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Radical-initiated cyclization as a key step for the synthesis of oxoprotoberberine alkaloids

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ABSTRACT

The oxoprotoberberine alkaloids **1a–d** have been synthesized efficiently from the enamide derivatives **2a–d** by a radical-initiated cyclization reaction utilizing *n*-Bu_3SnH/AIBN and CuCl. The enamide derivatives **2a–d** were prepared from phenylethylamine analogues **5a–b**, followed by acylation with acetic anhydride, Bischler–Napieralski cyclization with $POCl_3$ and benzoylation with the corresponding bromobenzoyl chloride, respectively.

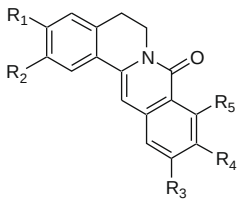
Protoberberines and relative analogues, 8-oxoprotoberberines (Fig. 1) are important group of isoquinoline alkaloids that possess a variety of pharmacological activities.[1,2] Many of them are found in medicinal plants of the genera *Berberis* and *Coptis*,[3,4] which have been used in China and Japan for centuries as a folk medicine in treatment of jaundice, dysentery, diarrhoea and hypertension. Oxoprotoberberine alkaloids with *ortho*-diphenolic substitution on Ring D are found to exhibit cytotoxic, antioxidant and dopaminergic activities.[5] 8-Oxoberberine (**1e**), a derivative of tetrahydroberberine, exerted antiarrhythmic activity and negative chronotropic actions on rat atrial preparations in our previous studies.[6] Recently, oxoprotoberberine alkaloids isolated from the stems of *Cocculus orbiculatus*[7] were also reported to inhibit basal and TPA-mediated PGE2 level.[8]

Many synthetic routes to the biologically active protoberberine or oxoprotoberberine alkaloids have been investigated for a long time.[9,10] Most of these synthetic strategies for oxoprotoberberine alkaloids involved the construction of protoberberine first, and followed by oxidative conversion in the reaction sequence. Herein we try to develop a facile synthesis of oxoprotoberberine alkaloids (**1a–d**) for further biological investigations. The retrosynthetic analysis to construct oxoprotoberberines is shown in Scheme 1. This synthetic strategy involved an intramolecular radical-initiated cyclization. The choice for the preparation of key intermediate enamides **2a–d** was based on our previous study on a one-pot reductive-cyclization synthesis of rutaecarpine. A key precursor of enamide with isomerized exocyclic double bond was formed during the benzoylation process.[11]

The enamide intermediates **2a–d** can be readily synthesized by treating dihyroisoquinolines **4a–b** with a variety of benzoyl chloride derivatives. The formation of enamides **2a–d** could offer a flexible synthetic approach to a range of oxoprotoberberine analogues. Substitutions on ring A or D are easily introduced using appropriate precursors.

The requisite dihydroisoquinolines **4a–b** can be prepared from commercially available phenylethylamines **5a–b** (Scheme 2). Treatment of phenylethylamines **5a–b** with acetic anhydride gave the N-acetylated products **6a–b**. Subsequent Bischler–Napieralski cyclization[12] employing $POCl_3$ in toluene afforded dihydroisoquinolines **4a–b** in good yields.

The bromobenzoyl chloride derivatives, prepared from the corresponding benzoic acids **3a–c** with $SOCl_2$, were added to the dihy-



1a-e

1a : $R_1 = R_2 = R_3 = R_4 = OMe$, $R_5 = H$
1b : $R_1 = R_2 = OMe$, $R_3 = R_4 = R_5 = H$
1c : $R_1 = R_4 = OMe$, $R_2 = R_3 = R_5 = H$
1d : $R_1 = OMe$, $R_2 = R_3 = R_4 = R_5 = H$
1e : $R_1 = R_2 = -OCH_2O-$, $R_4 = R_5 = OMe$, $R_3 = H$

Figure 1. Oxoprotoberberine analogues.

