Tetrahedron 71 (2015) 6116–6123

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Mechanically activated ring-opening reactions of *N*-acyl-1,2,3,4-tetrahydroisoquinolines derived from the synthesis of praziquantel intermediate

Jingbo Yu [a], Zhi Wang [a,b], Yang Zhang [a], Weike Su [a,*]

[a] National Engineering Research Center for Process Development of Active Pharmaceutical Ingredients, Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou 310014, PR China
[b] College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, PR China

ARTICLE INFO

Article history:
Received 4 May 2015
Received in revised form 28 June 2015
Accepted 29 June 2015
Available online 3 July 2015

Keywords:
Tetrahydroisoquinoline
Ring-opening reaction
Praziquantel
Ball milling

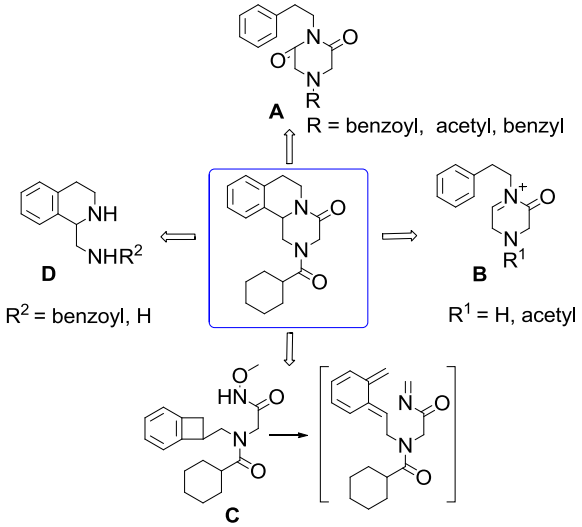
ABSTRACT

An unexpected DDQ-promoted ring-opening reaction of *N*-chloroacetyl-tetrahydroisoquinoline under ball milling conditions was revealed during the synthesis of Praziquantel. A variety of *N*-acyl-tetrahydroisoquinolines were then tested to further investigate the reaction, and plausible reaction mechanism was proposed. Ball milling was demonstrated to be an efficient tool to promote this oxidative ring-opening reaction to give products in satisfactory yields with good selectivity in short reaction times.

1. Introduction

Praziquantel (PZQ) is an anthelmintic developed by Bayer and Merck in 1970s, which effectively against flatworms and has been widely used in treatment of hydatid disease, cysticercosis, and toxocariasis. Hitherto, there have been considerable efforts at analog synthesis given PZQ's status as the preferred drug for the treatment of the more than 200 million patients currently infected with bilharziosis.[1,2] Although there have been a couple of synthetic routes to prepare PZQ via different intermediates (Scheme 1),[3] most of them are marred by one or another drawback such as multiple steps, harsh conditions, use of carcinogenic solvent, environmentally harmful reagents and toxic substrates. Therefore, it is still highly desirable to develop a simpler and more efficient synthetic protocol for the preparation of PZQ and analog under environmentally benign conditions.

Cross-dehydrogenative-coupling (CDC) reaction has been widely researched during the past decade, which shows as a mild method for the direct coupling of appropriate C–H bonds.[4] Our group had reported a 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-promoted solvent-free CDC reaction under ball-milling conditions.[5] During the study of a novel synthesis of PZQ, we planned to extend this solvent-free coupling method to the synthesis of 1-aminomethyl tetrahydroquinoline, a key-intermediate of praziquantel, by reduction and deprotection of the CDC product. Unexpectedly, the reaction was also found to afford oxidative



Scheme 1. Preparation of PZQ via different intermediates.

* Corresponding author. Tel.: +86 571 88320899; fax: +86 571 88320752; e-mail address: pharmlab@zjut.edu.cn (W. Su).

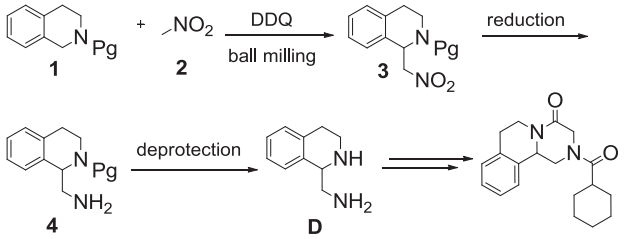
http://dx.doi.org/10.1016/j.tet.2015.06.105
0040-4020/

ring-opening products and acylated DDQ derivatives using different acyl protecting groups on tetrahydroisoquinoline.

Oxidative ring-opening reaction is one of the most important processes in organic transformations. The oxidative ring opening of heterocycles,[6] metal-containing heterocycles[7] and carbocycles[8] are well documented, these valuable ring-opened synthetic intermediates can be further manipulated to afford ring-contraction or ring-expansion products.[9] In addition, a great number of works have applied oxidative ring opening reaction to the synthesis and modification of bioactive natural products, such as Lavandulol,[10] (+)-Lycoricidine,[11] Taxane derivatives[12] and Paclitaxel analogs.[13] However, most of the oxidative ring-opening reactions are conducted in hazardous organic solvents, together with metal oxidants or other explosive oxidants. In this paper, we describe an efficient synthetic strategy of PZQ and the derivative solvent-free oxidative ring-opening reaction of *N*-acyl-1,2,3,4-tetrahydroisoquinolines under ball milling conditions.

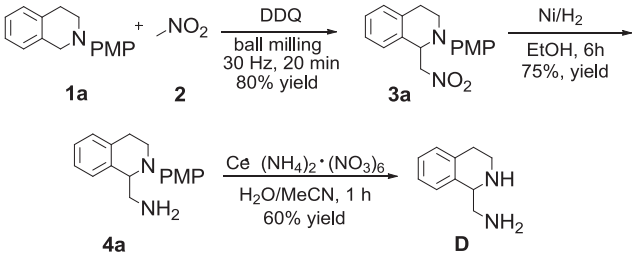
2. Results and discussion

Our synthetic strategy of PZQ by using 1-aminomethyl tetrahydroisoquinoline as key intermediate was shown in Scheme 2. CDC reaction was used to introduce the nitromethyl group to the *N*-protected 1,2,3,4-tetrahydroisoquinoline. Then the target product 1-aminomethyl tetrahydroisoquinoline could be obtained after a two-step sequence of reduction and deprotection. After the sequential formation of piperazinone and acylation, Praziquantel could be finally obtained.



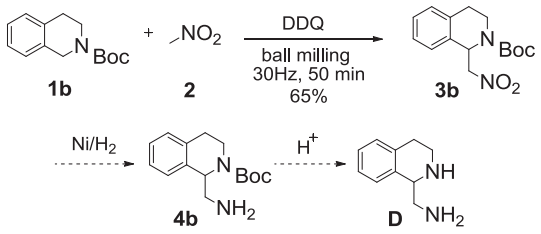
Scheme 2. Synthesis of PZQ with 1-aminomethyl tetrahydroisoquinoline as key intermediate.

