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# Base-promoted aerobic oxidation of *N*-alkyl iminium salts derived from isoquinolines and related heterocycles†

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Potassium *tert*-butoxide-promoted aerobic oxidation of *N*-alkyl iminium salts is reported. The reaction is atom-economical and environmentally friendly. Iminium salts derived from isoquinoline, quinoline, phenanthridine, phenanthroline, and phthalazine were successfully transformed into their corresponding unsaturated lactams with up to 95% yield under mild conditions in the absence of photocatalysts and metallic or organic catalysts. Owing to the general substrate scope, low cost, feasibility of scale up, wide availability of reagents, and green reaction conditions, this method shows great potential for preparing isoquinolones and related compounds. The method was applied for atom- and step-economical total synthesis of natural products such as norketoyobyrine.

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## Introduction

Oxidation is a fundamental transformation in organic chemistry and is commonly used to convert a variety of organic compounds. Oxygen ($O_2$), also known as dioxygen or molecular oxygen, is an abundant, inexpensive, clean, and atom-economical oxidant.[1] It constitutes approximately one fifth of the Earth's atmosphere, and reacts exothermically with most elements. However, oxygen has a triplet ground state, which poses a high barrier to reactions with molecules that are usually in the singlet state.[2] Two activating strategies for oxidation with oxygen are commonly used. One is the activation of oxygen by converting oxygen molecules from triplet ($^3O_2$) to singlet oxygen ($^1O_2$) or other reactive oxygen species (ROS).[3] The other is the activation of the substrate or catalyst by forming radicals through a single electron transfer process between the substrate and catalyst.[4] These strategies often require expensive photocatalysts and/or metal complexes as promoters.[5] Therefore, the development of environmentally friendly, mild, and low-cost oxidation approaches based on oxygen as the terminal oxidant would be desirable in the chemical community and is a key focus of green chemistry.[6]

Bases are also typically electron donors.[7] Oxygen molecules tend to be more reactive under an electron-rich alkaline environment than under neutral conditions. Numerous studies have reported that some organic molecules are prone to oxidation by oxygen (air) in a simple manner under alkaline conditions, whereas they can coexist in air for a long time under neutral conditions.[8] We envisaged that certain photocatalytic or metal-mediated oxidations may be promoted by the use of certain bases.

Isoquinolones and quinolones are present in various natural products and bioactive molecules.[9] Hence, synthetic methodologies for these structural scaffolds have drawn considerable interest.[10] Oxidation of *N*-alkyl iminium salts derived from isoquinolines and related heterocycles is a particularly straightforward strategy for the synthesis of isoquinolones and their analogues. Traditional approaches to this oxidation rely on the use of an excess of potassium ferricyanide as the oxidant, which unavoidably generates a large amount of harmful metal waste.[10e,f] In contrast, oxidation with oxygen as a green oxidant is an environmentally friendly method (Scheme 1).[10e–h] Using limited examples, Gngnon-Dubois *et al.* showed an access to isoquinolones and quinolones *via* an ultrasonic irradiation-accelerated nucleophilic addition of quinolinium and isoquinolinium salts with potassium *tert*-butoxide (*t*-BuOK) followed by silica gel-catalyzed aerobic oxidation.[10h] In 2017, Fu *et al.* realized photocatalytic oxidation of *N*-alkyl iminium salts with air.[10e] In 2018, Huang and Fu achieved the carbene-catalyzed aerobic oxidation of *N*-alkyl iso-

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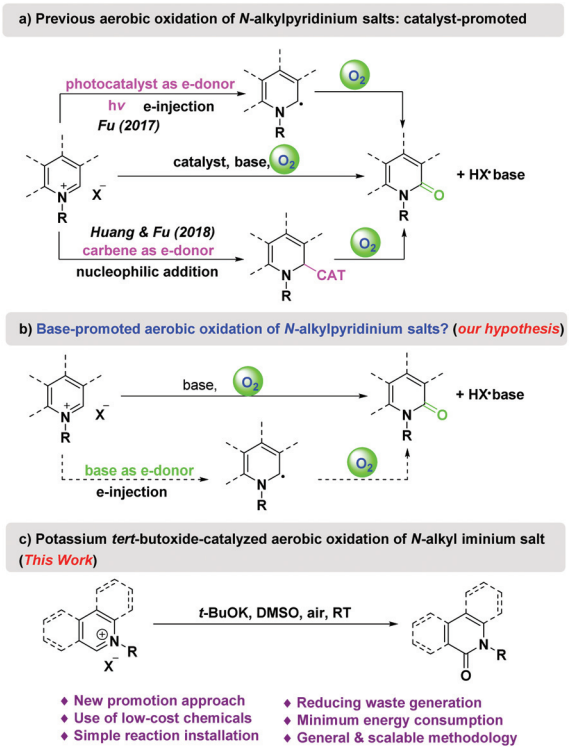


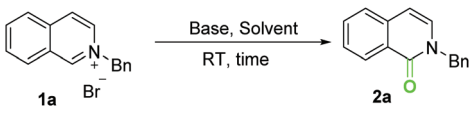

**Scheme 1** Selected literature precedents on aerobic oxidation of azine-derived *N*-alkyl iminium salts (a), idea (b) and advantages (c) of this work.

quinolinium salts.[10f] Herein, we describe *t*-BuOK-promoted aerobic oxidation of *N*-alkyl iminium salts. Compared to the previous methods, the main advantages of our process include lower reagent costs, less organic waste generation and energy consumption, and no requirement of a special reaction setup. Through the use of this method, the total synthesis of the natural alkaloid norketoyobyrine was accomplished using a concise route starting from isoquinoline and other inexpensive commercial chemicals.