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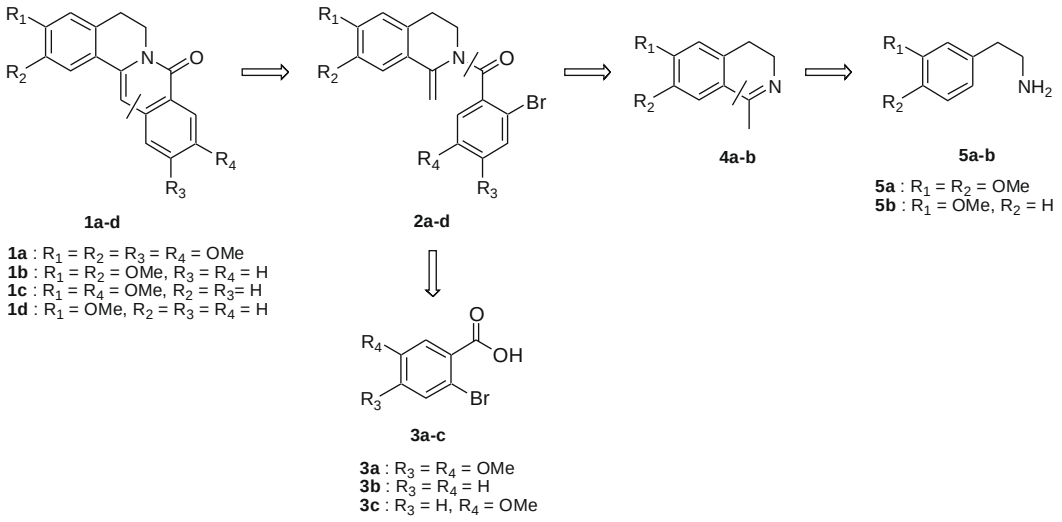
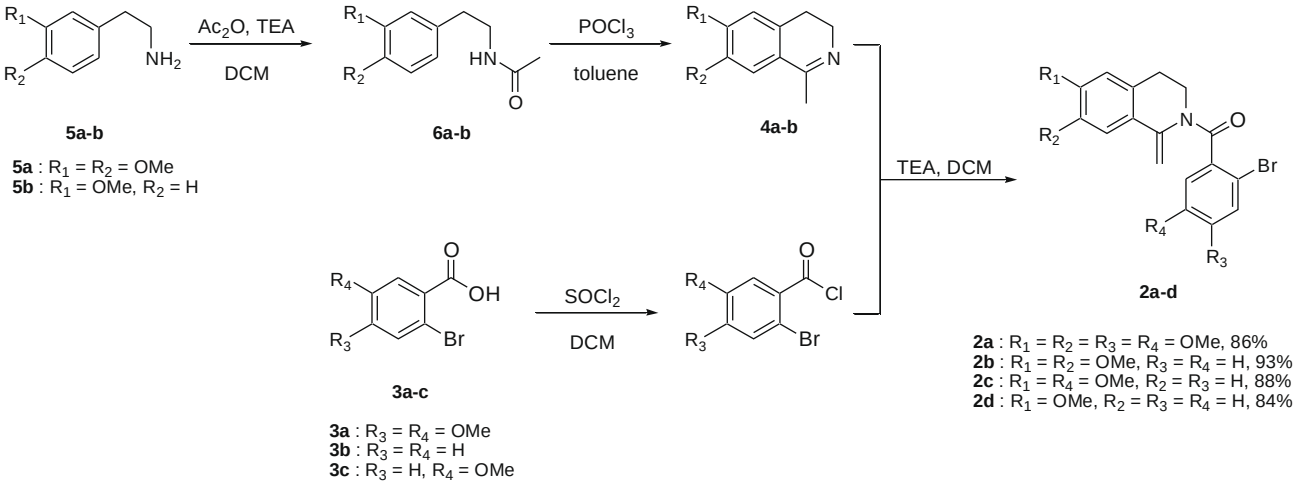
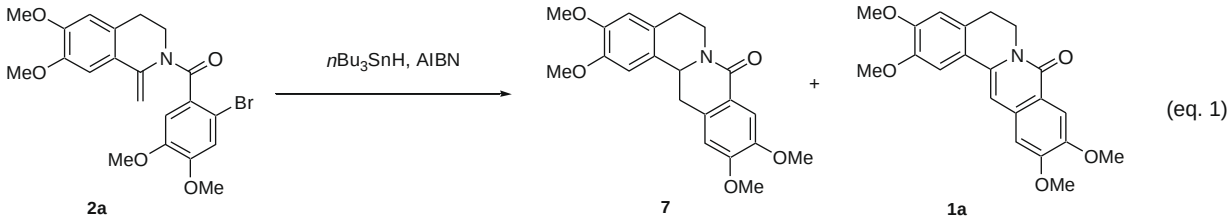


