A novel C-C radical-radical coupling reaction promoted by visible light: facile synthesis of 6-substituted N-methyl 5,6-dihydrobenzophenanthridine alkaloids

Zhaoying Liu, a Yajun Huang, a Hongqi Xie, a,b Wei Liu, a Jianguo Zeng, a,b Pi Cheng* a,b

a National and Provincial Union Engineering Research Center for the Veterinary herbal Medicine Resources and Initiative, Hunan Agricultural University, Changsha, Hunan 410128, China.
b Hunan Co-Innovation Center for Utilization of Botanicals Functional Ingredients, Hunan Agricultural University, Changsha, Hunan 410128, China.

*E-mail: picheng55@126.com; Fax: +86 731 84686560
# Table of contents

General..................................................................................................................................................3  
Experimental procedure for synthesis of compounds 14.................................................................3  
HPLC-Q-TOF analysis for the crude product from Table 1, entry 3.................................................4  
NMR spectra of byproduct from Table 1, entry 3.............................................................................5  
HPLC-Q-TOF analysis for the crude product of compound 14c.....................................................6  
HPLC-Q-TOF and GC-MS analysis for the radical trapping experiment......................................7  
Characteristic data of targets compounds 14....................................................................................9  
NMR spectra of compounds 14..........................................................................................................13  
NMR data and spectra of compounds 19..........................................................................................23  
NMR data and spectra of synthetic compound 4............................................................................26
General:

Column chromatography silica gel (200-300 mesh) and TCL plate were purchased from Qingdao Meijin Chemical Inc (Qingdao; China); HRMS data were obtained in the ESI mode on an Agilent 6530 Q-TOF/MS system; GC-MS data were obtained on an Agilent GCMS-QP2010 system. $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker 400 MHz spectrometer and chemical shifts were given in $\delta$ with TMS as an internal reference. Dihydrosanguinarine and dihydrochelerythrine were isolated from Macleaya Cordata in our lab.

Representative experimental procedure for visible light promoted synthesis of 6-substituted 5,6-dihydrobenzophenanthridine.

A solution of dihydrosanguinarine 5 (0.2 mmol), 3.0 eq of Na$_2$HPO$_4$, Ir(ppy)$_3$ (2 mol%) and 3.0 equiv of BrCH$_2$COOEt in DMF (2 mL) was firstly bubbled with nitrogen for 10 minutes and then irradiated with 25 W household compact fluorescent lamp under nitrogen atmosphere. After 24 h reaction, the resulting mixture was poured into water (50 mL) and then extracted with EtOAc (20 mL×3). The combined organic solution was then washed with water (20 mL×3). The organic layers were washed with brine and dried over MgSO$_4$. The solvent were removed via vacuo and the residue was purified by flash column chromatography (SiO$_2$) with petroleum ether/AcOEt (8:1) to give target compound 14a.
**HPLC-Q-TOF analysis for the crude product from Table 1, entry 3 (Na$_2$CO$_3$ used as base)**

Based on previous literature, if $\alpha$-bromo carbonyl compounds were used as radical precursor, Na$_2$HPO$_4$ was the mostly used deacid reagent along with DMF as solvent (Angew. Chem. Int. Ed. 2013, 52, 13289; Org. Lett., 2013, 18, 4884; Angew. Chem. Int. Ed. 2015, 54, 15545). Based on the reviewer’s comments, we analyzed the crude product when Na$_2$CO$_3$ was used. After 24 h reaction, HPLC-HRMS analysis (Figure 1s) showed that a major byproduct with m/z value of 405.1435 was detected (peak 2, Figure 1s). Because a positive mode was applied in the MS analysis, peak 2 (m/z = 405.1435) should belong to a byproduct that possessed two nitrogen atoms. Thus we suggested that if Na$_2$CO$_3$ was used in the reaction, dihydrosanguinarine would react with solvent DMF. This byproduct was unstable during the silica gel column chromatography isolation process, and we only obtained the byproduct with low purity.

