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A practical and highly efficient synthesis of lennoxamine and related isoindolobenzazepines

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Abstract—Lennoxamine and related isoindolobenzazepines were prepared in high yield by intramolecular condensation of aldehyde isoindolones under basic conditions followed by catalytic hydrogenation of the resulting dehydroisoindolobenzazepines.

1. Introduction

Lennoxamine (**1a**), an isoindolobenzazepine, was isolated from the Chilean plant *Berberis darwinii*.[1] Even though no important pharmacological activity of lennoxamine has been reported as normally found in the benzazepine derivatives,[2a–e] its unique structural features have captured the interest of many synthetic groups over the past 20 years.

The previous syntheses of lennoxamine and other isoindolobenzazepine derivatives could be classified into various approaches depending on the order of bond formation as shown in Figure 1.

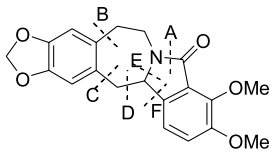
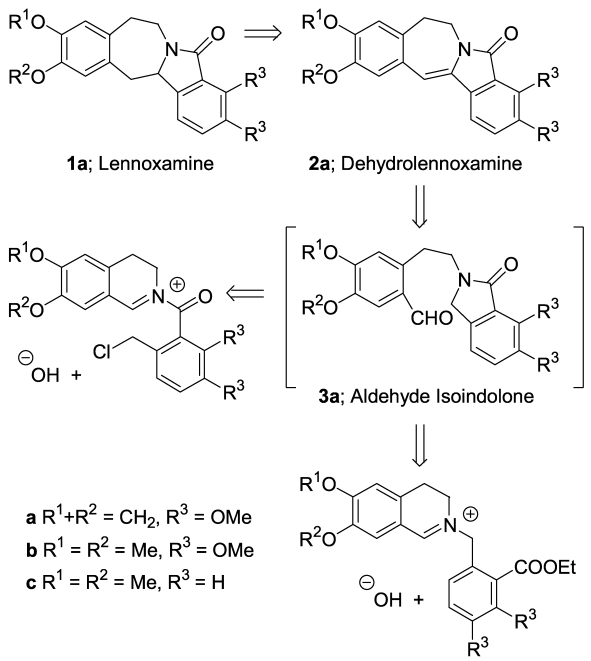


Figure 1.

The first approach involved prior construction of the benzazepine skeleton followed by isoindolone ring formaton via bond A[3a,b] or bond F.[4] The second approach concentrated on first the isoindolone ring formation which could then be manipulated to form the benzazepine ring via formation of bond B[5a–c] or bond C.[6a–c] Bond D formation of various phthalimide derivatives[7a–d] has been exploited in the third approach. The simultaneous formation of the isoindolone and the benzazepine skeleton was the focus of the fourth approach.[6c,8] The fifth approach utilized the rearrangement of various isoquinoline derivatives as a means to synthesize the isoindoloisoquinolines.[9a–e]

2. Results and discussion

In our previous synthetic routes (Scheme 1), the aldehyde isoindolone **3a** was the common unisolated intermediate which further cyclized smoothly to the dehydrolennoxamine



Scheme 1. Synthetic route.

Keywords: Lennoxamine; Isoindolobenzazepine alkaloids.
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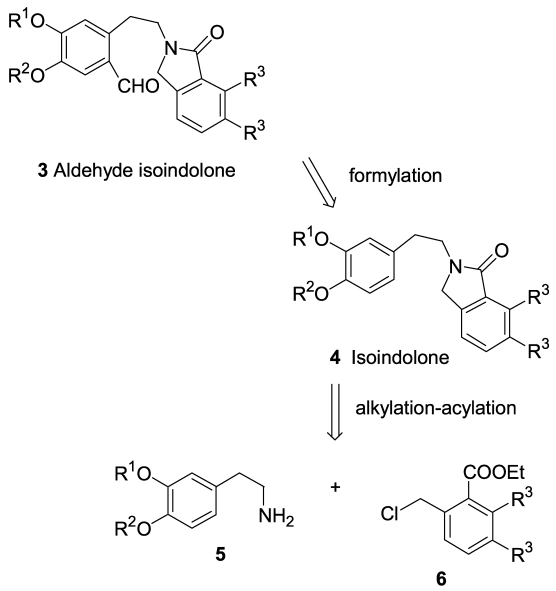
2a in high yield. The former pathway provided the desired isoindolone via hydroxide addition to the iminium salt to give the carbinolamine derivative which was opened to give the amide anion followed by intramolecular alkylation. The above pathway worked well only when the sixth position of the isoquinoline derivative was substituted with a methoxy group. The methoxy group apparently facilitated the breaking of the carbon–nitrogen bond to give the aldehyde and amide anion. Alternatively, in the other pathway, the methoxy group *ortho* to the carboethoxy group is required for the success of the synthesis. The methoxy group presumably activates the leaving group ability of the ester.[10] In this paper, we report a highly efficient, direct synthesis of aldehyde isoindolone which could be successfully cyclized to the isoindolobenzazepine derivatives irrespective of the oxygenation pattern on the aromatic ring.