## Results and discussion

We began our investigation by selecting 2-benzylisoquinolin-2-ium bromide **1a** as a model substrate (Table 1). In a dimethyl sulfoxide (DMSO) solution of potassium *tert*-butoxide, electron transfer between donors and electron-deficient π systems (electron acceptors) often occurs readily.[11] *N*-Alkyl isoquinolinium salts are electron-deficient π systems. We envisaged that electron transfer from a base or other electron donor species to the salts should also readily occur in DMSO. Thus, we conducted the oxidation of **1a** in air at room temperature (RT) with the use of DMSO as the solvent and *t*-BuOK as a base. Rewardingly, the desired isoquinolinone **2a** was obtained in good yield (entry 1). Solvent screening experiments showed that *tert*-butanol also realized the transformation with moderate yield. Other tested solvents gave disappointing results (entries 3–8). Base screening experiments (entries 9–14) indicated that *t*-BuOK was superior to KOH (entry 11 *vs.* 1) and

**Table 1** Optimization of the reaction conditions[a]




| Entry | Base (equiv.) | Solvent | Yield (%) |
|---|---|---|---|
| 1 | *t*-BuOK (3) | DMSO | 82 |
| 2 | *t*-BuOK (3) | *t*-BuOH | 52 |
| 3 | *t*-BuOK (3) | DMF | Trace |
| 4 | *t*-BuOK (3) | Dioxane | Trace |
| 5 | *t*-BuOK (3) | DCM | Trace |
| 6 | *t*-BuOK (3) | Toluene | Trace |
| 7 | *t*-BuOK (3) | MeCN | Messy |
| 8 | *t*-BuOK (3) | THF | Messy |
| 9 | *t*-BuOK (1.5) | MeCN | 31 |
| 10 | *t*-BuOK (1) | THF | 17 |
| 11 | KOH (3) | DMSO | 76 |
| **12** | ***t*-BuOK (2)** | **DMSO** | **95** |
| 13 | *t*-BuOK (1.5) | DMSO | 80 |
| 14 | $Cs_2CO_3$ (1.5) | DMSO | 33 |
| **15**[b] | **$Cs_2CO_3$ (1.5)** | **DMSO** | **86** |

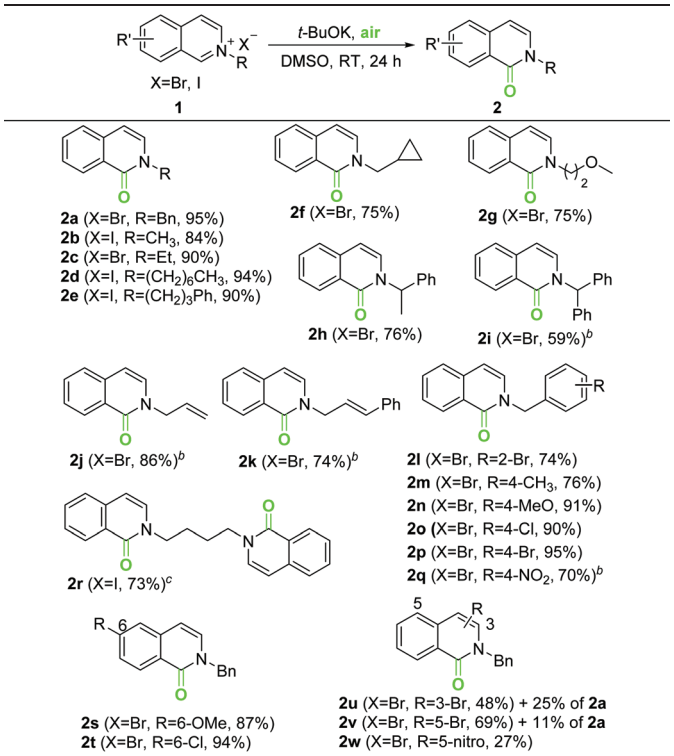
[a] Reaction conditions: **1a** (0.3 mmol), base, solvent (3 mL) at room temperature (RT) for 16 h (entries 1–10), or solvent (1.5 mL) at RT for 24 h (entries 11–15). [b] Hydrogen peroxide–urea (UHP, 1.5 equiv.) was employed.

$Cs_2CO_3$ (entry 14 *vs.* 13). A decrease in the amount of *t*-BuOK to 2 equivalents gave the best result (entry 12).[12,13]

Analysis of the composition of the final reaction mixture by NMR spectroscopy showed that 15%–30% of dimethyl sulfone was formed, but no dimethyl sulfide was detected.[13] We inferred that ROS were produced *in situ* in the aerobic oxidation process, because ROS are capable of converting sulfoxides to sulfones.[14] $Cs_2CO_3$ is a weaker base than *t*-BuOK but is not as efficient as the latter for oxidation (entry 14). Hydrogen peroxide was explored as an additional oxidant. A combination of hydrogen peroxide–urea (UHP) and $Cs_2CO_3$ also realized the transformation with high yield (entry 15), and provides a green alternative for use with strong base-sensitive substrates.