Figure 1s. HPLC-HRMS analysis of crude product using Na$_2$CO$_3$ as base
NMR spectra of byproduct from Table 1, entry 3

Figure 2s. NMR spectra of byproduct when Na$_2$CO$_3$ was used as base
**HPLC-Q-TOF analysis for the crude product of compound 14c**

We analyzed the crude product of 14c based on HPLC-HRMS technology (Figure 3s). Interestingly, target compound 14c was detected in moderate HPLC yield. But we didn’t isolate compound 14c after column chromatography at 0.2 mmol scales which indicated that compound 14c was not stable during purification process. To obtain pure compound 14c, the coupling reaction was performed in 0.6 mmol scales again, but only isolated in 8% yield.

Figure 3s. HPLC-HRMS analysis of crude product 14c

As shown in Figure 4s, we firstly isolated compound 14c by column chromatography, but an impurity generated during the isolation process (Figure 4, A). Thus, we purified combined fractions of compound 14c using preparation TLC again (Figure 4, B). But another impurity generated as shown in Figure 4, B. Finally, compound 14c was obtained only in 8% isolated yield. As a result, we thought that it was the poor stability of compound 14c but not the enolization of diethyl bromomalonate that led to the poor isolated yield.

Figure 4s. Column chromatography (A) and preparation TLC (B) isolation of compound 14c
HPLC-Q-TOF and GC-MS analysis for the radical trapping experiment

We proposed that hydrogen atom transfer (HAT) process existed between aminium radical cation 12 and
TEMPO. This HAT process promotes the yield of sanguinarine in the radical trapping experiment.

On the other hand, we analyzed the crude product from radical trapping experiment using GC-MS. The coupling product of TEMPO with radical 11 was detected as shown in Figure 6s:

Figure 6s. GC-MS analysis of crude product from radical coupling experiment
Characterization data of compounds 14

**Ethyl 2’-(5,6-dihydrosanguinarine-6-yl)acetate (14a):** Obtained as pale yellow amorphous powder, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 7.68 (d, $J = 8.4$ Hz, 1H), 7.56 (s, 1H), 7.47 (d, $J = 8.4$ Hz, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.09 (s, 1H), 6.86 (d, $J = 8.0$ Hz, 1H), 6.05-6.03 (m, 4H), 4.83 (t, $J = 8.0$ Hz, 1H), 4.16 (m, 2H), 2.66 (s, 3H), 2.39 (d, $J = 8.0$ Hz, 2H), 1.21 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 171.5, 148.2, 147.7, 147.2, 144.6, 139.4, 131.1, 127.8, 125.9, 124.1, 123.4, 120.1, 116.6, 115.8, 107.8, 104.4, 101.6, 101.1, 101.0, 60.5, 54.9, 43.2, 39.1, 14.4. HRMS (ESI$^+$): calcd 420.1441 for C$_{24}$H$_{22}$NO$_6$ [M+H]$^+$; found, 420.1450.

**Ethyl 2’-(5,6-dihydrosanguinarine-6-yl)propanoate (14b):** Obtained as white amorphous powder, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 7.16-7.64, 7.48-7.45 (m, 3H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.10 (two s, 1H), 6.90-6.85 (two d, $J = 8.0$ Hz, 1H), 4.51 (d, $J = 11.2$ Hz, 0.5H), 4.46 (d, $J = 9.2$ Hz, 0.5H), 4.18-3.98 (m, 2H), 2.68, 2.62 (two s, 3H), 2.48-2.38 (m, 1H), 1.14-1.05 (m, 6H). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 175.9, 174.7, 148.3, 148.0, 147.7, 147.6, 147.1, 147.0, 145.0, 139.9, 139.7, 131.2, 131.1, 127.6, 126.2, 124.0, 123.9, 123.5, 120.2, 120.0, 116.9, 116.8, 114.3, 107.9, 107.8, 104.6, 104.4, 101.4, 101.2, 100.8, 60.7, 60.4, 60.3, 60.0, 44.2, 43.7, 43.3, 42.9, 14.3, 14.2, 14.2, 14.1. HRMS (ESI$^+$): calcd 434.1598 for C$_{25}$H$_{24}$NO$_6$ [M+H]$^+$; found, 434.1597.

