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Potassium Superoxide as an Alternative Reagent for Winterfeldt Oxidation of β-Carbolines

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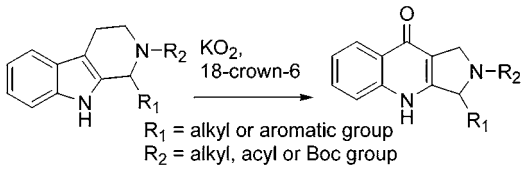
ABSTRACT



Potassium superoxide was examined as an alternative oxidation reagent for the Winterfeldt reaction. KO_2 was found to be superior to the original Winterfeldt protocol for base-sensitive substrates.

Phosphodiesterase 5 (PDE5) is the major cGMP-hydrolyzing enzyme in the human corpus carvernosum. It is well established that nitric oxide triggers the signal transduction pathway, and inhibition of PDE5 ultimately leads to enhanced penis erection.[1] Existing therapy by sildenafil, a PDE5 inhibitor for male erectile dysfunction (MED),[2] has some adverse cardiovascular side effects and causes visual disturbances due to PDE1 and PDE6 inhibition. It is our goal to identify more potent and selective PDE5 inhibitors for the treatment of erectile dysfunction (ED) and female sexual arousal disorders.[3] Recently, we reported a series of pyrimidinyl pyrroloquinolones **2** as more potent and selective PDE5 inhibitors than their nonoxidized precursors, β-carbolines **1**.[3e] As part of our continued efforts in this area, we attempted to use the Winterfeldt protocol[7] to oxidize acyl β-carbolines, such as furoyl derivatives **3** to pyrroloquinolones **4** but failed to obtain any products (Scheme 1).

Oxidation of 2,3-disubstituted indole derivatives with *m*-CPBA,[4] $NaIO_4$,[5] or singlet oxygen,[6] particularly 1,2,3,4-tetrahydro-β-carbolines with O_2/NaH or KO-*t*-Bu,[7] is well documented. Among these conditions, Winterfeldt's biomimetic autoxidation[7] appeared to be the only method that worked for the preparation of pyrroloquinolones, such as compounds **2**, for the PDE5 program. However, for substrates bearing functional groups sensitive to strong bases, i.e., NaH or KO-*t*-Bu, such as acyl β-carbolines, **9a** and **9b**, the Winterfeldt reaction failed to provide the desired products. Yet, compounds **10a** and **10b**, which are very potent PDE5

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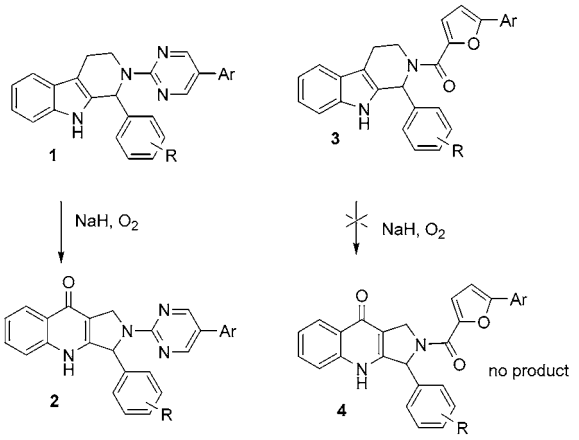
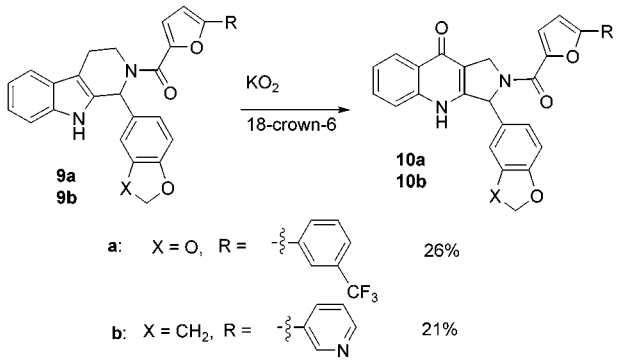
Scheme 1



inhibitors, can be obtained from the β-carboline precursors **9a** and **9b** upon treatment by KO_2/18-crown-6 in 26 and 21% yields, respectively (Scheme 2). Thus, our interest in finding

Scheme 2



a general method to oxidize 1,2,3,4-tetrahydro-β-carbolines bearing an amide functional group led us to the discovery of the inexpensive and commercially available potassium superoxide, KO_2, as an alternative reagent to Winterfeldt oxidation.