We initiated our synthesis from *N*-PMP tetrahydroisoquinoline, which was subjected to a solvent-free CDC reaction under ball-milling conditions (Scheme 3). The expected 1-nitromethyl tetrahydroisoquinoline **3a** was obtained in 20 min with 80% yield, which was followed by nitro reduction with Raney-Ni/H_2 under atmospheric pressure. After purification, PMP was removed by ammonium ceric nitrate (CAN)[14] to afford the target compound in 60% yield. Recently, Todd et al. reported their research on the synthesis of PZQ using **D** as key intermediate.[15] According to their work, the amino group of **4a** should be pre-protected before the removal of PMP, otherwise the deprotection yield would be very low. In our synthetic route, moderate deprotection yield was obtained but the



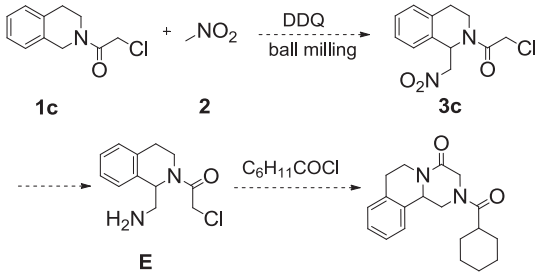
Scheme 3. Synthesis of 1-aminomethyl tetrahydro-isoquinoline from *N*-PMP tetrahydroisoquinoline **1a**.

procedure was found to be relatively difficult. To ease the deprotection, PMP was replaced by Boc group, which afforded **3b** as the CDC product (Scheme 4). However, it could hardly undergo nitro reduction and affording a hardly separable mixture.



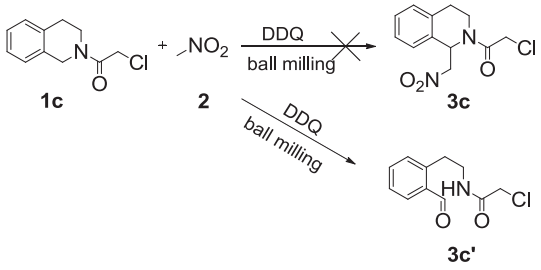
Scheme 4. Synthesis of 1-aminomethyl tetrahydro-isoquinoline from *N*-Boc tetrahydroisoquinoline **1b**.

Although the designed route in Scheme 3 gave the ideal products, the protection and deprotection of tetrahydroisoquinoline resulted in relatively low atom economy, which was not in accord with green chemistry. Therefore, we turned to use chloroacetyl as the protecting group, by which piperazinone might form directly after nitro reduction to eliminate the deprotection procedure (Scheme 5).



Scheme 5. Designed synthetic route of PZQ with 1-aminomethyl-2-chloroacetyl-tetrahydroisoquinoline **1c** as intermediate.

The *N*-chloroacetyl-tetrahydroisoquinoline **1c** was examined as substrate to perform the same CDC reaction under ball milling conditions. To our disappointment, though most of the substrate had reacted within 50 min of ball milling, no desired product could be isolated. After identification, we surprisingly found that oxidative ring-opening product benzaldehyde derivative **3c′** was obtained in 67% yield (Scheme 6). However, no matter changing the reactant ratio or the amount of DDQ, the reaction gave only the benzylaldehydes **3c′**. The best results were obtained when 1.1 equiv of DDQ was used, an excess of oxidant was detrimental to the yield of the product, whereas less than 1 equiv of DDQ would result in incomplete conversion of the starting materials. An examination of the effect of ball milling vibration frequency on the reaction was undertaken subsequently (Table 1). The yield declined with decreased frequencies, and almost no reaction occurred when the frequency was reduced to 15 Hz even with prolonged reaction times. Besides, without nitromethane, the reaction still proceeded



Scheme 6. Oxidative ring-opening reaction of *N*-chloroacetyl-tetrahydroquinoline **1c**.

Table 1
Influence of the ball mill vibration frequency on the reaction[a]

Entry	Frequency (Hz)	Time (min)	Yield[b] (%) of **3c′**
1	30	50	67
2	25	50	55
3	20	60	26
4	15	90	trace

[a] **1c** (1.0 mmol), DDQ (1.1 equiv, 0.25 g) and silica gel (0.5 g) were added to the stainless steel vial, milling at different Hz.
[b] Isolated yields based on **1c**.

to afford the oxidative ring-opening product. Comparative experiments[16] were performed under stirring conditions by using nitromethane or dichloromethane (DCM) as solvent, the corresponding reaction times were much longer (>10 h) and the product yields (60% and 45%, respectively) were lower than those obtained under milling conditions.

Oxidative ring-opening reaction of 2-aryl tetrahydroisoquinoline had been reported by Stanforth by using *N*-bromosuccinimide (NBS) as oxidant under refluxing condition in DCM.[17] However, the reaction was limited to electron-withdrawing *N*-aryl tetrahydroisoquinoline, especially for substrates that are prone to form intramolecular hydrogen bond. In our reaction, benzaldehydes **5**, which might play the role as the intermediates of taspine,[18] calcium receptor-active compounds[19] and EP_2 receptor antagonist,[20] were obtained probably due to the influence of ketone carbonyl on *N*-2-position resulting in the facile breaking and oxidation of the C–N bond under ball milling conditions.

The reaction scope was then investigated with various *N*-aroyl tetrahydroisoquinolines and the results were summarized in Table 2. In most of the reactions, DDQ acylation products **6**, which resulted from the nucleophilic substitution of DDQ and *N*-acyl substrates were surprisingly detected (Table 2, entries 1–4 and 7–9). For the substrates with *meta*-substituted aroyl in *N*-2-position, corresponding oxidative ring-opening products were readily obtained (Table 2, entries 3–4). Single oxidative ring-opening products were obtained when the substrates with *ortho*-substituted (methoxy) or poly-substituted (2,3,4,5-fluoro) aroyl at 2-nitrogen (Table 2, entries 5–6). In this case, steric hindrance of the *ortho* substituents prohibited the nucleophile substitution of aroyl. However, when *N*-alkanoyl tetrahydroisoquinoline **1j** was used as the substrate, the reaction afforded only a small amount (15%) of DDQ acylation product with lots of oxypolymerized by-products, indicating that aroyl group can facilitate the substrate to undergo oxidative ring-opening reaction.