The aldehyde isoindolone was synthesized by the route suggested by retrosynthetic analysis as shown in Scheme 2.



Scheme 2. Retrosynthetic analysis.

The aldehyde isoindolone **3** could be synthesized by formylation of the isoindolone precursor **4** which could conceivably be prepared by alkylation–acylation of the arylethylamine derivatives with ethyl 2-chloromethylbenzoates **6**.

To test the above idea, homoveratrylamine **5** was heated at reflux with ethyl 2-chloromethylbenzoate **6** in acetonitrile in the presence of triethylamine to give the expected isoindolone **4c** in 74% yield. Similarly, the other two isoindolones, **4a**, **4b** were obtained in 81 and 76% yields respectively from the reaction of the appropriate arylethylamines and ethyl 2,3-dimethoxy-6-chloromethylbenzoate.[11]

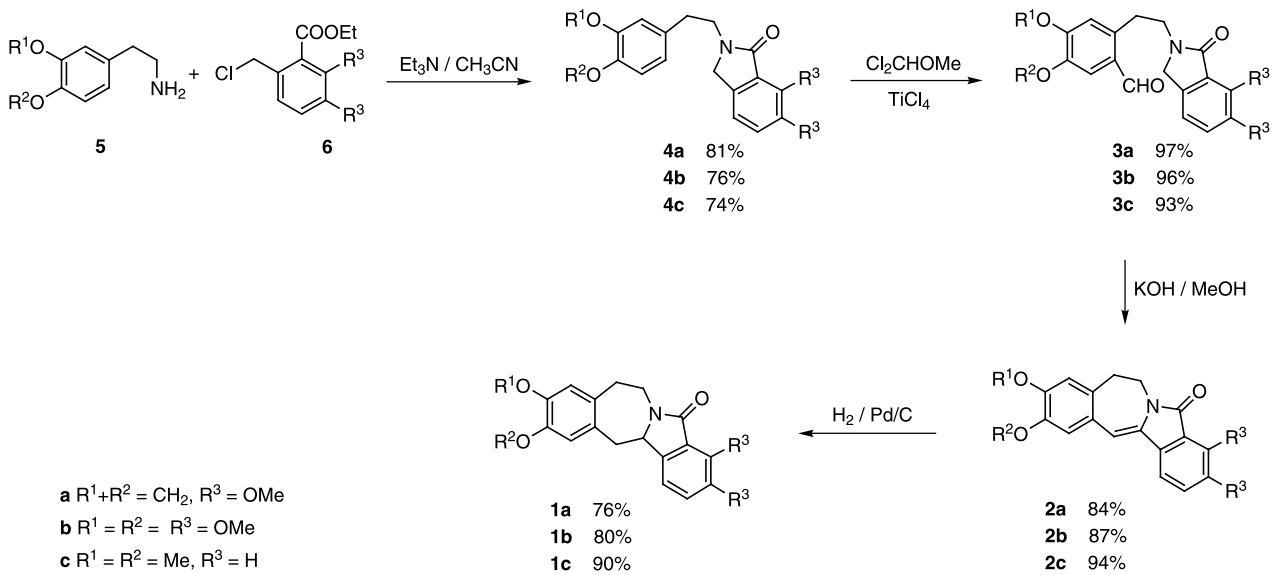
Formylation of the resulting isoindolones were carried out conveniently using dichloromethyl methyl ether and titanium tetrachloride in dichloromethane[12a–c] to give the aldehyde isoindolones, **3a**, **3b**, **3c** in excellent yields

The derived aldehyde isoindolones were cyclized smoothly in refluxing methanolic KOH to give the required dehydroisoindolobenzazepines, **2a**, **2b**, and **2c**, in excellent yields.