Scheme 1. Retrosynthetic analysis of **1a**–**d**.



Scheme 2. Synthesis of enamide derivatives **2a**–**d**.

Table 1
Radical cyclization reaction of enamide **2a**



Entry	Compound	Solvent	nBu$_3$SnH (equiv)	AIBN (equiv)	Product ratio (**7**: **1a**)	Yield (**7**+**1a**) (%)
1	**2a**	Benzene	2	0.1	6:1	46
2	**2a**	Benzene	3	0.1	6:1	44
3	**2a**	Benzene	2	0.2	4:1	48
4	**2a**	Benzene	2	0.5	1:3	32
5	**2a**	Toluene	2	0.2	4:1	38
6	**2a**	Toluene	2	0.4	1:3	30

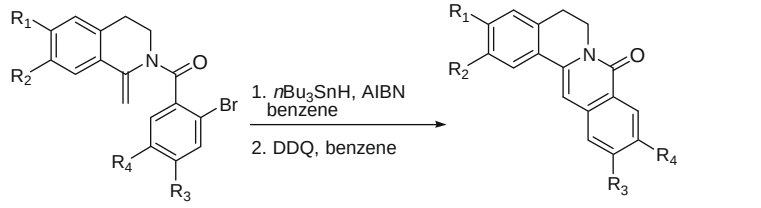
droisoquinolines **4a–b** to afford the requisite benzoylated enamide derivatives **2a–d** in good yields. Bromobenzoic acid derivatives **3a–c** are either commercially available or prepared according to the known procedures from benzaldehyde derivatives.[13,14]

We then took enamide **2a** to investigate the possibility of an intramolecular radical cyclization reaction (Table 1). The reaction solution was stirred in benzene or toluene at reflux under high dilution by adding n-Bu$_3$SnH/AIBN via syringe pump. Numerous

reaction conditions have been examined in the ring cyclization process. Sequential radical cyclization reaction and spontaneous oxidation of dehydrogenation process afforded **7** and **1a** as mixture of adducts. The desired products in this reaction process could be accomplished by adding *n*-Bu_3SnH and AIBN in a 5 h period under reflux in benzene (Table 1). The ratio of reaction adducts mixture **7** and **1a** was determined by signal integration of ^1H NMR of these two compounds.

The synthetic studies in Table 1 showed that radical cyclization of enamides **2a** could afford oxoprotoberberine **1a** and its C13-13a saturated adduct **7** in moderate yield. Slow addition of 2 equiv *n*-Bu_3SnH and 0.2 equiv AIBN to a benzene solution of **2a–d** under reflux condition for 5 h generated 8-oxoprotoberberines **1a–d** and related C13-13a saturated adducts in 48% yields (Table 1, entry 3). Alternatively, the radical cyclization mixtures were not purified. Subsequent dehydrogenation of the mixtures with DDQ gave oxoprotoberberines **1a–d** (Scheme 3). To our knowledge, there are only limited reports regarding the synthesis of oxoportoberberines using *n*-Bu_3SnH/AIBN-initiated reaction in moderate yields as we have achieved.[15] We then tried to reexamine the cyclization pathway to optimize the yield of oxoprotoberberine alkaloids.

