Synthesis of Oxychelerythrine Using Lithiated Toluamide-Benzonitrile Cycloaddition

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Oxychelerythrine, benzo[*c*]phenanthridine alkaloid, was synthesized from easily available starting toluamide 5 and benzonitrile 6 using toluamide-benzonitrile cycloaddition reaction in 6 steps.

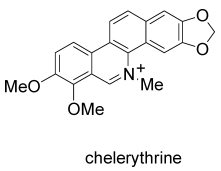
Key words benzo[*c*]phenanthridine; oxychelerythrine; cycloaddition

Chelerythrine, a natural benzo[*c*]phenanthridine alkaloid, has been reported to mediate a variety of biological activities including anti-tumor,[1] inhibition of protein kinase C,[2,3] induction of apoptosis through generation of reactive oxygen[4] and stimulation of GSH transport.[5] Recently, chelerythrine was also proved to inhibit the BclXL function[6] and it was considered to open up new therapeutic treatments, while the diverse modification of chemical structures has not been systematically exploited yet. Due to the interesting biological activities, the synthesis of fully aromatized benzo[*c*]-phenanthridine alkaloids has been attractive target for organic chemists.[7—11] For overcoming the disadvantages of reported methods we have investigated the efficient and rapid methods for above alkaloids and recently reported a versatile synthetic ways for these alkaloids such as oxynitidine, oxysanguinarine and oxyavicine using lithiated toluamide-benzonitrile cycloaddition.[12,13] To validate the general application of our developed cycloaddition method, we attempted to apply this to synthesis of oxychelerythrine.

Our strategy is based on the formation of 3-arylisoquinoline which could be transformed to benzo[*c*]phenanthridine alkaloid *via* intramolecular enamide ring formation reaction. The advantages of this methodology include easy access to the starting material and a one-pot procedure for constructing essential carbon atoms for desired alkaloid. Retrosynthetic consideration of oxychelerythrine indicates that the coupling of *o*-toluamide **5** with benzonitrile **6** affords 3-arylisoquinoline, which could be converted to an aldehyde and consecutive C ring construction of oxychelerythrine could be performed by an intramolecular ring cyclization method as outlined in Chart 1.

The starting benzylamine **1** was treated with ethyl chloroformate and *n*-BuLi to give benzoate **2**, which was then reduced with $NaBH_4$ in DMSO to afford *o*-methyl benzoate **3** in 84% overall yield.[14] After the hydrolysis of **3** with 10% NaOH, benzoic acid **4** was treated with oxalyl chloride/40% $MeNH_2$ to provide the *o*-methyl toluamide **5** in good yield as shown in Chart 2.

The toluamide-benzonitrile cycloadditon reaction and the synthesis of oxychelerythrine are shown in Chart 3. The deprotonation of **5** with two equivalent *n*-BuLi gave dianion, which was treated with MOM protected benzonitrile **6** to afford the 3-arylisoquinolin-1(2*H*)-one **7** in 40% yield. **7** was then reacted with MeI in the presence of 60% NaH to give *N*-methylated compounds **8** without giving *O*-methylated one in 80% yield. Deprotection of **8** with 10% HCl gave the alcohol **9** in 86% yield, which was oxidized with PDC to afford aldehyde **10** in 90% yield, which was then treated with Ph_3PCH_2OMe/*n*-BuLi to give the olefins **11** as *E*/*Z* (1 : 1) mixture in 56% yield. Hydrolysis of **11** with 10% HCl produced the desired benzo[*c*]phenanthridine compound oxychelerythrine **13** in 73% yield. In this reaction we assumed that hydrolysis produced the aldehyde **12** and the consecutive intramolecular enamide–aldehyde cyclization occurred under an acidic condition. After ring formation, dehydration would easily occur thus producing a fully aromatized ring system of benzo[*c*]phenanthridine. Herein, we have also accomplished the formal synthesis of chelerythrine because the process to this alkaloid from the corresponding oxychelerythrine was