Lennoxamine, **1a** as well as other isoindolobenzazepines, **1b**, **1c**, could be readily obtained by catalytic hydrogenation of the dehydro intermediates **2a**, **2b**, and **2c** in 76, 80 and 90% yields, respectively (Scheme 3).

3. Conclusion

We have successfully developed a practical and highly efficient synthetic route for lennoxamine and other related isoindolobenzazepines. The route involved condensing of aldehyde isoindolones under basic conditions followed by catalytic hydrogenation of the resulting dehydroisoindolobenzazepines. The key aldehyde isoindolones were derived in two steps from alkylation–acylation of arylethylamines with ethyl 2-chloromethylbenzoate derivatives and insertion



Scheme 3. Preparation of lennoxamine and its derivatives.

of the C-1 aldehyde onto the aromatic ring using dichloromethyl methyl ether and $TiCl_4$.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz respectively using TMS as an internal standard. Mass spectra were determined at an ionizing voltage of 70 eV. Column chromatographic purifications were carried out using silica gel (70–230 mesh).

4.2. General procedure for the synthesis of isoindolones

A solution of arylethylamine derivatives (1 mmol), ethyl 2-chloromethylbenzoates (1 mmol) and triethylamine (1.2 mmol) in CH_3CN (5 mL) was heated under reflux for 3 h under nitrogen atmosphere. CH_3CN was removed and the crude product was extracted with CH_2Cl_2 and washed with water. The organic extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness to give the crude amide as yellow solid, the product was further purified by column chromatography using 2% MeOH/CH_2Cl_2 as eluting solvent to give the isoindolones as pale yellow solid.

4.2.1. 2-(3,4-Methylenedioxyphenethyl)-6,7-dimethoxyphthalimidine (4a). Pale yellow crystals (81%), mp (EtOAc) 99–100 °C; IR (nujol) 1678 cm^{-1}; ^1H NMR δ 2.88 (t, 2H, J=7.5 Hz), 3.75 (t, 2H, J=7.5 Hz), 3.88 (s, 3H), 4.08 (s, 3H), 4.13 (s, 3H), 5.91 (s, 2H), 6.67 (dd, 1H, J=8.0, 1.6 Hz), 6.71 (d, 1H, J=8.0 Hz), 6.73 (d, 1H, J=1.6 Hz), 7.02, 7.06 (AB, 1H each, J=8.0 Hz). ^{13}C NMR δ 34.4, 44.3, 49.6, 56.7, 62.5, 100.8, 108.3, 109.0, 116.3, 117.6, 121.5, 125.0, 132.6, 134.5, 146.1, 147.1, 147.7, 152.2, 166.6. EIMS 341(M^+, 23), 206(96), 194(67), 193(16), 162(13), 149(16), 148(100), 135(13). Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.90; H, 5.80; N, 3.92.

4.2.2. 2-(3,4-Dimethoxyphenethyl)-6,7-dimethoxyphthalimidine (4b). Pale yellow crystals (76%), mp (EtOAc) 120–120.5 °C; IR (nujol) 1670 cm^{-1}; ^1H NMR δ 2.94 (t, 2H, J=7.5 Hz), 3.80 (t, 2H, J=7.5 Hz), 3.81 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 4.10 (s, 3H), 4.11 (s, 2H), 6.77 (d, 1H, J=8.5 Hz), 6.80 (dd, 1H, J=8.0, 0.4 Hz), 7.01, 7.07 (AB, 1H each, J=8.0 Hz). ^{13}C NMR δ 34.1, 44.2, 49.7, 55.72, 55.74, 55.81, 62.5, 111.3, 111.8, 116.3, 117.6, 120.5, 125.1, 131.4, 134.5, 147.1, 147.6, 148.9, 152.21, 166.6. EIMS 357(M^+, 13), 206(34), 165(14), 164(100). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.83; H, 6.60; N, 3.82.