Literature search showed that copper(I)-mediated halogen atom transfer radical cyclizations have attracted considerable research interest for years.[16] Recently, more copper(I)-mediated active reactions have been developed to facilitate the cyclization of monobromoderivatives.[17] Therefore, we envisaged the possibility of activating an intramolecular 6-endo ring cyclizations during the construction of oxoprotoberberines. We found that utilization of CuCl with *n*-Bu_3SnH/AIBN during this cyclization reaction process dramatically increased the yield of 8-oxoprotoberberine **1a** with minor amount of C13-13a saturated adduct **7** (Table 2). The addition of 2 equiv CuCl in *n*-Bu_3SnH/AIBN radical-initiated cyclization reaction afforded a clean ring-cyclized 8-oxoprotoberberine **1a** as the only product in 75% yield (Table 2, entry 3). However,



2a-d

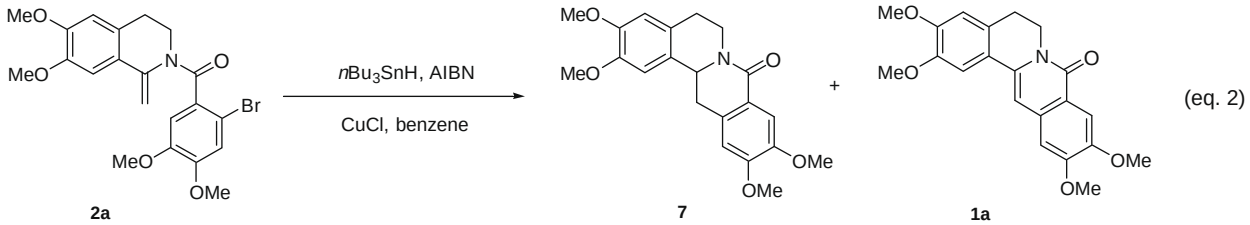
2a : $R_1 = R_2 = R_3 = R_4 = OMe$
2b : $R_1 = R_2 = OMe$, $R_3 = R_4 = H$
2c : $R_1 = R_4 = OMe$, $R_2 = R_3 = H$
2d : $R_1 = OMe$, $R_2 = R_3 = R_4 = H$

1a-d

1a : $R_1 = R_2 = R_3 = R_4 = OMe$, 58%
1b : $R_1 = R_2 = OMe$, $R_3 = R_4 = H$, 56%
1c : $R_1 = R_4 = OMe$, $R_2 = R_3 = H$, 45%
1d : $R_1 = OMe$, $R_2 = R_3 = R_4 = H$, 66%

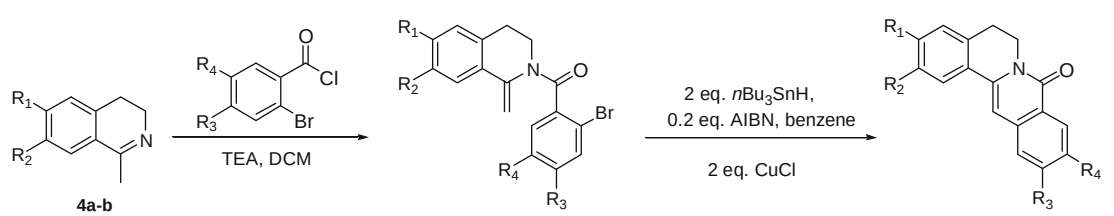
Scheme 3. Synthesis of **1a–d**.