With the optimized conditions in hand (Table 1, entry 12), we selected a series of isoquinolinium salts **1** to evaluate the reaction scope (Table 2). The reactivity of isoquinolinium salts containing various *N*-alkyl groups (**1a–1r**) was first investigated. Substrates bearing an *N*-benzyl or a linear *N*-alkyl group gave the corresponding isoquinolones in very good to excellent yields (**2a–2e**). Substrates bearing a cyclopropylmethyl, 2-methoxyethyl or a branched alkyl group also led to the oxidation products in good yields (**2f–2h**). In contrast, *N*-diphenylmethyl, *N*-allyl, and *N*-cinnamyl isoquinolinium salts failed to produce the intended isoquinolones **2i–2k** under the standard conditions, presumably because of the relatively strong acidity of these *N*-alkyl groups. Through the use of UHP and a weak base, **2i–2k** were obtained successfully. Substituents on the *N*-benzyl group of isoquinolinium salts had little effect on the oxidation, except for the nitro groups (**2q** *vs.* **21–2p**). The nitro substituents are strongly electron withdrawing and capable of increasing the acidity of the benzyl hydrogen atom, which

**Table 2** Reaction scope of *N*-alkyl isoquinolinium salts[a]



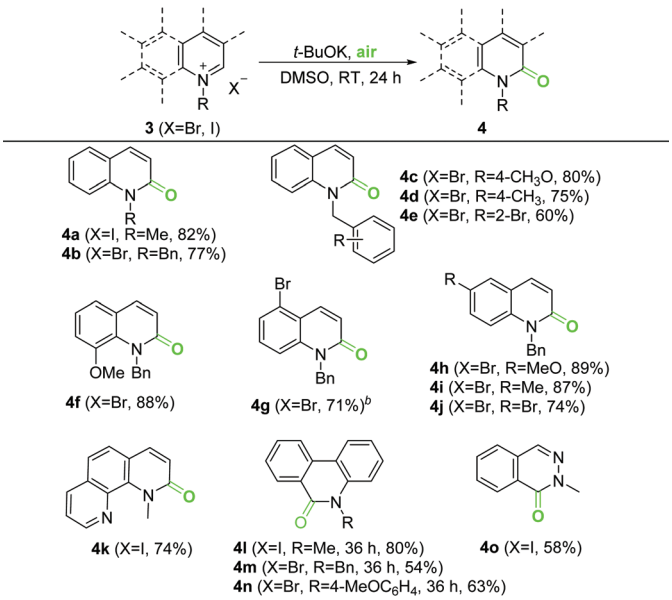

[a] Reaction conditions: **1** (0.3 mmol), *t*-BuOK (0.6 mmol), and DMSO (1.5 mL) at RT for 24 h unless otherwise noted. Yields of isolated products. [b] **1** (0.3 mmol), $Cs_2CO_3$ (0.45 mmol), and UHP (0.45 mmol). [c] **1** (0.3 mmol), *t*-BuOK (1.2 mmol), and DMSO (3 mL).

might obstruct the oxidation of **1q** in a strongly alkaline solution.[1,8c,11c] Through the use of UHP and $Cs_2CO_3$, **1q** was converted into **2q** with acceptable yield. Bis(isoquinolinium) salt **1r** was oxidized to **2r** in 73% yield under standard conditions. Substituted isoquinolinium salts **1s–1w** were then evaluated. The reactivity of the 6-position substituted substrates was similar to that of their unsubstituted counterparts (**2s–2t** *vs.* **2a–2e**). However, 3-bromo and 5-bromo isoquinolinium salts generated a certain amount of the debrominative oxygenation product **2a**, accompanied by the desired isoquinolones in moderate yields (**2u–2v**). Furthermore, 5-nitro-isoquinolone **2w** was obtained in poor yield, which further suggests that the nitro group prevented oxidation under standard conditions.

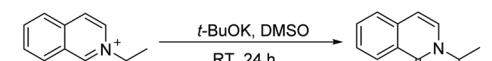
We next extended our method to other *N*-alkyl iminium salts. All reactions proceeded smoothly and led to the formation of the desired unsaturated lactams **4** in mostly good yields under optimal conditions (Table 3). Debrominative oxygenation of 5-bromo quinolinium **3g** was also observed (13% of **4b** plus 51% of **4g**). UHP-mediated oxidation overcame the debromination and produced **4g** in good yield. Phenanthridinium salts showed lower reactivity than the other tested iminium salts and required a prolonged reaction time of 36 h for full conversion (**4l–4n**).

Analysis of the unexpected outcomes of the oxidation helped us probe the reaction mechanism. Under standard conditions, the oxidation of *N*-diphenylmethyl substrate **1i** generated 76% of benzophenone and 64% of isoquinolin-1(2*H*)-one **2i′**, whereas the oxidation of *N*-(1-phenyl)ethyl substrate **1h** gave 76% of the intended oxidation product **2h** (eqn (1) and (2)).

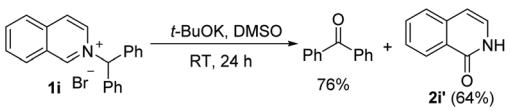
**Table 3** Reaction scope of other *N*-alkyl iminium salts[a]




[a] Conditions: **1** (0.3 mmol), *t*-BuOK (0.6 mmol), DMSO (1.5 mL) at RT for 24 h unless otherwise noted. Yields of isolated products. [b] **1** (0.3 mmol), $Cs_2CO_3$ (0.45 mmol), and UHP (0.45 mmol).