The substituents on tetrahydroisoquinoline could also play an important role in the reaction selectivity. The result turned out that 6,7-dimethoxyl tetrahydroisoquinolines took part in the reaction smoothly under the milling conditions, but providing large amount of acyl substituted DDQ. If the reaction was taken by intermittent milling with portion-wise addition of DDQ, a small amount of oxidative ring-opening product **5g** was obtained (Table 2, entry 8). However, in contrast with **1g**, only trace of ring-opening product **5h** was detected when **1l** was used as substrate (Table 2 entry 4 and 9). Aliphatic amides were also studied under continuous milling conditions, but after a long reaction time (>60 min), the substrates still remained unreacted (Table 2, entries 10–11). Comparative experiments[16] performed in solution were also studied, the results showed that longer reaction times were required to afford acyl substituted DDQ as the main product, but with poorer selectivity (Table 2, entries 1–3 and 5 in parentheses).

To extend the applicability of the ring-opening reaction, acyl-substituted benzazepine derivatives were tested as substrates under the above milling conditions. As shown in Table 3, the electronic nature of the aroyl substituents had no significant effect on the reaction. Both electron-withdrawing group and electron-donating group provided the product in moderate yields, but with relatively longer reaction times.

To gain a better understanding of the reaction mechanism, the following control experiments were carried out. First, the reaction of **1d** with DDQ was conducted under nitrogen atmosphere to reveal the source of oxygen in oxidative ring-opening products. The results showed that only 2,3-dichloro-5,6-dicyano-4-hydroxyphenyl benzoate **6a** was formed (Table 4, entry 1), which indicated that air was the oxygen source in oxidative ring-opening products. Various substrates were then tested under the same conditions to give nucleophilic substituted products, except for **4h** and **4i**, which still remained unreacted after a long reaction time (Table 4, entries 5–6). The influence of the substitutes at 2-position of tetrahydroisoquinoline was similar to that under ball milling conditions. Mechanical force was proved to be an efficient promotion for oxidative ring-opening reaction. However, when acyclic amides such as *N*,*N*-diethyl benzamide **1m**, *N*-acyl piperidine **1n**, 1-methyl-4-benzoyl piperazine **1o** and 1-methyl-4-acetyl piperazine **1p** (Table 4, entries 10–13) were used as substrates under the above nitrogen condition, no reaction took place, indicating tetrahydroisoquinoline played a role as a good-leaving group for the nucleophilic substitution reaction.

Additionally, it was found that when a typical radical scavenger, tetramethylpiperidine *N*-oxide (TEMPO, 1 equiv), was added into the reaction system under the standard conditions, the reaction was not appreciably suppressed, which excluded significant involvement of any radical intermediate. On the basis of these experimental results and previous reports,[21,22] a plausible reaction mechanism was suggested, as shown in Scheme 7. *N*-formyl tetrahydroisoquinoline was initially converted to imine-type intermediate **I** in the presence of DDQ, meanwhile DDQ was transformed into the corresponding anion oxygen intermediate **III**. Subsequently, **I** was transformed to **II** via oxidation by air, which then underwent C–N bond breaking and proton transferring to afford **5**. Meanwhile, **6** was obtained from the nucleophilic attack of **III** to the carbonyl of **I**, with dihydroisoquinolinium as the leaving molecule.

3. Conclusions

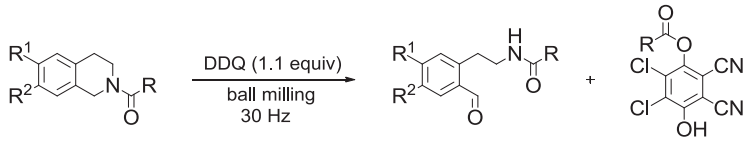
In summary, a new type of DDQ-promoted ring-opening reaction of *N*-acyl-tetrahydroisoquinoline was revealed to afford *ortho*-substituted benzaldehyde derivatives, the intermediates of several biological compounds, during the research of a novel synthesis of Praziquentel. Compared to traditional stirring conditions, ball milling was demonstrated to be an efficient tool to promote this oxidative ring-opening reaction combining the advantages of good selectivity, short reaction times, and free of reaction solvents. The reaction mechanism in both solution and under solvent-free conditions was preliminary explored. The detailed mechanism and its application in the preparation of bioactive products are under further study.

4. Experimental section

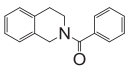
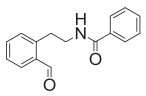
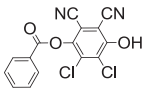
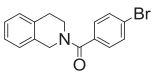
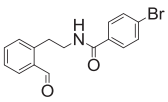
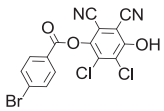
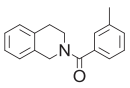
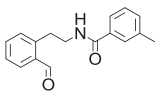
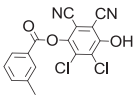
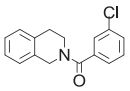
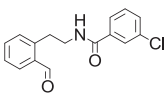
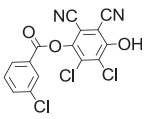
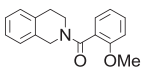
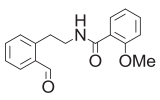
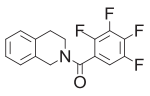
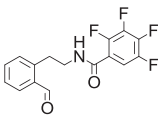
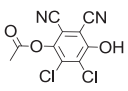
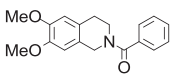
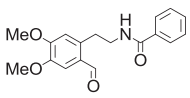
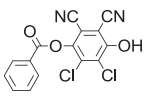
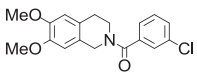
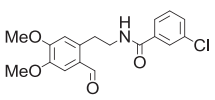
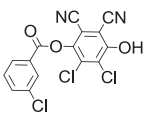
4.1. General information and materials

The reactions were conducted in a high-energy vibrational micromill (volume of stainless steel vial: 10 mL; diameter of stainless steel balls: 8.0 mm). Melting points (mp) were obtained on a digital melting point apparatus and uncorrected. ^{1}H NMR, ^{13}C NMR were recorded at 400 MHz and 100 MHz, respectively, and TMS as internal standard. Mass spectra were measured with an HRMS-APCI instrument or a low-resolution MS instrument using ESI or APCI ionization.