Table 2
Cu(I)-mediated radical cyclization



2a **7** **1a**

Entry	Compound	Solvent	nBu_3SnH (equiv)	AIBN (equiv)	CuCl (equiv)	Product ratio (**7**: **1a**)	Yield (**7**+**1a**) (%)
1	**2a**	Benzene	2	0.2	1	1: 2	50
2	**2a**	Benzene	2	0.2	1.5	1: 3	56
3	**2a**	Benzene	2	0.2	2	Only **1a**	75



4a-b

4a : $R_1 = R_2 = OMe$
4b : $R_1 = OMe$, $R_2 = H$

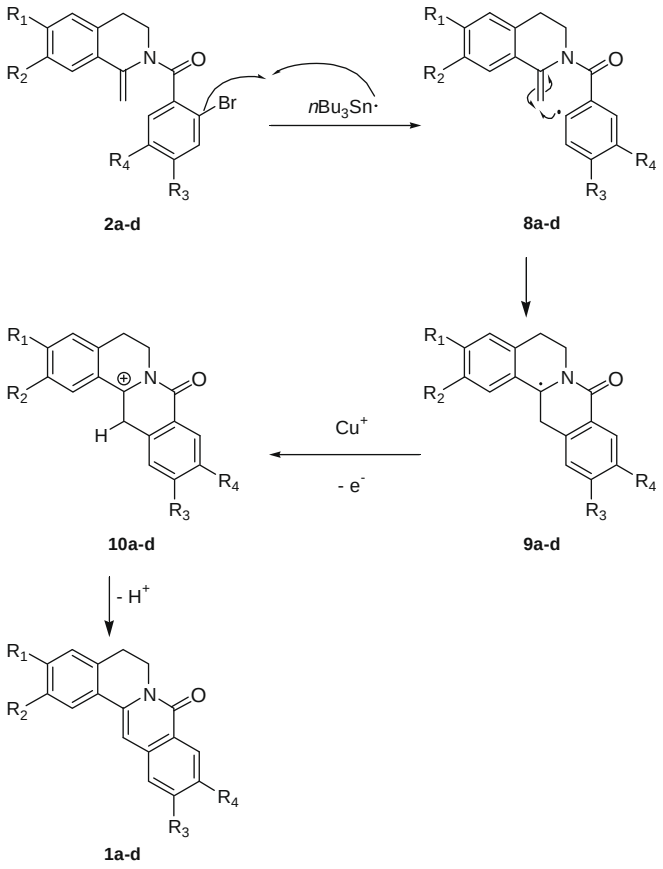
2a-d

2a : $R_1 = R_2 = R_3 = R_4 = OMe$, 86%
2b : $R_1 = R_2 = OMe$, $R_3 = R_4 = H$, 93%
2c : $R_1 = R_4 = OMe$, $R_2 = R_3 = H$, 88%
2d : $R_1 = OMe$, $R_2 = R_3 = R_4 = H$, 84%

1a-d

1a : $R_1 = R_2 = R_3 = R_4 = OMe$, 75%
1b : $R_1 = R_2 = OMe$, $R_3 = R_4 = H$, 78%
1c : $R_1 = R_4 = OMe$, $R_2 = R_3 = H$, 82%
1d : $R_1 = OMe$, $R_2 = R_3 = R_4 = H$. 78%

Scheme 4. Toal synthesis of **1a–d**.



Scheme 5. Cu(I)-mediated radical cyclization.

treating 1 or 1.5 equiv of CuCl in *n*-Bu_3SnH/AIBN radical-initiated cyclization generated a mixture of **7** and **1a** with only 50–56% of the ring-closure adducts (Table 2, entries 1 and 2). Presumably Cu(I) could activate this *n*-Bu_3SnH/AIBN-initiated radical reaction, and also accomplished a Cu(I)-oxidation during the cyclization process. As shown in Scheme 4, this radical cyclization reaction using *n*-Bu_3SnH/AIBN and 2 equiv of CuCl yielded the desired 8-oxoprotoberberine alkaloids **1a–d** with good yields.[18]

In conclusion, we have developed a new method for the synthesis of 8-oxoprotoberberines **1a–d**. These 8-oxoprotoberberines were formed presumably via the 6-endo cyclization of radical intermediates **8a–d** and subsequent Cu(I) oxidation of **10a–d** (Scheme 5). The Cu(I)-mediated *n*-Bu_3SnH/AIBN radical cyclization process is feasible to afford the oxoprotoberberine. Thus, the methodology applying CuCl to radical-initiated cyclization for the synthesis of alkaloids is noteworthy.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.095.