chelerythrine

Fig. 1. Structure of Chelerythrine

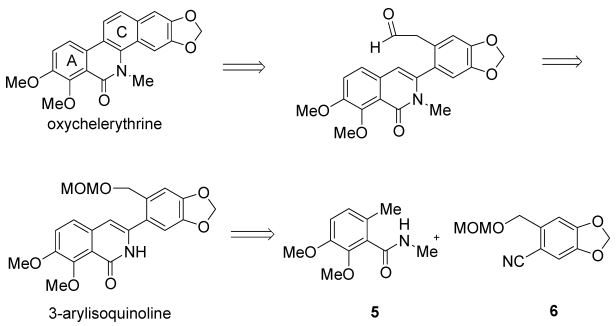


Chart 1. Retrosythesis of Chelerythrine

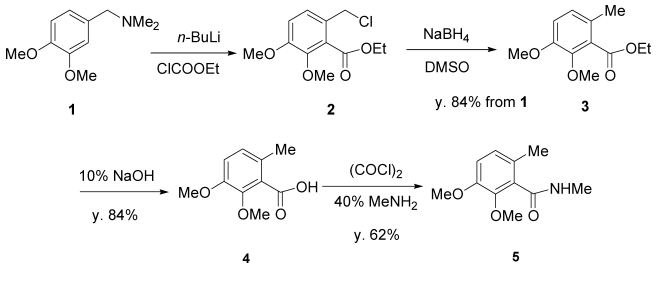


Chart 2. Synthesis of *N*-Methyltoluamide **5**

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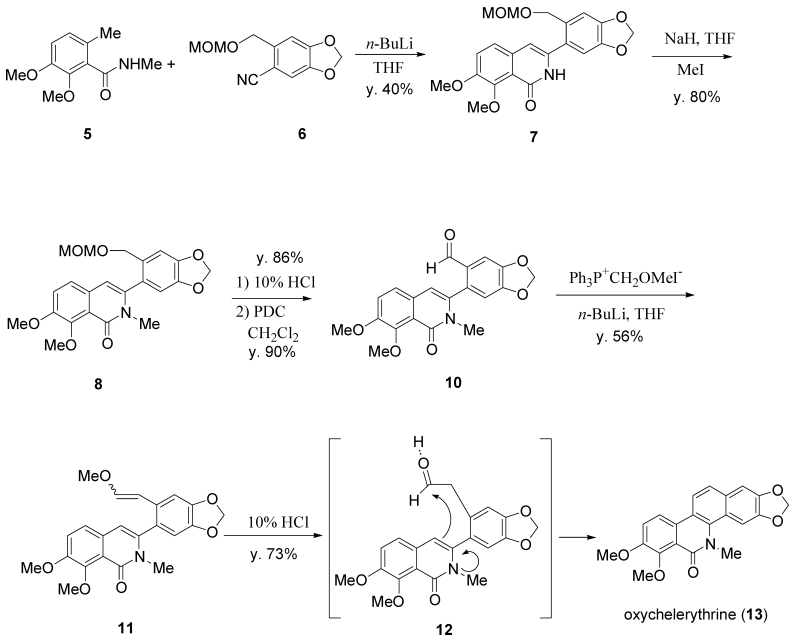

Chart 3. Synthesis of Chelerythrine

already established.[15)]

Thus we have synthesized oxychelerythrine in six steps from toluamide **5** and benzonitrile **6** using our developed synthetic methodology.

Experimental

Melting points were determined on an Electrothermal IA9200 melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Bruker AC 80 and a Varian 300 spectrometer, using TMS as the internal standard; chemical shifts are reported in parts per million and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). IR spectra were recorded on a Perkin-Elmer 783 spectrometer and a Nicolet instrument using KBr pellets. Elemental analyses were performed on a CaHo Erba elemental analyzer. Solvents were routinely distilled prior to use. Anhydrous THF was distilled from sodium-benzophenon ketyl. Column chromatography was performed on Merck silica gel 60 (70—230 mesh). TLC was carried out using plates coated with silicagel 60F 254 purchased from Merck Co. Reagents were obtained from commercial suppliers and were used without purification.