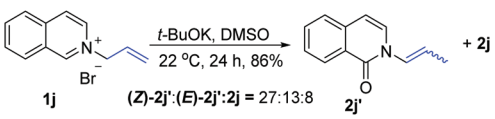



(1)

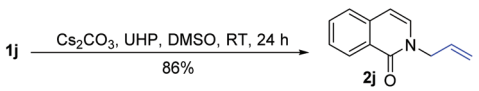



(2)

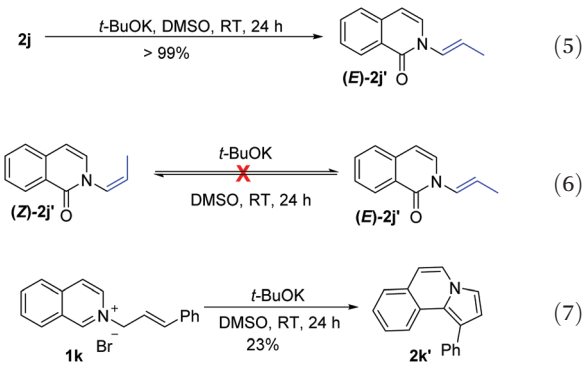
*t*-BuOK-mediated oxidation of **1j** mainly yielded the double bond-shifted product **2j′**,[15] whereas the UHP-mediated method gave the "normal" oxidation product **2j** (eqn (3) and (4)). Under standard conditions, **2j** quantitatively converted to (*E*)-**2j′**, whereas (*E*)-**2j′** and (*Z*)-**2j′** did not isomerize into each other (eqn (5) and (6)). Meanwhile, **1k** was oxidized into cyclic **2k′**, rather than the "normal" oxidation product **2k** (eqn (7)).




(3)




(4)



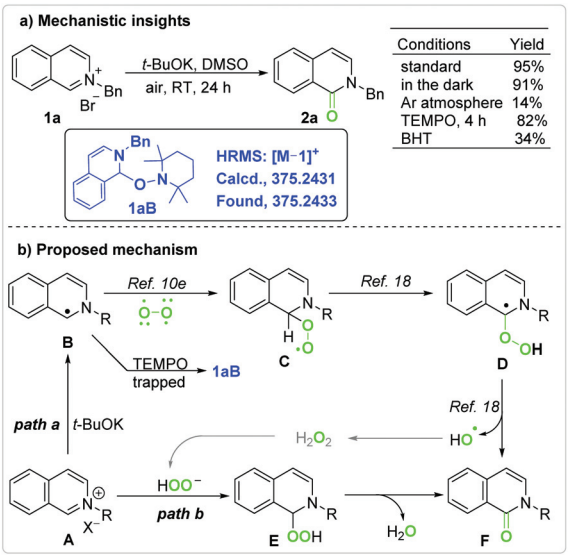

Mechanistic studies (Scheme 2a) indicated that the yield was hardly affected when the reaction was performed in the dark but sharply decreased under an inert atmosphere. The reaction was greatly limited by the radical inhibitor butylated hydroxytoluene (BHT, 2 equivalents),[16] but accelerated by the free radical 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 2 equivalents).

The reaction mechanism was further studied by high resolution mass spectroscopy (HRMS) with an ESI source (Fig. S6–S11†).[13] Under standard conditions, mass peaks at $m/z$ = 220.11 (M − 79 peak of **1a**) and 274.06 (M + 39 peak of **2a**) were detected; however, that at $m/z$ = 375.24 was not detected in the reaction mixture. On addition of TEMPO to the reaction mixture, a new mass peak at $m/z$ = 375.24 (M − 1 peak of **1aB**, Scheme 2a) was detected, which resulted from a radical intermediate being trapped by TEMPO. In the absence of *t*-BuOK, the addition of TEMPO did not lead to the formation of either **2a** or **1aB**. These observations indicate that the oxidation of **1a** was actually initiated by *t*-BuOK.

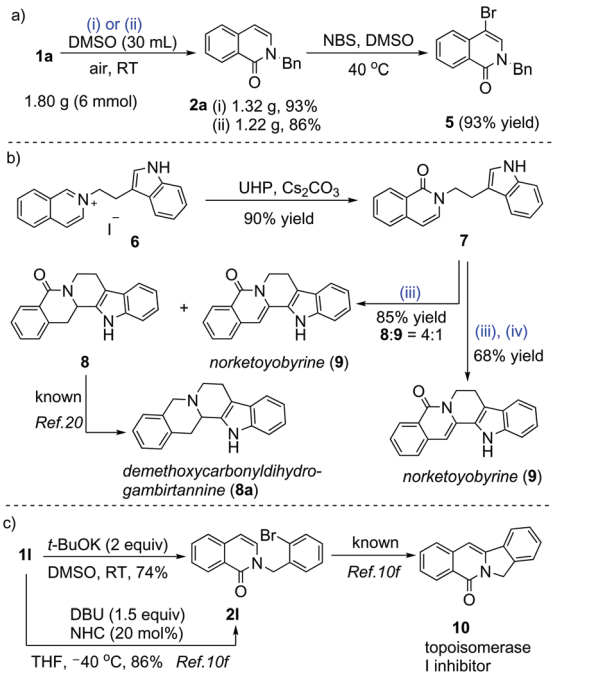
According to previous work and the above results, a possible mechanism for the *t*-BuOK-promoted aerobic oxidation is proposed in Scheme 2b. The reaction was initiated along path a. A single electron transfer (SET) from the base to iminium cation **A** provides radical **B**.[11,17] The cross coupling of carbon radical **B** with diradical molecular oxygen leads to alkylperoxyl radical **C**.[10e] Alkylperoxyl radical **C** is converted to α-hydroperoxy-α-carbon radical **D** *via* hydrogen atom transfer (HAT).[18] Radical **D** gives the final product **F** and a hydroxyl radical.[18] A hydroxyl radical evolves into hydrogen peroxide or other ROS that further oxidize **A** to yield **F** *via* pathways such as path b.[3,19]