Table 2
Reaction of **1** with DDQ under ball mill condition[a]

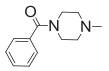


1 **5** **6**

Entry	Substrate	Product		Time (min)	Yield (%)[b] of **5** and **6**	
		5	**6**			
1	 **1d**	 **5a**	 **6a**	50 (480[d])	70 (35[e])	10 (50[e])
2	 **1e**	 **5b**	 **6b**	50 (540[d])	52 (20[e])	16 (60[e])
3	 **1f**	 **5c**	 **6c**	30 (360[d])	74 (40[e])	5 (45[e])
4	 **1g**	 **5d**	 **6d**	30	75	2
5	 **1h**	 **5e**	—	60 (960[d])	70 (58[e])	—
6	 **1i**	 **5f**	—	100	63	—
7	 **1j**	—	 **6e**	30	—	15
8[c]	 **1k**	 **5g**	 **6a**	60	49	38
9[c]	 **1l**	 **5h**	 **6d**	60	trace	86
10	 **1n**	—	—	60	—	—

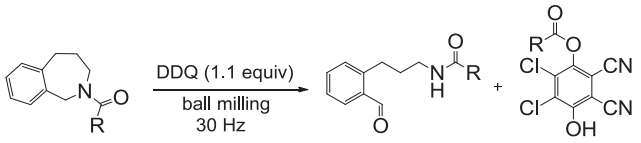
(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Product		Time (min)	Yield (%)[b] of **5** and **6**	
		5	**6**			
11	 **1o**	—	—	60	—	—

[a] *N*-acyl tetrahydroisoquinoline (1.0 mmol), DDQ (1.1 equiv, 0.25 g) and silica gel (0.5 g) were added to the stainless steel vial, milling at 30 Hz.
[b] Isolated yields based on **1**.
[c] Milling at 30 Hz for 10 min by a 5 min pause; DDQ was added in five portions.
[d] Reaction time of comparative experiment in solvent (CH_3NO_2, 10 mL).
[e] Isolated yields of the comparative experiment.

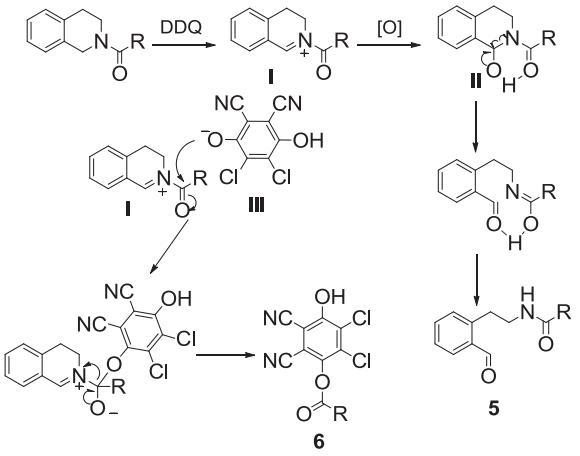
Table 3
Ring-opening reaction of *N*-acyl benzazepines[a]



7 **8** **6**

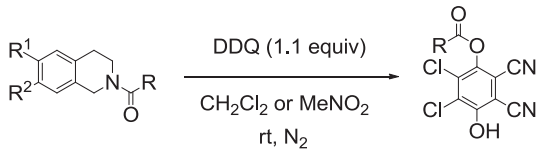
Entry	R		Product		Time (h)	Yield (%)[b] of **8** and **6**	
			8	**6**			
1	Ph	**7a**	**8a**	—	3.5	60	—
2	3-MeC_6H_4	**7b**	**8b**	**6c**	3	68	3
3	3-ClC_6H_4	**7c**	**8c**	**6d**	3	63	2

[a] *N*-acyl benzazepine (1.0 mmol), DDQ (1.1 equiv, 0.25 g) and silica gel (0.5 g) were added to the stainless steel vial, milling at 30 Hz.
[b] Isolated yields based on **7**.

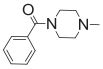


Scheme 7. Plausible reaction mechanism.

Table 4
Reaction of **1** with DDQ in solution under N_2 atmosphere[a]



1 **6**

Entry	1			Product	Time (h)	Yield (%)[b]
	R^1=R^2	R				
1	H	Ph	**d**	**6a**	3	90
2	H	4-BrC_6H_4	**e**	**6b**	3	90
3	H	3-MeC_6H_4	**f**	**6c**	4	88
4	H	3-ClC_6H_4	**g**	—	4	90
5	H	2-$MeOC_6H_4$	**h**	—	10	—
6	H	2,3,4,5-tetraFC_6H	**i**	—	10	—
7	H	H	**j**	**6e**	10	30
8	OMe	Ph	**k**	**6a**	3	85
9	OMe	3-ClC_6H_4	**l**	**6d**	4	92
10			**m**	—	10	—
11			**n**	—	10	—
12			**o**	—	10	—
13			**p**	—	10	—

[a] DDQ (1.1 mmol, 0.250 g) in 10 mL CH_2Cl_2 or $MeNO_2$ was added to *N*-acyl tetrahydroisoquinoline (1 mmol) under N_2 atmosphere.
[b] Isolated yields based on **1**.

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. 1-nitro-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **3a** and *tert*-butyl 1-(nitromethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate **3b** were prepared according to published procedures.[5]

*4.1.1. tert-Butyl 1-(nitromethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (**3b**).* Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.28–7.09 (m, 4H), 5.95–5.88 (m, 0.26H [minor]) 5.84 (dd, J=9.2, 3.6 Hz, 0.56H [major]), 4.72–4.62 (m, 1H), 4.60–4.53 (m, 1H), 4.33–4.24 (m, 0.59H [major]), 3.99–3.89 (m, 0.28H [minor]), 3.26–3.16 (m, 1H), 3.03–2.87 (m, 1H), 2.82–2.72 (m, 1H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 154.5 (minor), 153.6 (major), 135.1 (major), 134.8 (minor), 131.7 (minor), 131.5 (major), 129.4, 127.9 (2C), 126.6, 81.3 (major), 80.8 (minor), 79.1 (major), 78.6 (minor), 53.9 (major), 53.1 (minor), 39.3 (minor), 36.9 (major), 28.5 (minor), 28.4 (minor), 28.2 (major), 28.1 (major); MS (EI) *m/z* (%): 176 (4), 132 (24), 131 (89), 130 (100), 77 (25); HRMS (ESI) $C_{15}H_{21}N_2NaO_4$ ([M+Na]$^+$): calcd: 315.1315, Found: 315.1315.

4.2. Procedure for the preparation of 1-aminomethyl-2-(4-methoxy phenyl)-1,2,3,4-tetrahydroisoquinoline (4a)

Raney-Ni (150 mesh, 10 mL) was added to a solution of 1-nitro-2-PMP-1,2,3,4-tetrahydroisoquinoline (0.596 g, 2 mmol) in ethanol (30 mL), and stirred for 6 h under H_2 balloon (1 atm) at room temperature. After the completion of the reaction (monitored by TLC), the resulting mixture was filtered. Ethanol was distilled off under reduced pressure, then extracted with EA (4×10 mL). The combined organic layers were washed with brine (2×10 mL), dried over Na_2SO_4 and concentrated in vacuum. Purification by silica gel column chromatography using CH_2Cl_2/CH_3OH (v/v=30:1) as an eluent afforded **4a**.