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18. *8-Oxopseudopalmatine* (**1a**): mp 197–198 °C (lit.[10g] mp 198–199 °C). IR (KBr, cm^{-1}) 1645; ^1H NMR (300 MHz, $CDCl_3$) δ 2.95 (t, J = 6.3 Hz, 2H), 3.95 (s, 3H), 3.99 (s, 3H), 4.02 (s, 3H), 4.02 (s, 3H), 4.37 (t, J = 6.3 Hz, 2H), 6.75 (s, 1H), 6.84 (s, 1H), 6.95 (s, 1H), 7.25 (s, 1H), 7.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.16, 39.75, 56.03 (2C), 56.21 (2C), 101.06, 105.95, 107.78, 107.91, 110.59, 118.61, 122.57, 128.42, 132.16, 136.19, 148.48, 149.03, 150.16, 153.53, 161.42; LRMS (EI, 70 eV) m/z (%) 367 (M^+, 100%). *2,3-dimethoxy-8-oxoberberine* (**1b**): mp 190–191 °C (lit.[10m] mp 188–189 °C). IR (KBr, cm^{-1}) 1643; ^1H NMR (300 MHz, $CDCl_3$) δ 2.95 (t, J = 6.3 Hz, 2H), 3.95 (s, 3H), 4.00 (s, 3H), 4.37 (t, J = 6.3 Hz, 2H), 6.75 (s, 1H), 6.89 (s, 1H), 7.29 (s, 1H), 7.44 (t, J = 6.9 Hz, 1H), 7.55–7.66 (m, 2H), 8.43 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.11, 39.73, 56.03, 56.27, 101.42, 107.96, 110.52, 122.33, 124.57, 125.89, 126.15, 127.97, 128.74, 132.22, 136.67, 137.42, 148.50, 150.40, 162.21; LRMS (EI, 70 eV) m/z (%) 307 (M^+, 100%). *3,10-*

Dimethoxy-8-oxoberberine (**1c**): mp 187 °C. (lit.[10a] mp 180 °C). IR ($CHCl_3$, cm^{-1}) 1644; ^1H NMR (300 MHz, $CDCl_3$) δ 2.98 (t, J = 6.0 Hz, 2H), 3.86 (s, 3H), 3.94 (s, 3H), 4.38 (t, J = 6.0 Hz, 2H), 6.77 (d, J = 2.7 Hz, 1H), 6.87–6.90 (m, 2H), 7.24 (dd, J = 8.7, 2.7 Hz, 1H), 7.48 (d, J = 8.7 Hz, 1H), 7.72 (d, J = 8.7 Hz, 1H), 7.82 (d, J = 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.86, 39.77, 55.39, 55.64, 101.28, 107.57, 112.58, 113.59, 123.08, 125.52, 126.27, 127.62 (2C), 130.96, 135.30, 136.68, 158.32, 160.17, 161.77; LRMS (EI, 70 eV) m/z (%) 307 (M^+, 100%). *3-Methoxy-8-oxoberberine* (**1d**): mp 145–146 °C (lit.[10b] mp 143 °C). IR (KBr, cm^{-1}) 1643; ^1H NMR (300 MHz, $CDCl_3$) δ 2.97 (t, J = 6.3 Hz, 2H), 3.86 (s, 3H), 4.37 (t, J = 6.3 Hz, 2H), 6.77 (d, J = 2.4 Hz, 1H), 6.87–6.90 (m, 2H), 7.40 (t, J = 7.5 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 8.42 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.82, 39.57, 55.39, 101.32, 112.61, 113.62, 122.86, 124.45, 125.91, 126.04, 126.60, 127.91, 132.16, 136.77, 137.08, 137.44, 160.47, 162.16; LRMS (EI, 70 eV) m/z (%) 277 (M^+, 97.75%).