The utility of our protocol is exemplified in Scheme 3. Gram-scale preparation by this oxidation was feasible. The reaction efficiency was slightly affected when **1a** was used on a 6 mmol scale for both *t*-BuOK-promoted aerobic oxidation and UHP-mediated oxidation. The bromination of oxidation product **2a** with *N*-bromosuccinimide (NBS) under mild conditions led to 4-bromo isoquinolinone **5** in excellent yield (Scheme 3a).

Our oxidative method was successfully applied to the atom- and step-economical total synthesis of natural products (Scheme 3b). Consequently, norketoyobyrine (**9**) was synthesized in 61% total yield *via* the three-step sequence of oxidation, cyclization and dehydrogenative oxidation from isoquinolinium salt **6**. Reduction of intermediate **8** (dihydronorketoyobyrine) delivered demethoxycarbonyldihydrogambirtannine (**8a**) *via* a known process.[20] Gao *et al.* reported an elegant strategy for constructing natural products such as **9**.[9a] Our synthetic precursors for norketoyobyrine were more easily prepared compared to those using Gao *et al.*'s method. Our method used no protective groups and no unwanted carbon atoms were removed. Special and/or expensive reagents were avoided in each step.




**Scheme 2** Mechanistic insights (a) and the proposed mechanism (b).




**Scheme 3** Gram-scale synthesis and bromination of **2a** (a), total syntheses of norketoyobyrine and its related compounds (b), and formal synthesis of topoisomerase I inhibitor **10** (c). Conditions: (i) *t*-BuOK (2 equiv.); (ii) UHP (1.5 equiv.), $Cs_2CO_3$ (1.5 equiv.); (iii) $BF_3{\cdot}Et_2O$, MeCN, 85 °C; and (iv) $CeCl_3{\cdot}7H_2O$ (0.1 equiv.), air, *i*-PrOH, 50 °C.

Our oxidative method was also applicable to the formal synthesis of topoisomerase I inhibitor **10** (Scheme 3c).[9c] Compared with other green methods for the synthesis of **10** reported in the most recent literature,[10f] our protocol required neither the NHC catalyst nor cooling of the reaction system to far below ambient temperature. These features are beneficial in terms of reducing organic waste generation and energy consumption.

## Conclusions

In conclusion, we report here a mild and environmentally benign aerobic oxidative method for the simple synthesis of a wide variety of isoquinolinones and related heterocyclic derivatives. In the absence of commonly used promoters, such as metallic reagents, photocatalysts, and other additives, a series of N-heterocycle-derived *N*-alkyl iminium salts were successfully oxidized into their corresponding unsaturated lactams with the sole use of a base, a solvent, and ambient atmosphere at room temperature. The reaction was scaled up to produce grams of *N*-alkyl isoquinolin-1(2*H*)-one under mild conditions. Mechanistic studies indicated that the oxidation was initiated by *t*-BuOK, and the experimental observations were preliminarily in agreement with a radical mechanism. Through the use of the method, a highly efficient total synthesis of the natural alkaloid norketoyobyrine was accomplished in a concise manner starting from isoquinoline and other inexpensive commercial chemicals. The method combines several advantages, such as broad generality, low cost, wide availability of reagents, limited production of harmful waste, and ease of use. Overall, the present method ranks among the most economical and greenest methods reported for the oxidation of *N*-alkyl iminium salts.

## Experimental

### General procedures for the oxidation of *N*-alkyl iminium salts 1 & 3

The isolated products were confirmed by $^{1}$H NMR and $^{13}$C NMR. The characterization data are described in the ESI.† The exact time for each reaction is shown in Tables 2 and 3.

**Procedure (i), through *t*-BuOK-promoted aerobic oxidation.** To a mixture of *N*-alkyl iminium salt **1** or **3** (0.3 mmol) and potassium *tert*-butoxide (67 mg, 0.6 mmol) in a 5 mL reaction flask was added dimethyl sulfoxide (1.5 mL). The mixture was continuously stirred at room temperature until **1** or **3** was consumed as indicated by thin-layer chromatography (TLC, typically for 24 h). Then it was diluted with water (5 mL), and extracted with ethyl acetate (3 × 5 mL). The combined organic phase was dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to give the desired product **2** (for **1**) or **4** (for **3**).

**Procedure (ii), through UHP-mediated oxidation.** To a mixture of *N*-alkyl iminium salt **1** or **3** (0.3 mmol), cesium carbonate (147 mg, 0.45 mmol) and urea hydrogen peroxide (42 mg, 0.45 mmol) in a 5 mL flask was added dimethyl sulfoxide (1.5 mL). The mixture was continuously stirred at room temperature until **1** or **3** was consumed as indicated by TLC (typically for 24 h). Then it was diluted with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic phase was dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to give the desired product **2** (for **1**) or **4** (for **3**).