Brownish oil. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.21–7.03 (m, 4H), 6.92 (d, J=8.8 Hz, 2H), 6.77 (d, J=8.8 Hz, 2H), 4.48 (dd, J=8.4, 4.8 Hz, 1H), 3.73 (s, 3H), 3.57–3.47 (m, 2H), 3.10–3.01 (m, 1H), 3.00–2.85 (m, 2H), 2.63 (ddd, J=16.0, 4.0, 3.6 Hz, 1H), 2.34 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 153.2, 144.6, 136.1, 135.3, 128.7, 127.0, 126.4, 125.9, 118.8 (2C), 114.5 (2C), 62.4, 55.6, 46.8, 43.7, 26.1; MS (ESI): 269 ([M+H]$^+$).

4.3. Procedure for the preparation of 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline (D)

1-aminomethyl-2-(4-methoxyphenyl)-1,2,3,4 tetrahydro-isoquinoline **4a** (0.268 g, 1 mmol) in acetonitrile were added dropwise to a solution of ceric ammonium nitrate in 10 mL water at −10 °C under nitrogen atmosphere. The mixture was then stirred for 1 h at the same temperature. After a portion of solvent was distilled off under reduced pressure, hydrochloric acid was added, and refluxed for 1 h. The resulting mixture was cooled to room temperature by adding 10 mL water, the mixture was extracted with EtOAc (3×10 mL). The aqueous layer was basified to pH=9 with 2 M NaOH, then extracted with DCM (3×10 mL). The combined organic layers were washed with brine (2×10 mL), dried over Na_2SO_4 and concentrated in vacuum. Purification by silica gel column chromatography using CH_2Cl_2/CH_3OH/$NH_3\cdot H_2O$ (v/v/V=30:1:0.1)as an eluent afforded **D**.

Colorless oil.[23] ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.23–7.15 (m, 2H), 7.10–7.00 (m, 2H), 4.29 (t, J=12.0 Hz, 1H), 3.90–3.73 (m, 2H), 3.55–3.42 (m, 1H), 3.00–2.85 (m, 2H), 2.79–2.71 (m, 1H), 2.17 (br s, 3H); MS (EI) m/z (%): 132 (100).

4.4. General procedure for the ring-opening reactions of *N*-acyl-1,2,3,4-tetrahydroisoquinolines by ball milling

The following components were added to the screw-capped stainless steel vial: *N*-acyl-1,2,3,4-tetrahydroisoquinolines (1 mmol), DDQ (1.1 mmol), and silica gel (0.5 g), along with two stainless steel balls (d=8.0 mm), then the vial was placed in a vibrational micromill (MM 400), and the contents were ball milled at 30 Hz under room temperature. At the end of the experiment, all of the reaction mixture was scratched off the vessel and then directly separated and purified by column chromatography. Elution of the column with PE/EtOAc (v/v=15:1) afforded the title product.

*4.4.1. 2-Chloro-N-(2-formylphenethyl)acetamide (**3c′**).* Pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 10.13 (s, 1H), 7.80 (d, J=7.6 Hz, 1H), 7.57–7.51 (m, 1H), 7.46 (dd, J=7.6, 7.4 Hz, 1H), 7.31 (d, J=7.6 Hz, 1H), 6.84 (br s, 1H), 3.99 (s, 2H), 3.58 (q, J=6.8 Hz, 2H), 3.29 (t, J=6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 193.2, 165.9, 140.4, 134.5, 134.0, 133.8, 131.7, 127.3, 42.6, 41.1, 32.4; MS (ESI): 226, 228 ([M+H]$^+$); HRMS (ESI) $C_{11}H_{13}ClNNaO_2$ ([M+Na]$^+$): calcd: 248.0449, Found: 248.0450.

*4.4.2. N-(2-Formylphenethyl)benzamide (**5a**).*[24] Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 10.16 (s, 1H), 7.79 (dd, J=7.6, 1.2 Hz, 1H), 7.72–7.69 (m, 2H), 7.56–7.51 (m, 1H), 7.47–7.35 (m, 5H), 6.70 (br s, 1H), 3.73 (q, J=6.8 Hz, 2H), 3.36 (t, J=6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 194.1, 167.6, 141.5, 134.7, 134.2, 132.2, 131.5, 130.3, 128.7 (2C), 127.5, 127.4, 127.0 (2C), 42.1, 32.8; MS (ESI): 276 ([M+Na]$^+$).

*4.4.3. N-(2-Formylphenethyl)-4-bromo-benzamide (**5b**).* Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 10.12 (s, 1H), 7.59–7.49 (m, 5H), 7.44 (t, J=8.0 Hz, 1H), 7.37–7.28 (m, 2H), 6.80 (br s, 1H), 3.71 (q, J=6.8 Hz, 2H), 3.33 (t, J=6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 194.0, 166.3, 141.1, 134.6, 133.9, 133.1, 131.9, 131.6 (2C), 129.0, 128.4 (2C), 127.2, 125.9, 42.0, 32.4; MS (ESI): 354, 356 ([M+Na]$^+$); HRMS (ESI) $C_{16}H_{14}BrNNaO_2$ ([M+Na]$^+$): calcd: 354.0106, Found: 354.0104.

*4.4.4. N-(2-Formylphenethyl)-3-methylbenzamide (**5c**).* Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 10.12 (s, 1H), 7.78 (d, J=7.2 Hz, 1H), 7.57–7.40 (m, 3H), 7.38–7.25 (m, 4H), 6.66 (br s, 1H), 3.71 (q, J=6.8 Hz, 2H), 3.35 (t, J=6.8 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 193.6, 167.5, 141.2, 138.1, 134.2, 134.1, 133.8, 131.9, 131.8, 128.2, 127.8, 127.6, 127.1, 123.6, 41.7, 32.5, 21.5; MS (ESI): 290 ([M+Na]$^+$); HRMS (ESI) $C_{17}H_{17}NNaO_2$ ([M+Na]$^+$): calcd: 290.1157, Found: 290.1175.

*4.4.5. N-(2-Formylphenethyl)-3-chlorobenzamide (**5d**).* White crystals. Mp: 87.2–88.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 10.12 (s, 1H), 7.77 (dd, J=7.6, 1.2 Hz, 1H), 7.70–7.67 (m, 1H), 7.57–7.50 (m, 2H), 7.46–7.38 (m, 2H), 7.35–7.27 (m, 2H), 6.89 (br s, 1H), 3.70 (q, J=6.8 Hz, 2H), 3.33 (t, J=6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 193.8, 166.0, 141.0, 136.1, 134.5, 134.4, 134.2, 133.9, 131.8, 131.2, 129.6, 127.2, 124.8, 41.9, 32.4; MS (ESI): 310, 312 ([M+Na]$^+$); HRMS (ESI) $C_{16}H_{14}ClNNaO_2$ ([M+Na]$^+$): calcd: 310.0611, Found: 310.0619.

