_4–*H*), 7.96 (s, 1H, C_8–*H*), 8.75 (s, 1H, C_{11}–*H*), 8.86 (d, 1H, J = 5.3 Hz, C_5–*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.74 (2 × q), 21.91 (2 × q), 55.97 (q), 60.35 (q), 70.89 (d), 71.15 (d), 107.23 (d), 110.61 (d), 112.17 (d), 120.16 (s), 121.27 (s), 123.15 (d), 126.67 (s), 128.75 (s), 135.43 (s), 144.51 (d), 145.32 (s), 147.81 (s), 151.54 (s), 154.59 (s), 154.78 (s), 181.28 (s); EI-HRMS: m/z = 407.1732 (calcd for $C_{24}H_{25}NO_5$: 407.1733). Compound **2c**, mp = 182–184 °C; ^{1}H NMR (400 MHz, $CDCl_3$–MeOH-d_4) δ 3.79 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 6.88 (dd, 1H, J = 2.4 and 8.8 Hz, C_9–*H*), 7.47 (d, 1H, J = 9.2 Hz, C_2–*H*), 7.73 (d, 1H, J = 4.7 Hz, C_4–*H*), 7.77 (d, 1H, J = 9.2 Hz, C_3–*H*), 8.29 (d, 1H, J = 8.76 Hz, C_8–*H*), 8.35 (d, 1H, J = 2.4 Hz, C_{11}–*H*), 8.65 (d, 1H, J = 4.2 Hz, C_5–*H*); ^{13}C NMR (100 MHz, $CDCl_3$–MeOH-d_4)δ 55.15 (q), 56.25 (q), 112.27 (s), 113.51 (d), 113.78 (d), 119.67 (d), 124.89 (d), 124.99 (s), 125.85 (s), 130.72 (d), 130.79 (d), 132.30 (s), 136.57 (s), 141.81 (d), 144.55 (s), 158.99 (s), 164.19 (s), 180.69 (s); EI-HRMS: m/z = 291.0903 (calcd for $C_{18}H_{13}NO_3$: 291.0895). Compound **2d**, mp = 180–182 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.05 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 7.24 (s, 1H, C_3–*H*), 7.75 (d, 1H, J = 5.2 Hz, C_4–*H*), 8.34 (s, 1H, C_8–*H*), 8.85 (d, 1H, J = 5.2 Hz, C_5–*H*), 8.93 (s, 1H, C_{11}–*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.35 (q), 56.47 (q), 60.88 (q), 107.54 (d), 110.28 (d), 115.54 (s), 118.39 (s), 121.97 (s), 122.58 (d), 123.67 (d), 126.65 (s), 135.37 (s), 135.95 (s), 138.80 (s), 144.76 (s), 145.12 (d), 152.41 (s), 155.55 (s), 156.53 (s), 180.12 (s); EI-HRMS: m/z = 469.0439 (calcd for $C_{20}H_{14}F_3NO_7S$: 469.0443). Compound **2e**, mp = 190–192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 4.09 (s, 3H, OCH_3), 7.79 (s, 1H, C_3–*H*), 7.90 (d, 1H, J = 5.3 Hz, C_4–*H*), 7.98 (s, 1H, C_8–*H*), 8.63 (s, 1H, C_{11}–*H*), 9.03 (d, 1H, J = 5.3 Hz, C_5–*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.26 (q), 56.33 (q), 61.23 (q), 109.97 (d), 110.19 (d), 117.10 (s), 120.10 (d), 122.95 (s), 124.50 (d), 126.83 (s), 127.76 (s), 133.69 (s), 145.74 (d), 146.37 (s), 146.96 (s), 150.40 (s), 150.49 (s), 154.24 (s), 180.45 (s); EI-HRMS: m/z = 469.0447 (calcd for $C_{20}H_{14}F_3NO_7S$: 469.0443).
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24. Characterization data of compound **8**: mp = >260 °C; ^{1}H NMR (200 MHz, MeOH-d_4): δ 4.00 (s, 3H, OCH_3), 4.02 (s, 6H, 2 × OCH_3), 7.19 (s, 1H, C_3–*H*), 7.70 (d, 1H, J = 4.78 Hz, C_4–*H*), 7.88 (s, 1H, C_8–*H*), 8.59 (d, 1H, J = 4.60 Hz, C_5–*H*), 8.74 (s, 1H, C_{11}–*H*).