Potassium superoxide (KO_2) is known as a synthetically useful oxygen nucleophile.[8] KO_2 oxidation of indoles to quinolone derivatives in DMF in the presence of a phase transfer reagent is mild and efficient.[9] Herein we demonstrate that KO_2 can also successfully convert β-carbolines to pyrroloquinolones. Potassium superoxide has a pK_a of 4.8, which is similar to that of KOAc (pK_a = 4.75),[10] a much weaker base than KO-*t*-Bu. We found that KO_2 could be used in many cases when the Winterfeldt oxidation conditions (KO-*t*-Bu/O_2) failed to provide any desired products (vide infra).

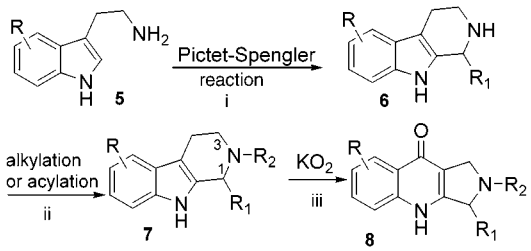
(8) Corey, E. J.; Nicolaou, K. C.; Shibasaki, M.; Machide, Y.; Shiner, C. S. *Tetrahedron Lett.* **1975**, *37*, 3183−86.

(9) (a) Balogh-Hergovich, E.; Spier, G. *Tetrahedron Lett.* **1982** *23*, 4473−5. (b) Itakura, K.; Uchida, K.; Kawakishi, S. *Tetrahedron Lett.* **1992**, *33*, 2567−2570.

(10) For the physical chemical properties of KO_2, see: Lee-Ruff, E. *Chem. Soc. Rev.* **1977**, *6*, 195−214.

The general synthetic route for the preparation of 1,2,3,4-tetrahydro-β-carbolines **7** is outlined in Scheme 3. Tryptamine

Scheme 3



or its derivatives **5** underwent Pictet−Spengler cyclizations (CH_2Cl_2, 0.14 M, 2 equiv of TFA, 25 °C) with alkyl or aryl aldehydes to afford the corresponding 1,2,3,4-tetrahydro-β-carbolines **6** in 50−89% yields. After N-acylation or N-alkylation, we turned our attention to the KO_2 oxidation of β-carbolines **7**. Generally, the reaction time varied from 2 to 16 h depending on the substrates. Over-oxidation or excess heat led to decomposition of some substrates. The reaction could be carried out at room temperature from 10 mg to 200 g scale in DMF, THF, or DMSO. The solvent study showed that DMF provided the best yield (Table 1). However, due

Table 1. Solvent and Phase Transfer Reagent Study[a]

solvent	phase transfer reagent	time	% yield
THF	18-crown-6	16 h	41
DMSO	18-crown-6	16 h	35
DMF	18-crown-6	16 h	52
DMF	Et_3BnNCl	4 d	41
DMF	Aliquat 336	42 h	58

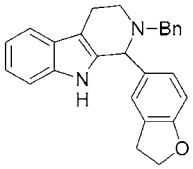
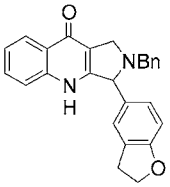
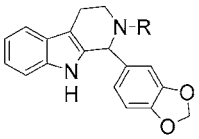
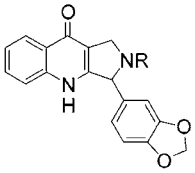
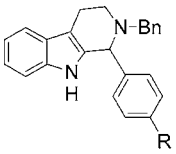
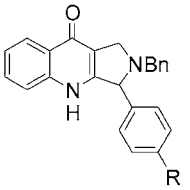
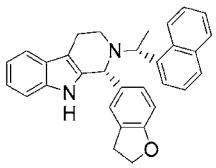
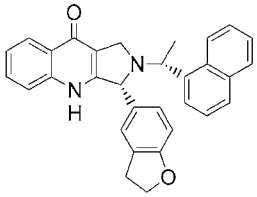
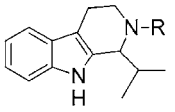
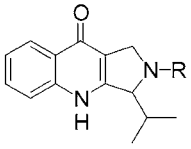
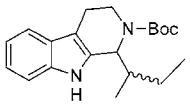
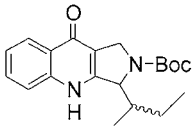
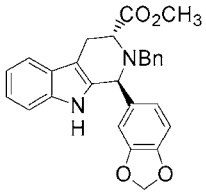
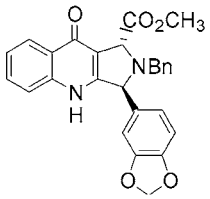
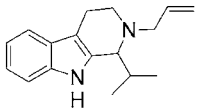
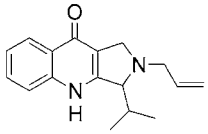
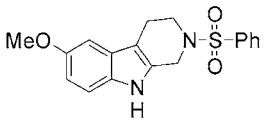
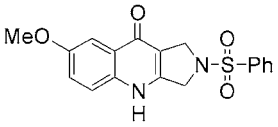
[a] This is for the transformation of β-carboline **7a** to pyrroloquinolones **8a**; see footnote 13 for a detailed procedure.