**Ethyl 2’-(5,6-dihydrosanguinarine-6-yl)maonlate (14c):** Obtained as white amorphous powder, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 7.71 (d, $J = 8.8$ Hz, 1H), 7.48 (d, $J = 8.4$ Hz, 1H), 7.42 (s, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.10 (s, 1H), 6.87 (d, $J = 8.4$ Hz, 1H), 6.03-6.00 (m, 4H), 5.10 (d, $J = 7.2$ Hz, 1H), 4.24-4.12 (m, 2H), 4.04-4.00 (m, 2H), 3.41 (d, $J = 7.2$ Hz, 1H), 2.67 (s, 3H), 1.14 (t, $J = 7.2$ Hz, 3H), 1.08 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 167.7, 166.9, 148.2, 147.7, 147.2, 145.5, 138.7, 131.2, 127.4, 126.2, 124.3, 123.6, 120.1, 117.0, 112.7, 108.3, 104.5, 101.6, 101.2, 100.8, 61.4, 61.4, 57.3, 55.5, 42.4, 14.1,
13.9. HRMS (ESI\(^+\)): calcd 492.1653 for C\(_{27}H_{26}NO_8^+\) [M+H]\(^+\); found, 492.1649.

6-Nitrilemethyl dihydrosanguinarine(14d): Obtained as pale yellow amorphous powder, \(^1\)H NMR (400MHz, CDCl\(_3\)): \(\delta\) 7.76 (s, 1H), 7.67 (d, \(J = 8.4\) Hz, 1H), 7.51 (d, \(J = 8.4\) Hz, 1H), 7.36 (d, \(J = 8.4\) Hz, 1H), 7.11 (s, 1H), 6.90 (d, \(J = 8.4\) Hz, 1H), 6.08-6.06 (m, 4H), 4.66 (t, \(J = 7.6\) Hz, 1H), 2.72 (s, 3H), 2.44 (d, \(J = 7.6\) Hz, 2H). \(^{13}\)C NMR (100MHz, CDCl\(_3\)): \(\delta\) 148.7, 148.1, 147.5, 145.0, 138.1, 131.4, 127.7, 125.4, 124.7, 122.9, 119.9, 117.8, 116.9, 113.8, 108.6, 104.4, 101.9, 101.3, 101.0, 54.6, 43.2, 22.6. HRMS (ESI\(^+\)): calcd 373.1183 for C\(_{22}H_{17}N_2O_4^+\) [M+H]\(^+\); found, 373.1191.

1'-phenyl-2'-(5,6-dihydrosanguinarine-6-yl)ethanone(14e):
 Obtained as pale yellow amorphous powder, \(^1\)H NMR (400MHz, CDCl\(_3\)): \(\delta\) 7.73 (d, \(J = 8.8\) Hz, 1H), 7.67 (d, \(J = 7.6\) Hz, 2H), 7.48 (d, \(J = 8.2\) Hz, 1H), 7.41 (t, \(J = 7.2\) Hz, 1H), 7.36 (d, \(J = 8.0\) Hz, 1H), 7.26-7.20 (m, 3H), 7.06 (s, 1H), 6.86 (d, \(J = 8.0\) Hz, 1H), 6.02 (dd, \(J = 1.2, 9.6\) Hz, 2H), 5.97 (dd, \(J = 1.2, 8.8\) Hz, 2H), 5.04 (dd, \(J = 4.8, 10.0\) Hz, 1H), 3.27 (dd, \(J = 10.0, 14.8\) Hz, 1H), 2.80-2.76 (m, 1H), 2.63 (s, 3H). \(^{13}\)C NMR (100MHz, CDCl\(_3\)): \(\delta\) 198.8, 148.0, 147.7, 147.3, 144.5, 137.4, 132.7, 131.1, 128.5, 128.4 (\(\times 4\)), 127.7, 126.0, 124.1, 123.5, 120.1, 116.6, 116.5, 107.7, 104.2, 101.7, 101.1, 101.0, 55.2, 43.2, 42.1. HRMS (ESI\(^+\)): calcd 452.1492 for C\(_{28}H_{22}NO_5^+\) [M+H]\(^+\); found, 452.1493.