*4.4.6. N-(2-Formylphenethyl)-2-methoxybenzamide (**5e**).* Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 10.23 (s, 1H), 8.18 (dd, J=7.6, 1.8 Hz, 1H), 7.94 (br s, 1H), 7.83 (dd, J=7.6, 1.2 Hz, 1H), 7.58–7.50 (m, 1H), 7.45–7.34 (m, 3H), 7.07–7.02 (m, 1H), 6.92 (d, J=8.0, Hz, 1H), 3.84 (s, 3H), 3.74 (q, J=6.8 Hz, 2H), 3.37 (t, J=6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 192.3, 165.1, 157.2, 141.7, 134.1, 133.6, 132.8, 132.5, 132.1, 131.6, 126.9, 121.1, 111.1, 55.8, 41.2, 32.5; MS (ESI): 306 ([M+Na]$^+$); HRMS (ESI) $C_{17}H_{17}NNaO_3$ ([M+Na]$^+$): calcd: 306.1106, Found: 306.1111.

*4.4.7. N-(2-Formylphenethyl)-2,3,4,5-tetrafluorobenzamide (**5f**).* Colorless crystals. Mp: 79.5–80.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 10.14 (s, 1H), 7.80 (d, J=7.2 Hz, 1H), 7.73–7.63 (m, 1H), 7.58–7.42 (m, 2H), 7.33 (d, J=7.6 Hz, 1H), 6.84 (br s, 1H), 3.74 (q, J=6.8 Hz, 2H), 3.36 (t, J=6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 193.2, 160.3, 140.6, 134.5, 134.3, 133.8, 131.7, 127.3, 112.7 (m), 41.9, 32.5; ^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ −137.0 (m, 1F), −139.6 (m, 1F), −149.4 (m, 1F), −153.9 (m, 1F); MS (ESI): 348 ([M+Na]$^+$); HRMS (ESI) $C_{16}H_{11}F_4NNaO_2$ ([M+Na]$^+$): calcd: 348.0624, Found: 348.0633.

4.5. Procedure for the preparation of *N*-(2-formyl-4,5-dimethoxyphenethyl)benzamide (5g)

The following components were added to the screw-capped stainless steel vial: *N*-(2-methoxybenzoyl) tetrahydroisoquinoline (0.267 g, 1.0 mmol), DDQ (0.05 g, 0.22 mmol), and silica gel (0.5 g), along with two stainless steel balls (d=8.0 mm). The vial was placed in a vibrational micromill (MM 400) and the contents were ball milled at 30 Hz, with a milling cycle of 10 min followed by a 5 min pause with addition of 0.05 g DDQ (0.22 mmol). This cycle can be repeated for five times by adding a total amount of 0.25 g DDQ (1.1 mmol) until the reaction was complete. All of the reaction mixture was finally scratched off the vessel and then directly separated and purified by column chromatography. Elution of the column with PE/EtOAc (v/v=10:1) afforded the product **5g**.

Colorless crystals. Mp: 142.9–143.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 10.08 (s, 1H), 7.71 (d, J=7.2 Hz, 1H), 7.50–7.39 (m, 3H), 7.28 (s, 1H), 6.78 (s, 1H), 6.61 (br s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.72 (q, J=6.8 Hz, 2H), 3.33 (t, J=6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 190.9, 167.3, 156.5, 151.8, 136.4, 134.3, 134.1, 131.3, 128.4 (2C), 126.7 (2C), 114.3, 113.9, 56.3, 56.2, 42.1, 31.7; MS (ESI): 312 ([M−H]$^-$); HRMS (ESI) $C_{18}H_{19}NNaO_4$ ([M+Na]$^+$): calcd: 336.1212, Found: 336.1206.

4.6. General procedure for the reaction of 1 with DDQ in solution

Under the protection of N_2, a solution of DDQ (0.250 g, 1.1 mmol) in DCM (10 mL) was added dropwise into *N*-benzoyl-1,2,3,4-tetrahydroisoquinoline, the mixture was stirred at room temperature for 3 h. After the reaction was complete, the mixture was filtered, and the residue recrystallized in DCM to afford 2,3-dichloro-5,6-dicyano-4-hydroxyphenyl formyl ester (**6**).

*4.6.1. 2,3-Dichloro-5,6-dicyano-4-hydroxyphenyl benzoate (**6a**).* Colorless crystals. Mp: 248.0–248.9 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.23 (d, J=7.2 Hz, 2H), 7.73 (dd, J=7.6, 7.2 Hz, 1H), 7.57 (dd, J=8.0, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 162.1, 148.9, 135.4, 135.0, 130.7 (2C), 128.9 (2C), 126.3, 110.8, 110.5; MS (ESI): 332 ([M−H]$^-$); HRMS (ESI) $C_{15}H_5Cl_2N_2O_3$ ([M−H]$^-$): calcd: 330.9677, Found: 330.9697.

*4.6.2. 2,3-Dichloro-5,6-dicyano-4-hydroxyphenyl 4-bromobenzoate (**6b**).* Colorless crystals. Mp: 248.5–249.2 °C; ^{1}H NMR (CDCl3, 400 MHz, ppm) δ 8.08 (d, J=8.4 Hz, 2H), 7.72 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 161.6, 148.8, 135.6, 132.5 (2C), 132.1 (2C), 130.8, 125.2, 110.9, 110.4; MS (ESI): 411 ([M−H]$^-$); HRMS (ESI) $C_{15}H_4BrCl_2N_2O_3$ ([M−H]$^-$): calcd: 408.8782, Found: 410.8765.

*4.6.3. 2,3-Dichloro-5,6-dicyano-4-hydroxyphenyl 3-methylbenzoate (**6c**).* Colorless crystals. Mp: 182.3–183.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.05–8.01 (m, 2H), 7.53 (d, J=8.0 Hz, 2H), 7.46 (d,=8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 162.4, 149.0, 138.9, 135.9, 131.2, 128.8, 128.0, 126.3, 110.9, 110.6, 21.4; MS (ESI): 346 ([M−H]$^-$); HRMS (ESI) $C_{16}H_7Cl_2N_2O_3$ ([M−H]$^-$): calcd: 344.9834, Found: 344.9872.

*4.6.4. 2,3-Dichloro-5,6-dicyano-4-hydroxyphenyl 3-chlorobenzoate (**6d**).* Colorless crystals. Mp: 205.7–207.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.29 (t, J=2.0 Hz, 1H), 8.14–8.09 (m, 1H), 7.747.67 (m, 1H), 7.53 (dd, J=8.0, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 161.3, 149.0, 135.7, 135.6, 135.4, 130.9, 130.5, 129.0, 128.4, 110.2, 110.6; MS (ESI): 366 ([M−H]$^-$); HRMS (ESI) $C_{15}H_4Cl_3N_2O_3$ ([M−H]$^-$): calcd: 364.9288, Found: 364.9277.