4.2.3. 2-(3,4-Dimethoxyphenylethyl)phthalimidine (4c). Pale yellow crystals (74%), mp (EtOAc–Hexane) 98–99 °C; IR (nujol) 1670 cm^{-1}; ^1H NMR δ 2.95 (t, 2H, J=7.0 Hz), 3.78 (s, 3H), 3.85 (s, 3H), 3.86 (t, 2H, J=7.0 Hz), 4.19 (s, 2H), 6.74 (s, 1H), 6.77 (d, 1H, J=8.0 Hz), 6.78 (d, 1H, J=8.0 Hz), 7.37 (d, 1H, J=7.0 Hz), 7.45 (t, 1H, J=7.0 Hz), 7.51 (td, 1H, J=7.0, 1.0 Hz), 7.85 (d, 1H, J=7.0 Hz). ^{13}C NMR δ 34.3, 44.2, 50.7, 55.74, 55.82, 111.3, 111.8, 120.5, 122.6, 123.5, 127.9, 131.11, 131.28, 132.8, 141.1, 147.6, 148.9, 168.4. EIMS 297(M^+, 13), 165(12), 164(100), 146(42), 91(15). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.59; H, 6.28; N, 4.76.

4.3. General procedure for the synthesis of aldehyde isoindolones

A solution of isoindolones (2.18 mmol) in 25 mL of dry CH_2Cl_2 was cooled in an ice bath, and 0.3 mL of dichloromethyl methyl ether was added. While the solution was stirred and cooled, 1.2 mL (10.91 mmol) of $TiCl_4$ was added. After the addition was complete, the mixture was stirred for 5 min in an ice bath and for 3 h at room temperature. The reaction mixture was then poured into a flask containing crushed ice and was shaken thoroughly. The organic layer was separated, and the aqueous solution was extracted with CH_2Cl_2. The combined organic solution was washed with water and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the white solid so obtained was further purified by column chromatography using 2% MeOH/CH_2Cl_2 as eluting solvent to give the aldehyde isoindolones as white solid.

4.3.1. 2-(2-Formyl-4,5-methylenedioxyphenethyl)-6,7-dimethoxyphthalimidine (3a). White crystals (97%), mp (EtOH) 175.5–176.5 °C; IR (nujol) 1670 (broad), 1748 cm^{-1}; ^1H NMR δ 3.32 (t, 2H, J=7.0 Hz), 3.74 (t, 2H, J=7.0 Hz), 3.89 (s, 3H), 4.08 (s, 3H), 4.28 (s, 2H), 6.05 (s, 2H), 6.82 (s, 1H), 7.06, 7.09 (AB, 1H each, J=8.0 Hz), 7.27 (s, 1H), 10.09 (s, 1H). ^{13}C NMR δ 31.4, 44.4, 49.6, 56.7, 62.5, 102.0, 111.1, 111.3, 116.4, 117.7, 124.9, 128.4, 134.5, 138.5, 147.1, 152.25, 152.29, 166.8, 190.1. EIMS 369 (M^+, 27), 206(100), 194(8), 162(9), 148(9). Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 65.11; H, 5.14; N, 3.79.

4.3.2. 2-(2-Formyl-4,5-dimethoxyphenylethyl)-6,7-dimethoxyphthalimidine (3b). White crystals (96%), mp (EtOH) 157–158 °C; IR (nujol) 1675 (broad), 1748 cm^{-1}; ^1H NMR δ 3.37 (t, 2H, J=7.0 Hz), 3.78 (t, 2H, J=7.0 Hz), 3.87 (s, 3H), 3.90 (s, 3H), 3.94 (s, 3H), 4.09 (s, 3H), 4.22 (s, 2H), 6.81 (s, 1H), 7.04, 7.08 (AB, 1H each, J=8.0 Hz), 7.33 (s, 1H), 10.15 (s, 1H). ^{13}C NMR δ 30.7, 44.2, 49.7, 56.0, 56.2, 56.8, 62.5, 113.6, 114.0, 116.3, 117.7, 124.9, 126.8, 134.5, 136.2, 147.1, 147.8, 152.2, 153.6, 166.8, 190.5. EIMS 385(M^+, 31), 207(13), 206(100), 193(14), 192(19), 164(31). Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.31; H, 6.05; N, 3.80.