### Gram-scale preparation of 2a

**(i) Preparation through *t*-BuOK-promoted aerobic oxidation.** To a mixture of *N*-benzylisoquinolin-2-ium bromide **1a** (1.80 g, 6.0 mmol) and potassium *tert*-butoxide (1.35 g, 12.0 mmol) in a 100 mL flask was added DMSO (30 mL) with stirring. The reaction mixture was continuously stirred in air at room temperature until **1a** was consumed as indicated by TLC (*ca.* 72 h). Then it was diluted with ethyl ester (70 mL) and water (70 mL) and extracted with EtOAc (3 × 70 mL). The combined organic phase was dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1) to provide *N*-benzyl isoquinolin-1(2*H*)-one **2a** as a yellow solid (1.32 g, 93% yield).

**(ii) Preparation through UHP-mediated oxidation.** To a mixture of *N*-benzylisoquinolin-2-ium bromide **1a** (1.80 g, 6.0 mmol), cesium carbonate (2.93 g, 9.0 mmol) and urea hydrogen peroxide (847 mg, 9.0 mmol) in a 100 mL reaction flask was added DMSO (30 mL) with stirring. The reaction mixture was continuously stirred in air at room temperature until **1** was consumed as indicated by TLC (*ca.* 24 h). Then it was diluted with ethyl ester (70 mL) and water (70 mL) and extracted with EtOAc (3 × 70 mL). The combined organic phase was dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1) to provide *N*-benzylisoquinolin-1(2*H*)-one **2a** as a yellow solid (1.22 g, 86%).

### Bromination of 2a with *N*-bromosuccinimide

A 10 mL reaction flask was charged with a solution of *N*-benzylisoquinolin-1(2*H*)-one **2a** (71 mg, 0.3 mmol) and NBS (133 mg, 0.75 mmol) in DMSO (1.5 mL). The reaction mixture was continuously stirred at 40 °C until **2a** was consumed as indicated by TLC (*ca.* 18 h). Then it was diluted with ethyl acetate (5 mL) and water (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with water and saturated brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1) to provide *N*-benzyl-4-bromoisoquinolin-1(2*H*)-one **5** as a white solid (87 mg, 93%).[10c] $^{1}$H NMR (600 MHz, $CDCl_3$) $\delta$ 8.40 (d, $J$ = 8.0 Hz, 1H), 7.73 (d, $J$ = 8.1 Hz, 1H), 7.69–7.60 (m, 1H), 7.48 (t, $J$ = 7.6 Hz, 1H), 7.29–7.26 (m, 3H), 7.25–7.20 (m, 3H), 5.12 (s, 2H). $^{13}$C NMR

(151 MHz, $CDCl_3$) $\delta$ 161.4, 136.3, 135.47, 133.0, 131.8, 129.0, 128.5, 128.15, 128.10, 127.9, 126.6, 125.9, 100.2, 51.8.

### Total synthesis of norketoyobyrine (9)

**Aerobic oxidation of iminium salt 6.** A 100 mL flask was charged with 2-(2-(1*H*-indol-3-yl)ethyl)isoquinolin-2-ium iodide **6** (800 mg, 2 mmol), cesium carbonate (977 mg, 3.0 mmol) and UHP (282 mg, 3.0 mmol), and cooled in an ice-bath. Then DMSO (7.5 mL) and DMF (7.5 mL) were added with stirring. The reaction mixture was continuously stirred in an ice-bath until **6** was consumed as indicated by TLC (*ca.* 36 h). It was diluted with ethyl acetate (15 mL) and water (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phase was washed with water and saturated brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 2 : 1) to provide 2-(2-(1*H*-indol-3-yl)ethyl) isoquinolin-1(2*H*)-one **7** as a yellow solid (519 mg, 90% yield), m. p. 120–130 °C. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 8.49 (d, $J$ = 8.0 Hz, 1H), 8.04 (s, 1H), 7.70 (d, $J$ = 7.9 Hz, 1H), 7.62 (t, $J$ = 7.4 Hz, 1H), 7.49 (d, $J$ = 7.4 Hz, 1H), 7.47 (d, $J$ = 8.3 Hz, 1H), 7.43–7.33 (m, 1H), 7.21 (t, $J$ = 7.4 Hz, 1H), 7.14 (t, $J$ = 7.4 Hz, 1H), 6.94 (s, 1H), 6.78 (d, $J$ = 7.3 Hz, 1H), 6.32 (d, $J$ = 7.3 Hz, 1H), 4.30 (t, $J$ = 7.3 Hz, 2H), 3.42–3.14 (m, 2H). $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 162.1, 137.2, 136.4, 132.1, 132.0, 127.8, 127.3, 126.6, 126.3, 125.8, 122.5, 122.2, 119.6, 118.7, 112.4, 111.2, 105.4, 50.3, 25.0. HRMS (ESI-TOF) calcd for $C_{19}H_{16}N_2NaO$ $[M + Na]^+$: 311.1155; found 311.1153.