1'-(-4-Nitrophenyl)-2'-(5,6-dihydrosanguinarine-6-yl)ethanone(1f):
 Obtained as light red amorphous powder, \(^1\)H NMR (400MHz, CDCl\(_3\)): \(\delta\) 7.95 (d, \(J = 8.8\) Hz, 2H), 7.72 (d, \(J = 8.4\) Hz, 1H), 7.68 (d, \(J = 8.4\) Hz, 2H), 7.49 (d, \(J = 8.4\) Hz, 1H), 7.36 (d, \(J = 8.0\) Hz, 1H), 7.03 (s, 1H), 6.99 (d, \(J = 8.0\) Hz, 1H), 6.07 (dd, \(J = 1.2, 4.8\) Hz, 2H), 5.90 (dd, \(J = 1.2, 16\) Hz, 2H), 4.97 (dd, \(J = 4.4, 10.4\) Hz, 1H), 3.35 (dd, \(J = 12.8, 10.4\) Hz, 1H), 2.72 (dd, \(J = 4.4, 12.8\) Hz, 1H), 2.56 (s, 3H). \(^{13}\)C NMR (100MHz, CDCl\(_3\)): \(\delta\) 198.2, 150.0, 147.8, 147.6, 147.4, 144.5, 141.7, 138.8, 131.0, 129.2 (\(\times 2\)), 127.4, 125.8, 124.4, 123.6, 123.5 (\(\times 2\)), 120.1, 116.8, 115.7, 108.1, 104.3, 101.8, 101.3, 100.4, 56.6, 43.2, 41.7. HRMS (ESI\(^+\)): calcd 497.1343 for
1'--(4-methoxyphenyl)-2'-((5,6-dihydrosanguinarine-6-yl)ethanone (14g): Obtained as pale yellow amorphous powder, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 7.75 (d, $J = 8.8$ Hz, 1H), 7.59 (d, $J = 8.8$ Hz, 2H), 7.50 (d, $J = 8.8$ Hz, 1H), 7.38 (d, $J = 8.4$ Hz, 1H), 7.13 (s, 1H), 6.88 (d, $J = 8.0$ Hz, 1H), 6.65 (d, $J = 8.8$ Hz, 2H), 6.06-5.95 (m, 4H), 5.03 (dd, $J = 10.4$, 4.8 Hz, 1H), 3.79 (s, 3H), 3.27 (dd, $J = 14.4$, 10.4 Hz, 1H), 2.67(dd, $J = 14.4$, 4.4 Hz, 1H), 2.63 (s, 3H). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 197.5, 163.3, 147.9, 147.5, 147.3, 144.5, 139.6, 131.0, 130.7, 130.6 ($\times$2), 127.8, 126.0, 124.0, 123.6, 120.1, 116.7, 116.5, 113.4 ($\times$2), 107.7, 104.0, 101.7, 101.2, 101.1, 55.7, 55.4, 43.1, 41.4. HRMS (ESI$^+$): calcd 482.1598 for C$_{29}$H$_{24}$NO$_6^+$ [M+H]$^+$; found, 482.1599.

