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Diethyl Phosphite Promoted Electrochemical Oxidation of Tetrahydroisoquinolines to 3,4-Dihydroisoquinolin-1(2*H*)-ones

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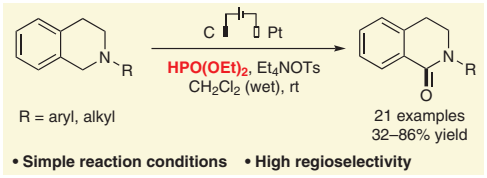

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Abstract A diethyl phosphite mediated electrochemical oxidation strategy for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones from tetrahydroisoquinolines under mild conditions has been developed. This protocol provides an environmentally friendly and simple way for the construction of C=O bonds in an undivided cell unit.

Key words electrochemistry, oxidation, diethyl phosphite, tetrahydroisoquinoline, C=O bond formation

Isoquinoline alkaloids represent an important group of natural products and exhibit a broad spectrum of biological activities.[1] Isoquinolin-1(2*H*)-one derivatives exist extensively in naturally and biologically interesting molecules such as baluchistanamine, ruprechstyril, dorianine, and thalflavine depicted in Figure 1.[2] Traditional methods for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones generally rely on multi-step processes,[3] transition-metal catalysts,[4] a photocatalyst,[5] and/or stoichiometric oxidants,[6] which would produce undesired waste. More recently, Lee and co-workers developed an efficient oxidation reaction of *N*-substituted tetrahydroisoquinolines to dihydroisoquinolones using eosin Y as an organo-photocatalyst and oxygen as a green oxidant.[7]

Organic electrosynthesis, which achieves redox reactions with traceless electric current, is accepted to be an environment-friendly and enabling synthetic tool.[8] In 2013, Zeng and Little described the electrochemical oxidative functionalization of benzylic C–H bonds for the synthesis of *N*-alkyl tetrahydroisoquinolones using bromide ion/2,2,6,6-tetramethylpiperidinyl-*N*-oxyl dual redox catalysts in a two-phase electrolytic system.[9] Recently, we reported a metal- and reagent-free electrochemical CDC reaction of

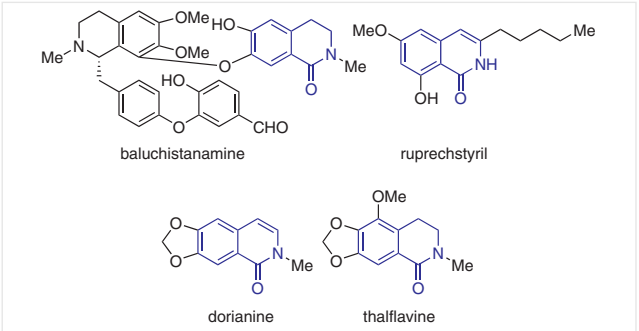

Figure 1 Naturally occurring isoquinolin-1(2*H*)-one derivatives

tetrahydroisoquinolines with phosphites and indole using an undivided cell.[10] As shown in Scheme 1, when tetrahydroisoquinoline **1a** was treated with diethyl phosphite **2a** under mild electrochemical conditions to prepare aminophosphonate **3a**, 2% yield of the lactam **4a** was also isolated. Intrigued by these findings and in continuation of our research into the development of environmentally benign synthetic methods, we developed an efficient operationally simple protocol, with no chemical oxidant needed and mild reaction conditions, for the synthesis of isoquinolones **4** from tetrahydroisoquinolines **1** by a one-pot direct electrochemical oxidative C=O bond formation in an undivided cell. Herein, the details of these studies are presented.

Initially, simple prolonging the reaction time from 4 hours to 11 hours led to the desired lactam **4a** in 43% yield (Scheme 1 and Table 1, entry 1). The choice of electrolyte has a substantial impact on the reaction outcome.

We identified the optimal reaction conditions for the oxidation reaction with Et_4NOTs instead of $^nBu_4NBr$, which involved constant-current electrolysis using a graphite rod anode and a Pt plate cathode in CH_2Cl_2 at room temperature, and the desired isoquinolone **4a** was obtained in 86%

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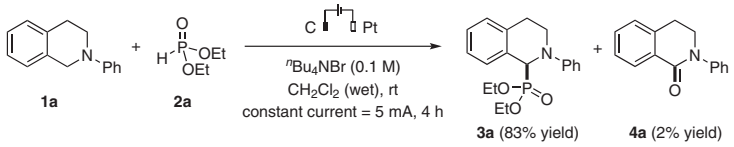
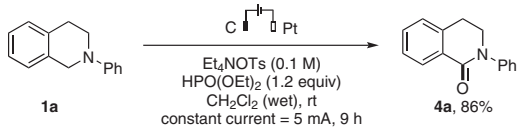


Scheme 1 Electrochemical oxidative C–P and C=O bond formation of tetrahydroisoquinolines

yield (entry 2).[11] In comparison, reduced yields were obtained when the reaction conditions were modified in one of the following manners: changing the electrolyte to ^{n}Bu$_4$NPF$_6$ (entry 3), removing (entry 4) or reducing (entry 5) the amount of diethyl phosphite, switching to other nucleophiles including H_2O (entry 6), MeOH (entry 7), and morpholine (entry 8), using other solvents such as EtOH (entry 9) or MeCN (entry 10), or adjusting the current to 10 mA (entry 11). A control experiment revealed that no desired product **4a** was observed in the absence of supplying electricity (entry 12).