to the exothermicity of the oxidation, for the large-scale reactions, KO_2 is preferably added at 0 °C and then the reaction mixture is allowed to slowly warm to ambient temperature. According to the mechanism proposed for the oxidation of indole derivatives by G. Speier et al.,[9a] for each equivalent of substrate, 2 equiv of KO_2 are required to generate the anionic indolyl intermediate. We tested KO_2 ratios from 2 to 12 equiv and found that 4.0 equiv of KO_2 are sufficient to drive the reaction to completion. We also compared different phase transfer reagents, i.e., 18-crown-6,[8] Et_3BnNCl,[9a] and Aliquat 336[11] (see Table 1). We found that the addition of 18-crown-6 or Aliquat 336 provided higher yields than Et_3BnNCl. Additionally, 18-crown-6 accelerated the reaction rate greater than Aliquat 336. Therefore, we chose 18-crown-6 as the phase transfer reagent and DMF as the solvent for the remaining substrates.

Table 2 summarizes the results of the KO_2 oxidation of 1,2,3,4-β-carbolines **7** to quinolones **8**. Generally, KO_2

(11) Lissel, M.; Dehmlow, E. V. *Tetrahedron Lett.* **1978**, *19*, 3689.

Table 2. KO_2 Oxidations of 1,2,3,4-β-Carbolines to Pyrroloquinolones[a,13]

entry	substrate	product	time	yield (%)
1	 **7a**	 **8a**	16 h	52
2	 **7b** R = Bz	 **8b** R = Bz	22 h	24
3	**7c** R = Boc	**8c** R = Boc	16 h	37
4	**7d** R = Bn	**8d** R = Bn	16 h	53
5	 **7e**, R = H	 **8e**, R = H	12 h	54
6	**7f**, R = NO_2	**8f**, R = NO_2	1 h	0
7	**7g**, R = Cl	**8g**, R = Cl	22h	48
8	 **7h**	 **8h**	6 h	52
9	 **7i**, R = Boc	 **8i**, R = Boc	6 h	75
10	**7j**, R = Bz	**8j**, R = Bz	6 h	48
11	 **7k**	 **8k**	6 h	61
12	 **7l**	 **8l**	6 h	52
13	 **7m**	 **8m**	6 h	55
14	 **7n**	 **8n**	6 h	71

[a] General reaction condition: β-carboline (1 equiv), 18-crown-6 (1 equiv), and KO_2 (4 equiv) in DMF (0.16 M) at 25 °C were stirred until the starting material disappeared. Different protecting groups were compared in entries 2−4. See footnote 13 for a detailed experimental procedure.

oxidation of **7** provided moderate to good yields of quinolones **8**. The method works for β-carbolines generated from both aromatic and aliphatic aldehydes with yields ranging from 48 to 75%.

Winterfeldt oxidation did not provide any pyrroloquinolone products from benzoyl- or Boc-protected β-carbolines **7b** and **7c** (entries 2 and 3). Initially, we tested the KO_2 method on these two substrates, in which R_1 is a phenyl group bearing an electron-donating group. To our delight, we could isolate the pyrroloquinolone product in moderate yields. In the case where R_1 was a 3,4-methylene-dioxyphenyl group, the product yield was dependent upon the functional group R_2 on the amine (entries 2−4, R_2 = Bz, Boc, and Bn and the yields were 24, 37 and 53% for substrates **7b**, **7c**, and **7d** respectively). When R_1 was an alkyl group (entries 9 and 10), similar functional groups on the amine (Boc or Bz) led to slightly higher yields (75 and 48% for substrates **7i** and **7j**, respectively). When R_1 was a phenyl group, β-carboline **7e** (entry 5) proceeded to give pyrroloquinolone **8e** in good yield. However, when R_1 was a *p*-NO_2 phenyl group, β-carboline **7f** (entry 6) was dehydrogenated upon treatment with KO_2, even at −60 °C. Interestingly, when R_1 was a *p*-Cl phenyl group, β-carboline **7g** (entry 7) proceeded well to provide pyrroloquinolone **8g**. For optically pure starting material **7h** (entry 8), this method provided product **8h** smoothly without any epimerization.