Ethyl 2,3-Dimethoxy-6-methylbenzoate (3) To a solution of benzylamine **1** (39 g, 200 mmol) in dry THF (500 ml) was added *n*-BuLi (88 ml of 2.5 M in hexane, 220 mmol) at 0 °C and the reaction was stirred at the same temperature for 1 h. After cooling the reaction vessel to −78 °C, ethyl chloroformate (45.6 g, 420 mmol) was added all at once. The reaction mixture was warmed to room temperature and stirred for 12 h. The solvent was evaporated off and the residue was dissolved with DMSO (300 ml). To this $NaBH_4$ (7.6 g, 200 mmol) was added and the reaction was stirred for 4 h at 60 °C. The reaction was quenched with water and extracted with ether. The organic layers were washed with water, brine and dried over anhydrous sodium sulfate. After removing the solvent, the residue was purified by column chromatography with *n*-hexane–ethyl acetate (10 : 1) to afford the benzoate **3** as a yellow oil[16)] (37.6 g, 84%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.88 (s, 1H), 6.85 (s, 1H), 4.39 (q, J=7.1 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 2.23 (s, 3H), 1.37 (t, J=7.1 Hz, 3H). MS *m/z* (%): 224 (M^+, 100).

2,3-Dimethoxy-6-methylbenzoic Acid (4) The reaction mixture of benzoate **3** (22.4 g, 100 mmol) and 10% NaOH (150 ml) in MeOH (150 ml) was refluxed for 12 h. After cooling the reaction mixture, methanol was evaporated off and the mixture was extracted with methylene chloride. The aqueous layer was separated and acidified with concentrated HCl. The residue was then extracted with methylene chloride. The organic layers were washed with water, brine, dried and concentrated to provide benzoic acid **4** as a yellow solid (16.5 g, 84%). mp 89.8—91.7 °C. (lit.[16)] 89—90 °C). IR (KBr) cm^{-1}: 1700 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.92 (m, 2H), 3.93 (s, 3H), 3.86 (s, 3H), 2.39 (s, 3H). MS *m/z* (%): 196 (M^+, 30).

2,3-Dimethoxy-*N*-6-dimethylbenzamide (5) To a suspension of benzoic acid **4** (16.5 g, 84 mmol) and pyridine (12 ml) in CH_2Cl_2 (80 ml) was slowly added oxalyl chloride (45 ml, 515 mmol) with stirring. After an additional 2 h stirring, the excess of oxalyl chloride was removed by co-distillation with benzene. The residue was dissolved in CH_2Cl_2 (60 ml) and 40% methylamine (52.2 g, 1.68 mol) was added at 0 °C. After 1 h, the reaction was diluted with water and the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were washed with water, brine, dried and then concentrated. The residue was purified by recrystallization with ether to give amide **5** as a yellow solid (10.9 g, 62%). mp 132.1—133.9 °C. IR (KBr) cm^{-1}: 3280 (NH), 1640 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.87 (d, J=8.1 Hz, 1H), 6.80 (d, J=8.1 Hz, 1H), 5.85 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.00 (d, J=4.9 Hz, 3H), 2.26 (s, 3H). MS *m/z* (%): 209 (M^+, 75), 179 (100), 136 (20). *Anal.* Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.28; H, 7.38; N, 6.70.