Having optimized the reaction conditions, we next examined the generality of the oxidation reaction by testing a series of tetrahydroisoquinoline substrates (Table 2). To our satisfaction, a variety of functional groups, including strong electron-donating (*ortho*-, *meta*- and *para*-MeO), a mild electron-donating (*para*-Me), moderate electron-withdrawing (*ortho*-, *meta*- and *para*-F, *para*-Cl), and strong electron-withdrawing (*para*-CF_3, *para*-COMe) substituents at the *N*-phenyl ring, were well tolerated in the reaction system (**4a–k**). Tetrahydroisoquinolines bearing other *N*-aryl rings including naphthalene could be accessed (**4m**). Moreover, it is noteworthy that various alkyl substituents, including (un)substituted benzyl (**4n–r**), *n*-butyl (**4s**), allyl (**4t**), 2-ethoxy-2-oxoethyl (**4u**), and hydroxyethyl (**4v**), underwent a smooth oxidation reaction, furnishing the desired products **4n–v** in moderate to good yields (Table 2).

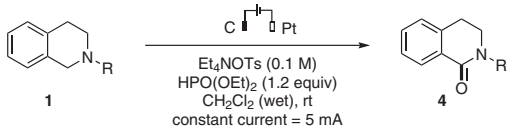
Table 1 Optimization of the Reaction Conditions[a]



Entry	Variation from reaction conditions above	Yield (%)[b]
1	^{n}Bu$_4$NBr instead of Et$_4$NOTs, 11 h	43
2	none	86
3	^{n}Bu$_4$NPF$_6$ instead of Et$_4$NOTs, 8 h	46
4	no HPO(OEt)$_2$, 7 h	36
5	0.2 equiv HPO(OEt)$_2$ was used	57
6	H_2O instead of HPO(OEt)$_2$, 6 h	18
7	MeOH instead of HPO(OEt)$_2$, 7 h	46
8	morpholine instead of HPO(OEt)$_2$, 5 h	27
9	EtOH instead of CH$_2$Cl$_2$, 8 h	5
10	CH$_3$CN instead of CH$_2$Cl$_2$, 10 h	25
11	10 mA instead of 5 mA, 5 h	77
12	no electric current, 11 h	0

[a] Reaction conditions: graphite rod anode (*d* = 5 mm), Pt plate cathode (0.5×0.5 cm), constant current = 5 mA, **1a** (0.25 mmol), diethyl phosphite (0.3 mmol), Et$_4$NOTs (0.5 mmol), CH$_2$Cl$_2$ (5 mL), undivided cell, rt, 9 h.
[b] Isolated yield.

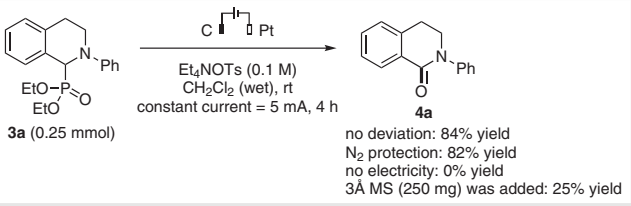
Table 2 Synthesis of Dihydroisoquinolones **4**[a]



Entry	R	Time (h)	Product	Yield (%)[b]
1	Ph	9	**4a**	86
2	*p*-MeOC$_6$H$_4$	7	**4b**	76
3	*m*-MeOC$_6$H$_4$	9	**4c**	59
4	*o*-MeOC$_6$H$_4$	8	**4d**	59
5	*p*-MeC$_6$H$_4$	5	**4e**	79
6	*p*-FC$_6$H$_4$	7	**4f**	62
7	*m*-FC$_6$H$_4$	6	**4g**	68
8	*o*-FC$_6$H$_4$	8	**4h**	55
9	*p*-ClC$_6$H$_4$	7	**4i**	70
10	*p*-CF$_3$C$_6$H$_4$	9	**4j**	65
11	*p*-AcC$_6$H$_4$	9	**4k**	40
12	*p*-O$_2$NC$_6$H$_4$	9	**4l**	trace
13	naphthalen-1-yl	6	**4m**	72
14	Bn	5	**4n**	58
15	*m*-MeOC$_6$H$_4$CH$_2$	4	**4o**	43
16	*o*-MeC$_6$H$_4$CH$_2$	4	**4p**	54
17	*o*-ClC$_6$H$_4$CH$_2$	4	**4q**	52
18	*p*-NCC$_6$H$_4$CH$_2$	5	**4r**	73
19	^{n}Bu	4	**4s**	72
20	allyl	6	**4t**	32
21	EtO$_2$CCH$_2$	6	**4u**	47
22	HOCH$_2$CH$_2$	6	**4v**	38