*4.6.5. 2,3-Dichloro-5,6-dicyano-4-hydroxyphenyl acetate (**6e**).* Colorless crystals. Mp: 180.1–181.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 166.0, 148.5, 135.1, 110.5 (2C), 20.3; MS (ESI): 270 ([M−H]$^-$); HRMS (ESI) $C_{10}H_3Cl_2N_2O_3$ ([M−H]$^-$): calcd: 268.9521, Found: 268.9510.

4.7. General procedure for the ring-opening reactions of *N*-acyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepines by ball milling

The following components were added to the screw-capped stainless steel vial: *N*-acyl-2,3,4,5-tetrahydro-1H-benzo[*c*]azepines (1 mmol), DDQ (1.1 mmol), and silica gel (0.5 g), along with two stainless steel balls (d=8.0 mm), then the vial was placed in a vibrational micromill (MM 400), and the contents were ball milled at 30 Hz under room temperature. At the end of the experiment, all of the reaction mixture was scratched off the vessel and then directly separated and purified by column chromatography. Elution of the column with PE/EtOAc (v/v=4:1) afforded the title product.

*4.7.1. N-(3-(2-Formylphenyl)propyl)benzamide (**8a**).* Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 10.12 (s, 1H), 7.94–7.87 (m, 2H), 7.79 (d, J=7.2 Hz, 2H), 7.55–7.39 (m, 5H), 7.31 (d, J=7.6 Hz, 1H), 6.98 (br s, 1H), 3.58–3.44 (m, 2H), 3.13 (t, J=7.8 Hz, 2H), 1.98–1.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 193.6, 167.3, 144.0, 135.1, 134.4, 133.8, 133.4, 131.2, 131.1, 128.3 (2C), 126.8 (2C), 126.6, 39.6, 31.2, 30.6. MS (ESI): 290.2 ([M+Na]$^+$); HRMS (ESI) $C_{17}H_{17}NNaO_2$ ([M+Na]$^+$): calcd: 290.1151, Found: 290.1153.

*4.7.2. N-(3-(2-Formylphenyl)propyl)-3-methylbenzamide (**8b**).* Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 10.13 (s, 1H), 7.79 (d, J=7.6 Hz, 1H), 7.71 (s, 1H), 7.67 (d, J=7.2 Hz, 1H), 7.55–7.28 (m, 1H), 7.41 (t, J=7.2 Hz, 1H), 7.35–7.26 (m, 3H), 6.90 (br s, 1H), 3.55–3.46 (m, 2H), 3.13 (t, J=8.0 Hz, 2H), 2.40 (s, 3H), 1.96–1.85 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 193.4, 167.6, 159.2, 144.0, 138.1, 134.8, 134.4, 133.8, 131.8, 131.2, 128.2, 127.7, 126.7, 123.7, 39.6, 31.3, 30.7. MS (ESI): 304.3 ([M+Na]$^+$); HRMS (ESI) $C_{18}H_{19}NNaO_2$ ([M+Na]$^+$): calcd: 304.1308, Found: 304.1321.

*4.7.3. N-(3-(2-Formylphenyl)propyl)-3-chlorobenzamide (**8c**).* Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 10.11 (s, 1H), 7.93–7.90 (m, 1H), 7.80 (d, J=7.2 Hz, 1H), 7.56–7.50 (m, 1H), 7.48–7.35 (m, 3H), 7.32 (d, J=7.6 Hz, 1H), 7.05 (br s, 1H), 3.55–3.46 (m, 2H), 3.13 (t, J=7.8 Hz, 2H). 1.96–1.85 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 193.9, 166.0, 143.9, 136.3, 135.6, 134.6, 133.9, 131.3, 131.2, 129.7, 127.4, 126.8, 124.9, 39.7, 31.1, 30.8. MS (ESI): 302.3 ([M+H]$^+$); HRMS (ESI) $C_{17}H_{16}ClNNaO_4$ ([M+Na]$^+$): calcd: 324.0762, Found: 324.0754.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (No. 21406201) and the Special Program for Key Basic Research of the Ministry of Science and Technology, China (No. 2014CB460608) for financial support. We also thank Dr. Tucai Zheng in Quzhou University for his assistance in the preparation of this manuscript.

Supplementary data

Supplementary data (NMR spectra of the products can be founded in the Supplementary data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tet.2015.06.105.

References and notes

1. Steinmann, P.; Keiser, J.; Bos, R.; Tanner, M.; Utzinger, J. *Lancet Infect. Dis.* **2006**, *6*, 411–425.
2. Fenwick, A.; Savioli, L.; Engels, D.; Bergquist, R.; Todd, M. H. *Trends Parasitol.* **2003**, *19*, 509–515.
3. (a) Maffrand, J. P. U. S. Patent 4 523 013, **1983**; (b) Frehel, D.; Maffrand, J. P. *Heterocycles* **1983**, *20*, 1731–1735; (c) Berkowitz, W. F.; John, T. V. *J. Org. Chem.* **1984**, *49*, 5269–5271; (d) Yuste, F.; Pallas, Y.; Barrios, H.; Ortiz, B.; Sanchez-Obregon, R. *J. Heterocycl. Chem.* **1986**, *23*, 189–190; (e) Kim, J. H.; Lee, Y. S.; Park, H.; Kim, C. S. *Tetrahedron* **1998**, *54*, 7395–7400; (f) Kim, J. H.; Lee, Y. S.; Kim, C. S. *Heterocycles* **1998**, *48*, 2279–2285; (g) E1-Fayyoumy, S.; Mansour, W.; Todd, M. H. *Tetrahedron Lett.* **2006**, *47*, 1287–1290; (h) Roszkowski, P.; Maurin, J. K.; Czarnockia, Z. *Tetrahedron: Asymmetry* **2006**, *17*, 1415–1419.
4. (a) Girard, S. A.; Knauber, T.; Li, C. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74–100; (b) Zheng, C.; You, S. L. *RSC Adv.* **2014**, *4*, 6173–6214; (c) Li, C. J. *From C–H to C–C Bonds: Cross-dehydrogenative-coupling*; The Royal Society of Chemistry: Cambridge, 2015.
5. Su, W. K.; Yu, J. B.; Li, Z. H.; Jiang, Z. J. *J. Org. Chem.* **2011**, *76*, 9144–9154.
6. The oxidative ring opening of furans: (a) Blankm, S. J.; Stephens, C. E. *Tetrahedron Lett.* **2006**, *47*, 6849–6850; (b) Sayama, S. *Synth. Commun.* **2007**, *37*, 3067–3075; (c) Hayes, S. J.; Knight, D. W; Smith, A. W. T.; O'Halloran, M. J. *Tetrahedron Lett.* **2010**, *51*, 720–723; (d) Asta, C.; Conrad, J.; Mika, S.; Beifuss, U. *Green. Chem.* **2011**, *13*, 3066–3069; (e) Brust, A.; Lichtenthaler, F. W. *Green. Chem.* **2013**, *15*, 1368–1372. The oxidative ring opening of thiophenes: (f) Nandakumar, M.; Sivasakthikumaran, R.; Mohanakrishnan, A. K. *Eur. J. Org. Chem.* **2012**, 3647–3657. The oxidative ring opening of pyrroles: (g) Sessler, J. L.; Shevchuk, S. V.; Callaway, W.; Lynch, V. *Chem. Commun.* **2001**, 968–969. The oxidative ring opening of other heterocycles: (h) Antoniotti, S.; Duñach, E. *Eur. J. Org. Chem.* **2004**, 3459–3463; (i) Luo, Z. B.; Wu, J. Y.; Hou, X. L.; Dai, L. X. *Org. Biomol. Chem.* **2007**, *5*, 3428–3430.