7,8-Dimethoxy-3-(6-methoxymethoxymethylbenzo[1,3]dioxol-5-yl)-2*H*-isoquinolin-1-one (7) To a solution of amide **5** (1.96 g, 9.4 mmol) in dry THF (30 ml) was added *n*-BuLi (9 ml of 2.5 M in hexane, 22.5 mmol) at −20 °C and maintained the reaction temperature never exceeded to 20 °C. After the addition was completed, the red orange solution was stirred for 1 h at 0 °C. The reaction vessel was cooled to −50 °C and benzonitrile **6** (1.4 g, 6.3 mmol) was added. The reaction mixture was stirred for 20 min at the same temperature and then allowed to warm up to room temperature. The reaction was quenched with water and extracted with ethyl acetate. The organic layers were washed with water, brine and dried over sodium sulfate. After removing the solvent *in vacuo*, the residue was purified by column chromatography with *n*-hexane–ethyl acetate (1 : 1) to afford 3-arylisoquinoline **7** as a yellow solid (1.01 g, 40%). mp 151.0—154.2 °C. IR (KBr) cm^{-1}: 3400 (NH), 1650 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34 (d, J=9.0 Hz, 1H), 7.27 (d, J=9.0 Hz, 1H), 6.96 (s, 1H), 6.93 (s, 1H), 6.37 (s, 1H), 6.04 (s, 2H), 4.83 (s, 2H), 4.47 (s, 2H), 3.98 (s, 3H), 3.97 (s, 3H), 3.43 (s, 3H). MS, *m/z* (%): 399 (M^+, 18), 354 (42), 336 (70), 222 (100), 162 (38). *Anal.* Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 63.45; H, 5.27; N, 3.66.

7,8-Dimethoxy-3-(6-methoxymethoxymethylbenzo[1,3]dioxol-5-yl)-2-methyl-2*H*-isoquinolin-1-one (8) To a solution of amide **7** (600 mg, 1.5 mmol) in THF (10 ml) was added 60% NaH dispersion (128 mg, 3.2 mmol) at 0 °C under nitrogen. The resulting mixture was stirred at the same temperature for 1 h. After removal of the ice bath, methyl iodide (425 mg, 3 mmol) in THF (3 ml) was added and the reaction mixture was warmed up to 60 °C and stirred for 2 h. The reaction was quenched with water and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, brine and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by column chromatography on silica gel with *n*-hexane–ethyl acetate (1 : 1) to give *N*-methylated

amide **8** as a yellow oil (496 mg, 80%). IR neat cm^{-1}: 1650 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.33 (d, J=9.0 Hz, 1H), 7.20 (d, J=9.0 Hz, 1H), 7.03 (s, 1H), 6.72 (s, 1H), 6.29 (s, 1H), 6.04 (s, 2H), 4.57 (s, 2H), 4.35 (s, 2H), 4.02 (s, 3H), 3.96 (s, 3H), 3.25 (s, 3H), 3.25 (s, 3H). MS *m*/*z* (%): 413 (M^+, 46). HR-MS-EI (Calcd for $C_{22}H_{23}NO_7$): 413.4196, found: 413.4193.

3-(6-Hydroxymethylbenzo[1,3]dioxol-5-yl)-7,8-dimethoxy-2-methyl-2*H*-isoquinolin-1-one (9) To a solution of *N*-methyl amide **8** (415 mg, 1 mmol) in methanol (15 ml) was added concentrated HCl (1 ml) and the reaction mixture was refluxed for 3 h. After removal of the methanol *in vacuo*, the residue was poured into water and extracted with ethyl acetate. The ethyl acetate extracts were washed with water, brine and dried over anhydrous sodium sulfate. The solvent was evaporated off and the residue was purified by column chromatography on silica gel with *n*-hexane–ethyl acetate (1 : 2) to give the alcohol **9** as a white solid (317 mg, 86%). mp 171.6—173.2 °C. IR (KBr) cm^{-1}: 3400 (OH), 1645 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.32 (d, J=9.0 Hz, 1H), 7.19 (d, J=9.0 Hz, 1H), 7.08 (s, 1H), 6.71 (s, 1H), 6.29 (s, 1H), 6.04 (s, 2H), 4.46 (s, 2H), 4.01 (s, 3 H), 3.95 (s, 3H), 3.24 (s, 3H). MS, *m*/*z* (%): 369 (M^+, 100). *Anal.* Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 65.23; H, 5.48; N, 3.97.