**Cyclization of isoquinolone 7.** A 10 mL screwtop pressure Schlenk tube was charged with a solution of 2-(2-(1*H*-indol-3-yl) ethyl)isoquinolin-1(2*H*)-one **7** (29 mg, 0.1 mmol) in $CH_3CN$ (2 mL). $BF_3{\cdot}Et_2O$ (43 μL, 0.35 mmol) was added with stirring. The tube was sealed with a screw stopper and stirred for 48 h at 85 °C. After cooling it to RT, the mixture was diluted with dichloromethane (5 mL) and water (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic phase was dried over anhydrous $CaCl_2$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (PE/DCM = 1 : 10) to provide 24 mg of a yellow solid. The $^1$H NMR spectrum indicated that it consisted of dihydronorketoyobyrine **8** and norketoyobyrine **9** in a ratio of 4 to 1. Thus, the total yield of the two compounds was 85%. Dihydronorketoyobyrine **8** (major).[20a] $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.11 (s, 1H), 8.00 (d, $J$ = 7.6 Hz, 1H), 7.55 (d, $J$ = 6.9 Hz, 1H), 7.47 (t, $J$ = 6.3 Hz, 1H), 7.44 (d, $J$ = 7.7 Hz, 1H), 7.40–7.33 (m, 2H), 7.13–7.06 (m, 1H), 7.02 (t, $J$ = 7.4 Hz, 1H), 5.15–4.94 (m, 2H), 3.60 (dd, $J$ = 15.8, 3.8 Hz, 1H), 2.96 (dd, $J$ = 12.4, 3.1 Hz, 2H), 2.89 (d, $J$ = 11.7 Hz, 1H), 2.82–2.69 (m, 1H). $^{13}$C NMR (151 MHz, DMSO-$d_6$) $\delta$ 164.3, 137.4, 136.9, 134.19, 132.49, 129.3, 128.4, 127.7, 127.6, 126.7, 121.7, 119.2, 118.4, 111.6, 107.8, 52.2, 39.6, 34.8, 21.1. Norketoyobyrine **9** (minor).[9a] $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.71 (s, 1H), 8.25 (d, $J$ = 8.0 Hz, 1H), 7.71 (t, $J$ = 7.5 Hz, 1H), 7.62 (d, $J$ = 5.6 Hz, 1H), 7.58 (d, $J$ = 5.3 Hz, 1H), 7.41 (br.s, 2H), 7.22 (t, $J$ = 7.6 Hz, 1H), 7.12–7.06 (m, 2H), 4.41 (t, $J$ = 6.5 Hz, 2H), 3.10 (t, $J$ = 6.6 Hz, 2H). $^{13}$C NMR (151 MHz, DMSO-$d_6$) $\delta$ 161.2, 138.0, 136.1, 132.6, 132.3, 128.1, 127.5, 126.07, 125.9, 125.5, 124.5, 123.5, 119.4, 119.1, 112.5, 111.6, 99.0, 40.4, 19.3.

**Oxidation of 3,4-dihydroisoquinolin-1(2*H*)-one 8.** To a 10 mL flask was added a mixture of **8** and **9** (29 mg, ratio: 4 : 1, 0.1 mmol) in i-PrOH (4 mL). The flask was placed in an oil-bath at 50 °C and stirred until the solid was completely dissolved. Then $CeCl_3{\cdot}7H_2O$ (0.01 mmol, 4 mg) was added. The reaction mixture was stirred until **8** was consumed as indicated by TLC (*ca.* 2.5 h). It was cooled to RT, neutralized to pH 8–9 with saturated $NaHCO_3$, and completely extracted with EtOAc (8 × 3 mL). The combined organic layers were washed with saturated brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure to afford the crude product, which was purified by silica gel chromatography (PE/$CH_2Cl_2$ = 1 : 5) to give norketoyobyrine **9** as a yellow solid (23 mg, 80%).[9a] $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.70 (s, 1H), 8.24 (d, $J$ = 8.5 Hz, 1H), 7.75–7.67 (m, 1H), 7.62 (d, $J$ = 7.9 Hz, 1H), 7.59 (d, $J$ = 7.9 Hz, 1H), 7.47 (d, $J$ = 8.1 Hz, 0H), 7.43 (d, $J$ = 8.4 Hz, 1H), 7.22 (t, $J$ = 7.6 Hz, 1H), 7.11–7.03 (m, 2H), 4.40 (t, $J$ = 6.6 Hz, 2H), 3.09 (t, $J$ = 6.6 Hz, 2H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 161.7, 138.5, 136.6, 133.1, 132.8, 128.6, 128.0, 126.6, 126.4, 126.0, 125.0, 124.0, 120.0, 119.6, 113.0, 112.1, 99.5, 40.9, 19.8.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

1 K. Fang, G. Li and Y. She, *J. Org. Chem.*, 2018, **83**, 8092.
2 W. T. Borden, R. Hoffmann, T. Stuyver and B. Chen, *J. Am. Chem. Soc.*, 2017, **139**, 9010.
3 Y. Nosaka and A. Y. Nosaka, *Chem. Rev.*, 2017, **117**, 11302.
4 Y. Li, S. A. Rizvi, D. Hu, D. Sun, A. Gao, Y. Zhou, J. Li and X. Jiang, *Angew. Chem., Int. Ed.*, 2019, **58**, 13499.
5 W. Fan and P. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 12201.
6 M. Liu, H. Wang, H. Zeng and C.-J. Li, *Sci. Adv.*, 2015, **1**, e1500020.
7 A. Studer and D. P. Curran, *Nat. Chem.*, 2014, **6**, 765.
8 For selected examples, see: (*a*) W. E. Doering, G. Cortes and L. H. Knox, *J. Am. Chem. Soc.*, 1947, **69**, 1700; (*b*) W. E. Doering and R. W. Haines, *J. Am. Chem. Soc.*, 1954, **76**, 482; (*c*) G. E. Lewis, *J. Org. Chem.*, 1965, **30**, 2433; (*d*) T. Siu, D. Qin and S. J. Danishefsky, *Angew. Chem., Int.*

 

*Ed.*, 2001, **40**, 4713; (*e*) Y.-F. Liang and N. Jiao, *Angew. Chem., Int. Ed.*, 2014, **53**, 548.