7. (a) Ruwet, A.; Meessen, J.; Renson, M. *Bull. Soc. Chim. Belg.* **1969**, *78*, 459–464; (b) Dereu, N.; Renson, M. *J. Organomet. Chem.* **1983**, *258*, 163–169; (c) Okuma, K.; Kojima, K.; Koga, Y.; Shioji, K. *Heterocycles* **2000**, *52*, 1021–1024; (d) Sashida, H.; Satoh, H.; Ohyanagi, K.; Kaname, M. *Molecules* **2010**, *15*, 1466–1472.
8. (a) Nakamura, M.; Inoue, T.; Nakamura, E. *J. Organomet. Chem.* **2001**, *624*, 300–306; (b) Barluenga, J.; González-Bobes, F.; Ananthoju, S. R.; García-Martín, M. A.; González, J. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3389–3392; (c) Herrera, A. J.; Rondón, M.; Suárez, E. *J. Org. Chem.* **2008**, *73*, 3384–3391; (d) Lu, L. B.; Shi, M. *Chem.—Eur. J.* **2011**, *17*, 9070–9075; (e) Ren, R.; Yang, H.; Zheng, Y.; Ng, S.; Zhao, J. S. *Can. J. Chem. Eng.* **2013**, *91*, 776–782; (f) Piech, K.; Bally, T.; Allen, A. D.; Tidwell, T. T. *J. Org. Chem.* **2013**, *78*, 2908–2913.
9. (a) Lange, U.; Plizko, W.; Blechert, S. *Tetrahedron* **1995**, *51*, 5781–5788; (b) Walsh, J. G.; Furlong, P. J.; Byrne, L. A.; Gilheany, D. G. *Tetrahedron* **1999**, *55*, 11519–11536; (c) Trost, B. M.; Dong, G. B. *J. Am. Chem. Soc.* **2006**, *128*, 6054–6055; (d) Do, Y. S.; Sun, R.; Kim, H. J.; Yeo, J. E.; Bae, S.; Koo, S. *J. Org. Chem.* **2009**, *74*, 917–920; (e) Tsuchida, H.; Tamura, M.; Hasegawa, E. *J. Org. Chem.* **2009**, *74*, 2467–2475; (f) Kafka, S.; Proisl, K.; Kašpárkková, V.; Urankar, D.; Kimmel, R.; Košmrlj, J. *Tetrahedron* **2013**, *69*, 10826–10835.
10. Kim, H. J.; Su, L.; Jung, H.; Koo, S. *Org. Lett.* **2011**, *13*, 2682–2685.
11. Yadav, J. S.; Satheesh, G.; Murthy, C. V. S. R. *Org. Lett.* **2010**, *12*, 2544–2547.
12. Gelmi, M. L.; Nava, D.; Leone, S.; Pellegrino, S.; Baldelli, E.; Zunino, F.; Zunino, F.; Cappelletti, G.; Cartelli, D.; Fontana, G. *J. Org. Chem.* **2008**, *73*, 8893–8900.
13. Appendino, G.; Danieli, B.; Jakupovic, J.; Belloro, E.; Scambia, G.; Bombardelli, E. *Tetrahedron Lett.* **1997**, *38*, 4273–4276.
14. (a) Overman, L. E.; Owen, C. E.; Pavan, M. P. *Org. Lett.* **2003**, *5*, 1809–1812; (b) Shimizu, M.; Kimura, M.; Watanabe, T.; Tamaru, Y. *Org. Lett.* **2005**, *7*, 637–640; (c) Liao, W. W.; Ibrahem, I.; Córdova, A. *Chem. Commun.* **2006**, 674–676; (d) Giera, D. S.; Sickert, M.; Schneider, C. *Synthesis* **2009**, 3797–3802; (e) Schultz, D. M.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 2962–2965.
15. Tsang, A. S. K.; Ingram, K.; Keiser, J.; Hibbert, D. B.; Todd, M. H. *Org. Biomol. Chem.* **2013**, *11*, 4921–4924.
16.. Comparative experiments: A solution of DDQ (0.250 g, 1.1 mmol) in 10 mL dichloromethane or nitromethane was added dropwise into *N*-acyl-1,2,3,4-tetrahydroisoquinolines (1 mmol). The mixture was stirred at 40 °C for appropriate time. The mixture was concentrated in vacuo, and then purified by silica gel column chromatography using PE/EtOAc (*v*/*v*=15:1) to afford the product.
17. (a) Stanley, A. L.; Stanforth, S. P. *J. Heterocycl. Chem.* **1995**, *32*, 569–571; (b) Hedley, K. A.; Stanforth, S. P. *Tetrahedron* **1992**, *48*, 743–750.
18. Zhang, J.; Zhang, Y. M.; Shan, Y. Y.; Li, N.; Ma, W.; He, L. C. *Eur. J. Med. Chem.* **2010**, *45*, 2798–2805.
19. Fensholdt, J. W. O. Patent 2010 136 036 A2, **2010**.
20. Buchmann, B. D. E. Patent 10 2009 049 662 A1, **2011**.
21. (a) Li, Z. P.; Li, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 11810–11811; (b) Tsang, A. S. K.; Todd, M. H. *Tetrahedron Lett.* **2009**, *50*, 1199–1202; (c) Tsang, A. S. K.; Par, k. S. J.; Todd, M. H. In *From C–H to C–C Bonds: Cross-dehydrogenative-coupling*; Li, C. J., Ed.; The Royal Society of Chemistry: Cambridge, 2015; Vol. 11, pp 254–294.
22. Yu, J. B.; Li, Z. H.; Jia, K. Y.; Jiang, Z. J.; Liu, M. L.; Su, W. K. *Tetrahedron Lett.* **2013**, *54*, 2006–2009.
23. Jones, R. C. F.; Smallridge, M. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 385–391.
24. Al-Hiari, Y. M.; Sweileh, B. A.; Shakya, A. K.; Sheikha, G. A.; Almuhtaseb, S. I. *Jordan J. Pharm. Sci.* **2009**, *2*, 1–21.