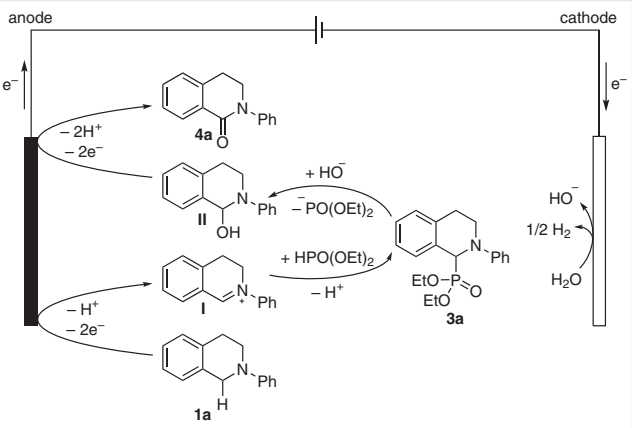
[a] Reaction conditions: graphite rod anode (*d* = 5 mm), Pt plate cathode (0.5×0.5 cm), constant current = 5 mA, **1** (0.25 mmol), diethyl phosphite (0.3 mmol), Et$_4$NOTs (0.5 mmol), CH$_2$Cl$_2$ (5 mL), undivided cell, rt.
[b] Isolated yield.

Control experiments showed that 84% yield of product **4a** was obtained when intermediate **3a** was treated under the standard conditions (Scheme 2). Moreover, 82% yield of product **4a** was isolated under N_2 protection, and no desired product was observed without electricity. These results further exclude that oxygen is the oxidation source in this reaction. Additionally, when the above reaction was conducted in the presence of 3Å molecular sieves, the desired product **4a** was suppressed and only 25% yield was obtained.



Scheme 2 Control experiments

On the basis of the observations above and literature reports,[9] a possible mechanism for the electrochemical oxidative reaction was proposed (Scheme 3). As a start, compound **1a** loses two electrons and a proton on the surface of the anode to generate the iminium-ion intermediate **I**. Intermediate **I** is captured by diethyl phosphite to afford compound **3a**. Meanwhile, concomitant cathodic reduction of H_2O releases H_2 and HO^-. Compound **3a** undergoes subsequent nucleophilic substitution with HO^- to generate intermediate **II**. Intermediate **II** is further oxidized to give the desired product **4a**. The mechanism is consistent with the result of entry 1 (Table 1); prolonging the reaction time will increase the concentration of HO^- and favor the formation of the desired product **4a**.



Scheme 3 Proposed mechanism

In summary, we have successfully developed a diethyl phosphite mediated electrochemical oxidation strategy for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones from tetrahydroisoquinolines using an undivided cell. This reaction could be carried out at room temperature without the use of any oxidants. This process offers an alternative to conventional methods that require metal catalysts or chemical oxidants and represents an environmentally benign tool for oxidative C=O bond formation.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690704.

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(11) **2-Phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (4a); Typical Procedure**
A 10 mL distillation flask equipped with a magnetic stirring bar

was charged with diethyl phosphite (42 mg, 0.3 mmol), wet CH_2Cl_2 (5.0 mL), 2-phenyl-1,2,3,4-tetrahydroisoquinoline **1a** (52 mg, 0.25 mmol), and Et_4NOTs (151 mg, 0.5 mmol). The resulting suspension was stirred until complete dissolution was achieved. The flask equipped with graphite rod anode (d = 5 mm) and Pt plate cathode (0.5×0.5 cm). The reaction mixture was stirred and electrolyzed at a constant current of 5 mA at rt for 9 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL), washed successively with water (10 mL) and brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (silica gel, petroleum ether–ethyl acetate 20:1) afforded the desired product **4a** 48 mg (86%) as a white solid; mp 119–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19–8.14 (m, 1 H), 7.51–7.34 (m, 6 H), 7.29–7.21 (m, 2 H), 4.04–3.97 (m, 2 H), 3.15 (t, J = 6.6 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8, 143.1, 138.3, 132.0, 129.7, 128.9, 128.7, 127.1, 126.9, 126.2, 125.3, 49.4, 28.6.