4.3.3. 2-(2-Formyl-4,5-dimethoxyphenylethyl)phthalimidine (3c). White crystals (93%), mp (EtOAc–hexane) 144–145 °C, lit.[9a] 148–150 °C; IR (nujol) 1680 (broad), 1748 cm^{-1}; ^1H NMR δ 3.39 (t, 2H, J=7.0 Hz), 3.84 (s, 3H), 3.85 (t, 2H, J=7.0 Hz), 3.94 (s, 3H), 4.32 (s, 2H), 6.80 (s, 1H), 7.32 (s, 1H), 7.41 (d, 1H, J=7.0 Hz), 7.46 (t, 1H, J=7.0 Hz), 7.52 (td, 1H, J=7.0, 1.0 Hz), 7.85 (d, 1H, J=7.0 Hz), 10.14 (s, 1H). ^{13}C NMR δ 30.9, 44.1, 50.6, 56.0, 56.2, 113.7, 114.3, 122.7, 123.5, 126.8, 128.0, 131.3, 132.7, 136.1, 141.2, 147.8, 153.7, 168.5, 190.7. EIMS 325(M^+, 10), 192(38), 191(48), 146(80), 105(100), 77(55), 51(20). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.81; H, 6.11; N, 4.31.

4.4. General procedure for the synthesis of dehydroisoindolobenzazepine derivatives

Aldehyde (1 mmol) was dissolved in a solution of KOH (500 mg) in MeOH (25 mL) and the mixture was heated at reflux for 1 h. MeOH was removed by evaporation and water was added. The aqueous mixture was extracted with CH_2Cl_2 and dried. The organic extracts were evaporated to dryness under reduced pressure. The crude product was recrystallized from MeOH to give the required dehydroisoindolobenzazepines.

4.4.1. 3,4-Dimethoxy-7,8-dihydro-10,11-methylenedioxy-5*H*-isoindolo[1,2-*b*][3]benzazepine-5-one (2a). Yellow crystals (84%), mp (MeOH) 208–209 °C, lit.[6b] 209–211 °C, lit.[9e] 213–214 °C. The spectroscopic data of compounds **2a**, **2b**, and **2c** are the same as those previously published.[9c]

4.4.2. 3,4-Dimethoxy-7,8-dihydro-10,11-dimethoxy-5*H*-isoindolo[1,2-*b*][3]benzazepine-5-one (2b). Yellow crystals (87%), mp (MeOH) 185–189 °C, lit.[9c] 185–189 °C.

4.4.3. 7,8-Dihydro-10,11-dimethoxy-5*H*-isoindolo[1,2-*b*][3]benzazepine-5-one (2c). Yellow crystals (94%), mp (MeOH) 192–194 °C, lit.[6a] 195–196 °C, lit.[9a] 190–192 °C.

4.5. General procedure for the synthesis of isoindolobenzazepine derivatives

To a stirred solution of dehydroisoindolobenzazepines (250 mg) in EtOAc (15 mL), 10% Pd on carbon (51 mg) was slowly added. The mixture was hydrogenated (1 atm, balloon) and when the reaction was complete (TLC showed the absence of the highly fluorescent spot of the starting material), catalyst residue was removed by filtration, washed with EtOAc, and evaporated to dryness to give the required isoindolobenzazepines.

4.5.1. 3,4-Dimethoxy-13,13a-tetrahydro-10,11-methylenedioxy-5*H*-isoindolo[1,2-*b*][3]benzazepine-5-one (1a). White crystals (76%), mp (MeOH) 226–227 °C, lit.[1] 225 °C, lit.[3a] 228–229 °C. lit.[9e] 235–235.5 °C.

4.5.2. 3,4-Dimethoxy-13,13a-tetrahydro-10,11-dimethoxy-5*H*-isoindolo[1,2-*b*][3]benzazepine-5-one (1b). White crystals (80%), mp (MeOH) 213–214 °C, lit.[9c] 213–214 °C.

4.5.3. 7,8,13,13a-Tetrahydro-10,11-dimethoxy-5*H*-isoindolo[1,2-*b*][3]benzazepine-5-one (1c). White crystals (90%), mp (EtOAc) 178–179 °C, lit.[5c] 178–179 °C, lit.[6c] 179 °C.

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