Ethyl 2'-(5,6-dihydrochelerythrine-6-yl)acetate (14h): Obtained as pale yellow amorphous powder, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 7.70 (d, $J = 8.8$ Hz, 1H), 7.55 (d, $J = 8.8$ Hz, 1H), 7.54 (s, 1H), 7.47 (d, $J = 8.8$ Hz, 1H), 7.10 (s, 1H), 6.96 (d, $J = 8.8$ Hz, 1H), 6.03 (s, 2H), 5.00 (dd, $J = 4.4$, 14.4 Hz, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.72 (t, $J = 7.2$ Hz, 2H), 2.65 (s, 3H), 2.33 (m, 2H), 1.82 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 171.8, 152.2, 148.1, 147.6, 145.9, 139.5, 131.2, 128.1, 127.7, 125.1, 123.9, 123.2, 119.9, 118.9, 111.8, 104.4, 101.1, 101.1 (overlapped), 61.2, 60.4, 56.0, 55.2, 43.0, 39.3, 14.4. HRMS (ESI$^+$): calcd 436.1755 for C$_{25}$H$_{26}$NO$_6^+$ [M+H]$^+$; found, 436.1750.

Ethyl 2'-(5,6-dihydrochelerythrine-6-yl)propanoate (14i): Obtained as white amorphous powder, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 7.71 (d, $J = 8.4$ Hz, 1H), 7.70 (d, $J = 8.4$ Hz, 1H), 7.62 (s, 1H), 7.54 (d, $J = 8.4$ Hz, 2H), 7.49 (s, 1H), 7.46 (d, $J = 8.8$ Hz, 1H), 7.45 (d, $J = 8.4$ Hz, 1H), 7.10 (s, 2H), 6.97 (d, $J = 8.8$ Hz, 1H), 6.96 (d, $J = 8.4$ Hz, 1H), 6.04 (s, 2H), 6.02 (s, 2H), 4.71-4.68 (m, 2H), 4.15-4.03 (m, 4H), 3.94 (s, 3H), 3.94 (s, 3H), 3.91 (s, 3H), 3.91 (s, 3H), 2.68 (s, 3H), 2.61 (s, 3H), 2.53-2.49 (m, 1H), 2.36-2.32 (m, 1H), 1.40 (t, $J = 7.2$ Hz, 3H).
1.07 (t, J = 7.2 Hz, 3H), 1.00 (d, J = 7.2 Hz, 3H), 0.94 (d, J = 7.2 Hz, 3H). \(^1\)C NMR (100MHz, CDCl\(_3\)): \(\delta\) 176.4, 174.7, 152.1, 152.1, 148.2, 147.9, 147.6, 147.5, 147.2, 146.5, 140.0, 131.2, 131.1, 127.4, 127.1, 126.9, 125.9, 125.5, 125.2, 124.1, 123.8, 123.7, 123.4, 119.9, 119.8, 119.2, 118.8, 111.7, 111.7, 104.5, 104.4, 101.1, 101.0, 100.9, 61.0, 61.0, 60.4, 60.4, 60.2, 60.0, 55.9, 55.9, 44.8, 43.5, 43.5, 42.4, 14.4, 14.2, 14.2, 13.2.

HRMS (ESI\(^+\)): calcd 450.1911 for C\(_{26}\)H\(_{28}\)NO\(_6\)\(^+\) [M+H]\(^+\); found, 450.1912.

**2-(chelerythrine-6-yl)-1-phenylethanone(14j):** Obtained as pale yellow amorphous powder, \(^1\)H NMR (400MHz, CDCl\(_3\)): \(\delta\) 7.73 (d, J = 8.8 Hz, 3H), 7.57 (d, J = 8.8 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.27-7.25 (m, 2H), 7.21 (s, 1H), 7.05 (s, 1H), 6.98 (d, J = 8.4 Hz, 1H), 5.96 (dd, J = 1.2, 9.2 Hz, 2H), 5.20 (dd, J = 3.6, 10.8 Hz, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 3.15 (dd, J = 11.2, 10.8 Hz, 1H), 2.76 (dd, J = 3.6, 10.8 Hz, 1H), 2.59 (s, 3H). \(^{13}\)C NMR (100MHz, CDCl\(_3\)): \(\delta\) 199.0, 152.3, 147.9, 147.6, 145.7, 139.6, 137.4, 132.6, 131.1, 128.7, 128.4(\(\times\)2), 128.3(\(\times\)2), 127.6, 125.2, 123.9, 123.3, 119.8, 118.9, 111.7, 104.2, 101.2, 101.0, 61.1, 56.0, 55.8, 43.0, 42.2. HRMS (ESI\(^+\)): calcd 468.1805 for C\(_{29}\)H\(_{26}\)NO\(_5\)\(^+\) [M+H]\(^+\); found, 468.1820.
$^1$H NMR and $^{13}$C NMR spectra of compounds 14
NMR data and spectra of compounds