The following cases distinguished the KO_2 method more from the Winterfeldt conditions. For entry 12, the KO_2 method provided the desired product **8l** in 52% yield without epimerization, while the KO-*t*-Bu/O_2 method only led to dehydrogenated or hydrolyzed starting material. Moreover, the KO-*t*-Bu/O_2 method failed to provide any desired pyrroloquinolones in entries 13 and 14 for substrates **7m** and **7n**, due to the fact that KO-*t*-Bu isomerized the allyl group (entry 13) and cleaved the N−SO_2Ph bond (entry 14). In entry 14, Winterfeldt oxidation actually generated fully aromatized β-carboline as the major product. Yet, because of the mild basicity of KO_2, **7m** and **7n** proceeded well to pyrroloquinolones **8m** and **8n**.

This method also has its limitations. For 3-chloro-1-(6-methoxy-1,3,4,9-tetrahydro-β-carbolin-2-yl)-propan-1-one **7o**, even the mild basicity of KO_2 led to the β-elimination of HCl and consequently generated the α,β-unsaturated amide, 2-acryloyl-7-methoxy-1,2,3,4-tetrahydro-pyrrolo[3,4-b]quinolin-9-one in only 15% yield. KO_2 oxidation of 2-oxiranylmethyl-2,3,4,9-tetrahydro-1*H*-β-carboline **7p** also failed to provide the desired quinolone probably due to the ring opening of the epoxide. Judged by HPLC-MS, the product mixture contained several diol derivatives. Moreover, substrates bearing radical-sensitive functionalities such as aryl bromide[12a] or 1,2-diphenol[12b] should not be used in this reaction due to the possible side reactions caused by indolyl radical intermediate generated during the reaction process. Since Winterfeldt oxidation might go through an anionic intermediate, in this sense, KO_2 oxidation method is complementary to the Winterfeldt condition.

In conclusion, we have developed a mild and efficient method for the synthesis of pyrroloquinolones by KO_2. β-Carbolines bearing a variety of functional groups can be effectively oxidized using inexpensive and widely available reagents. This is a superior method to Winterfeldt oxidation for base-sensitive substrates.

Acknowledgment. The authors thank Ms. Mary Evangelisto and Dr. Naresh Jain for technical support and Dr. Raymond Ng for helpful discussions.

Supporting Information Available: Experimental details and characterization for all new compounds (^{1}H NMR and mass spectral data). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Typical procedure of KO_2 oxidation. Preparation of **1,2,3,4-tetrahydro-2-benzyl-3-(2,3-dihydrobenzofuran-5-yl)-9*H*-pyrrolo-[3,4-b]-quinolin-9-one (8a).** To a solution of **7a** (entry 1 in Table 2) (60 mg, 0.16 mmol) and 18-crown-6 (42 mg, 0.16 mmol) in DMF (1 mL) was added KO_2 (45 mg, 0.63 mmol) in one portion at 25 °C. The reaction mixture turned red and was stirred for 16 h. Several drops of water were added to consume the extra KO_2. The mixture was then partitioned between ethyl acetate and water. The aqueous phase was extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product, which was purified by silica gel column chromatography using 1:1 EtOAc−hexane as eluent to give **8a** as a white solid (32.5 mg, 52%): ^{1}H NMR 300 MHz ($CDCl_3$) δ 3.21 (t, J = 8.7 Hz, 2H), 3.51∼3.72 (m, J = 11.8 Hz, 2H), 4.02 (d, J = 12.2 Hz, 1H), 4.41 (d, J = 11.8 Hz, 1H), 4.61 (t, J = 8.7 Hz, 2H), 4.95 (s, 1H), 6.81 (d, J = 8.1 Hz, 1H), 7.21−7.41 (m, 8H), 7.55 (t, J = 8.3 Hz, 1H), 7.91 (s, 1H), 8.41 (d, 1H, J = 7.56 Hz); MS (*m*/*z*) 395 (MH^+); HRMS calcd MH^+ for $C_{26}H_{22}N_2O_2$, 395.1759; found, 395.1743. Anal. Calcd for $C_{26}H_{22}N_2O_2 \cdot 0.6\ H_2O$: C, 77.05; H, 5.77; N, 6.91. Found C, 77.17; H, 5.50; N, 6.87.