9 (*a*) K. Li, J. Ou and S. Gao, *Angew. Chem., Int. Ed.*, 2016, **55**, 14778; (*b*) K. H. Raitio, J. R. Savinainen, J. Vepsäläinen, J. T. Laitinen, A. Poso, T. Jävinen and T. Nevalainen, *J. Med. Chem.*, 2006, **49**, 2022; (*c*) D. B. Khadka and W.-J. Cho, *Bioorg. Med. Chem.*, 2011, **19**, 724.

10 For selected examples, see: (*a*) C. S. Yeung, T. H. H. Hsieh and V. M. Dong, *Chem. Sci.*, 2011, **2**, 544; (*b*) D. Wang, R. Zhang, R. Deng, S. Lin, S. Guo and Z. Yan, *J. Org. Chem.*, 2016, **81**, 11162; (*c*) W.-K. Luo, X. Shi, W. Zhou and L. Yang, *Org. Lett.*, 2016, **18**, 2036; (*d*) T.-H. Wang, W.-C. Lee and T.-G. Ong, *Adv. Synth. Catal.*, 2016, **358**, 2751; (*e*) Y. Jin, L. Ou, H. Yang and H. Fu, *J. Am. Chem. Soc.*, 2017, **139**, 14237; (*f*) G. Wang, W. Hu, Z. Hu, Y. Zhang, W. Yao, L. Li, Z. Fu and W. Huang, *Green Chem.*, 2018, **20**, 3302; (*g*) A. Motaleb, A. Bera and P. Maity, *Org. Biomol. Chem.*, 2018, **16**, 5081; (*h*) M. Gngnon-Dubois and A. Meola, *Synth. Commun.*, 1995, **25**, 2999.

11 (*a*) G. A. Russell, E. G. Jansen, H.-D. Becker and F. Smentowski, *J. Am. Chem. Soc.*, 1962, **84**, 2652; (*b*) G. A. Russell, A. J. Moye and K. Nagpal, *J. Am. Chem. Soc.*, 1962, **84**, 4154; (*c*) G. A. Russell and E. G. Janzen, *J. Am. Chem. Soc.*, 1962, **84**, 4153; (*d*) G. A. Russell, E. G. Janzen and E. T. Strom, *J. Am. Chem. Soc.*, 1962, **84**, 4155.

12 The NMR spectra of the reaction mixture showed that the substrate (**1a**) was completely converted to the intended compound (**2a**). Considering the environmental friendliness and excellent yield obtained by the use of *t*-BuOK, we did not further try organic bases.

13 For details, see the ESI.†

14 For an example of oxidation of sulfoxides to sulfones with peroxides, see: S.-K. Wang, X. You, D.-Y. Zhao, N.-J. Mou and Q.-L. Luo, *Chem. – Eur. J.*, 2017, **23**, 11757.

15 The isolated major isomer of **2j′** was the *Z*-configuration that is less stable than the *E*-configuration. The ratio of *Z*/*E* isomers is approximately 2 : 1 at 22 °C. When the reaction temperature was increased to 33 °C, the ratio of *Z*/*E* isomers decreased to 1 : 1 (Fig. S5†). For an explanation of the unexpected stereoselectivity, see the ESI.†

16 For an example of a free radical mechanism being affected by TEMPO and BHT, see ref. 14.

17 (*a*) SET between ground-state *t*-BuOK and neutral molecule benzophenone occurred at 70 °C. See: G. Nocera, A. Young, F. Palumbo, K. J. Emery, G. Coulthard, T. McGuire, T. Tuttle and J. A. Murphy, *J. Am. Chem. Soc.*, 2018, **140**, 9751. Accordingly, SET between ground-state *t*-BuOK and cation acceptor A can occur at RT since cations are more susceptible to electrons than neutral molecules.(*b*) For an example of *t*-BuOK-initiated free radical reactions at RT, see: W.-T. Li, W.-H. Nan and Q.-L. Luo, *RSC Adv.*, 2014, **4**, 34774; (*c*) *t*-BuOK may induce certain species to yield other electron donor(s) in DMSO. It cannot be ruled out that other *in situ* formed electron donors initiate the oxidation. For examples of *t*-BuOK-promoted free radical reactions, see ref. 11.

18 I. Hermans, J. Peeters and P. A. Jacobs, *J. Org. Chem.*, 2007, **72**, 3057.

19 The oxidation with UHP-$Cs_2CO_3$ supports path b. Only one pathway for reactive oxygen species-mediated oxidation is shown; others may be operative.

20 (*a*) G. D. Pandey and K. P. Tiwari, *Synth. Commun.*, 1980, **10**, 523; (*b*) I. Ninomiya, T. Naito and H. Takasugi, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1865.