5-methylphenanthridin-6(5H)-one (19a): Obtained as white amorphous powder, 
$^1$H NMR (400MHz, CDCl$_3$): $\delta$ 8.53 (dd, J = 0.8, 8.0 Hz, 1H), 8.19 (d, J = 7.6 Hz, 2H), 7.71 
(brt, J = 7.2 Hz, 1H), 7.55 (brt, J = 7.2 Hz, 1H), 7.49 (brtt, J = 7.6 Hz, 1H), 7.34 (dd, J = 
1.2, 8.8 Hz, 1H), 7.25 (brt, J = 7.2 Hz, 1H), 3.76 (brs, 3H). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 161.6, 138.0, 133.5, 
132.4, 129.5, 128.7, 125.6, 123.2, 122.4, 121.6, 119.2, 115.0, 23.0. HRMS (ESI$^+$): calcd 210.0913 for 
C$_{14}$H$_{12}$NO$^+$ [M+H]$^+$; found, 210.0917.

2-fluoro-8,9-dimethoxy-5-methylphenanthridin-6(5H)-one (19b): Obtained as 
white amorphous powder, $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 7.89 (s, 1H), 7.45 (dd, J = 
2.8, 9.6 Hz, 1H), 7.41 (s, 1H), 7.33 (dd, J = 4.8, 9.2 Hz, 1H), 7.22-7.18 (m, 1H), 
4.08 (s, 3H), 4.03 (s, 3H), 3.78 (s, 3H). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 160.9, 158.5 (d, $^3$J$_{F-C}$ = 249.9 Hz), 
153.4, 150.4, 134.1, 127.4, 120.5 (d, $^3$J$_{F-C}$ = 2.8 Hz), 120.1, 116.6 (d, $^3$J$_{F-C}$ = 8.3 Hz), 115.9 (d, $^2$J$_{F-C}$ =23.2 
Hz), 109.3, 108.6 (d, $^2$J$_{F-C}$ = 23.7 Hz), 102.8, 56.4, 56.3, 30.3. HRMS (ESI$^+$): calcd 288.1030 for C$_{16}$H$_{15}$FNO$_3$$^+$
[M+H]$^+$; found, 288.1023.
**NMR data and spectra of synthetic compound 4**

6-hydroxy 5,6-dihydrosanguinarine(4): Obtained as white amorphous powder, $^1$H NMR (400MHz, CDCl$_3$): δ 7.68 (d, $J = 7.6$ Hz, 1H), 7.56 (s, 1H), 7.49 (d, $J = 8.4$ Hz, 1H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.11 (s, 1H), 6.86 (d, $J = 8.0$ Hz, 1H), 6.05 (s, 2H), 6.03 (s, 2H), 4.51-4.47 (m, 1H), 3.82-3.77 (m, 2H), 2.70 (s, 3H), 1.80-1.77 (m, 1H), 1.59-1.55 (m, 1H). $^{13}$C NMR (100MHz, CDCl$_3$): δ 148.6, 147.7, 147.2, 144.5, 139.1, 131.2, 127.3, 125.6, 124.5, 124.0, 120.2, 117.0, 116.8, 107.6, 104.7, 101.6, 101.3, 100.1, 61.6, 56.9, 43.2, 35.4. HRMS (ESI$^+$): calcd 378.1336 for C$_{22}$H$_{20}$NO$_5$ [M+H]$^+$; found, 378.1340.