6-(7,8-Dimethoxy-2-methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)benzo[1,3]dioxole-5-carbadehyde (10) To a solution of alcohol **9** (290 mg, 0.78 mmol) in methylene chloride (15 ml) was added PDC (440 mg, 1.17 mmol) and the mixture was stirred for 2 h. Reaction mixture was filtered and washed with methylene chloride. The solvent was evaporated off and the residue was purified by column chromatography on silica gel with *n*-hexane–ethyl acetate (2 : 1) to afford the aldehyde **10** as a pale white solid (257 mg, 90%). mp 209.6—212 °C. IR (KBr) cm^{-1}: 1680, 1650 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.80 (s, 1H), 7.47 (s, 1H), 7.34 (d, J=9.0 Hz, 1H), 7.20 (d, J=9.0 Hz, 1H), 6.83 (s, 1H), 6.31 (s, 1H), 6.16 (s, 2H), 4.08 (s, 3H), 3.99 (s, 3H), 3.30 (s, 3H). MS *m*/*z* (%): 367 (M^+, 100), 352 (40), 338 (25), 190 (50). *Anal.* Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.47; H, 4.89; N, 3.68.

7,8-Dimethoxy-3-[6-(2-methoxyvinyl)benzo[1,3]dioxol-5-yl]-2-methyl-2*H*-isoquinolin-1-one (11) To a solution of (methoxymethyl)triphenylphosphonium chloride (178 mg, 0.52 mmol) in dry THF (15 ml) was added *n*-BuLi (0.35 ml of 1.6 M in hexane, 0.56 mmol) at 0 °C and the mixture was stirred for 1 h at 0 °C. To this a solution of aldehyde **10** (50 mg, 0.14 mmol) in THF (5 ml) was added and the reaction mixture was stirred for 3 h at room temperature. The reaction was quenched with water and extracted with ethyl acetate. The organic layers were washed with water, brine and dried over sodium sulfate. After removal of the solvent, the residue was purified by column chromatography with *n*-hexane–ethyl acetate (3 : 1) to afford the mixture **11** as *cis*/*trans* (1 : 1) as a brown oil (30 mg, 56%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (*cis*): 7.77 (s, 1H), 7.31 (d, J=9.0 Hz, 1H), 7.19 (d, J=8.9 Hz, 1H), 6.70 (s, 1H), 6.28 (s, 1H), 6.00 (s, 2H), 5.98 (d, J=7.1 Hz, 1H), 4.86 (d, J=7.1 Hz, 1H), 4.02 (s, 3H), 3.96 (s, 3H), 3.75 (s, 3H), 3.25 (s, 3H). δ (*trans*): 7.20 (d, J=9.0 Hz, 1H), 7.19 (d, J=9.0 Hz, 1H), 6.89 (s, 1H), 6.88 (d, J=12.8 Hz, 1H), 6.70 (s, 1H), 6.28 (s, 1H), 6.00 (s, 2H), 5.48 (d, J=12.8 Hz, 1H), 3.47 (s, 3H), 3.25 (s, 3H). MS *m*/*z* (%): 395 (M^+, 30), 258 (42), 229 (100), 201 (58).

Oxychelerythrine (13) A solution of *cis*/*trans* isomer **11** (25 mg, 0.06 mmol) in methanol (5 ml) and HCl 10% (3 ml) was refluxed for 3 h. After the removal of methanol, the residue was poured into water and extracted with ethyl acetate. The ethyl acetate extracts were washed with water, brine and dried over anhydrous sodium sulfate. The solvent was evaporated off and the residue was purified by column chromatography on silica gel with *n*-hexane–ethyl acetate (1 : 2) to give oxychelerythrine **13** as a solid (16 mg, 73%). mp 198—199 °C. (lit.[17] 197—198 °C). IR (KBr) cm^{-1}: 1645 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.00 (d, J=9.0 Hz, 1H), 7.98 (d, J=9.0 Hz, 1H) 7.58 (d, J=9.0 Hz, 1H), 7.38 (d, J=9.0 Hz, 1H), 7.52 (s, 1H), 7.16 (s, 1H), 6.10 (s, 2H), 4.08 (s, 3H), 3.98 (s, 3H), 3.90 (s, 3H). MS *m*/*z* (%): 363 (M, 35), 348 (15), 334 (14), 305 (18), 190 (20), 57 (100). *Anal.* Calcd for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72; N, 3.85. Found: C, 69.63; H, 4.69; N, 3.87.

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