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Highly Efficient Oxidation of Amines to Imines by Singlet Oxygen and Its Application in Ugi-Type Reactions

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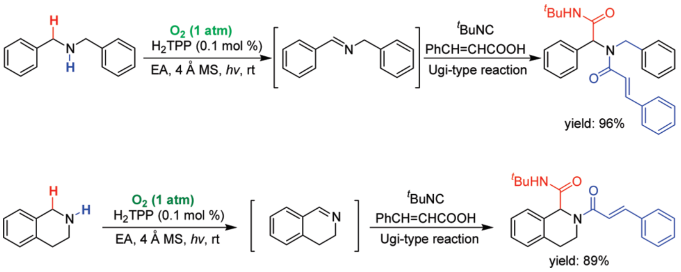
ABSTRACT



A variety of secondary benzylic amines were oxidized to imines in 90% to >99% yields by singlet oxygen generated from oxygen and a porphyrin photosensitizer. On the basis of these reactions, a protocol was developed for oxidative Ugi-type reactions with singlet oxygen as the oxidant. This protocol has been used to synthesize C1- and N-functionalized benzylic amines in up to 96% yields.

Selective oxidation of amines is important in organic synthesis owing to the immense applications of the oxidation products such as imines in the synthesis of biologically active nitrogen containing organic compounds.[1] Significant efforts have been made to develop mild and practical oxidation reactions for the synthesis of imines from secondary amines; notable examples include stoichiometric oxidation with *N*-*tert*-butylphenylsulfinimidoyl chloride[2] or 2-iodoxybenzoic acid (IBX),[3] metal-catalyzed oxidation with ^{t}BuOOH, PhIO, *N*-methylmorpholine *N*-oxide, 2,6-dimethoxybenzoquinone, or $K_2S_2O_8$,[4] iridium-catalyzed dehydrogenation,[5] along with ruthenium-,[6] cobalt-,[7] copper-,[8] palladium-,[9] and gold-catalyzed[10] aerobic oxidation.

Our studies on oxidation of secondary amines to imines with singlet oxygen ($^1O_2$) were prompted by the recent surge of interest to develop practical aerobic oxidation reactions[11] and the well-documented use of singlet oxygen as an

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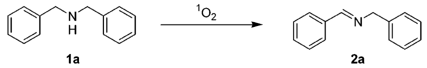
important tool in organic synthesis.[12] In literature, singlet oxygen has been extensively used for organic transformations including the ene reaction, cycloaddition, and heteroatom oxidation.[12] Reaction of singlet oxygen with amines has received considerable attention,[12f] including recent examples of oxidation of tertiary amines such as $PhCH_2NMe_2$ and $ArCH_2N(R)CH_2Ar'$ to aldehydes or N-dealkylation products.[13] However, reports on the singlet oxygen oxidation of secondary amines to imines are sparse; an example is the dehydrogenation of an *N*-neopentyl allylic amine by singlet oxygen with *meso*-tetraphenylporphyrin (H_2TPP) as a photosensitizer.[14]

We aim to find a clean oxidation of secondary amines to imines with singlet oxygen and directly use the in situ formed imine products for further functionalization. In this regard, our attention was attracted by the recent work of Zhu and co-workers on the development of an oxidative Ugi-type reaction,[15] a key step of which is the oxidation of secondary benzylic amine to imine by IBX, followed by reaction of the imine with isocyanide and carboxylic acid. Given the immense applications of Ugi-type multicomponent reactions in organic synthesis,[16] a challenging study of interest is to perform the oxidative Ugi-type reaction with green oxidants such as singlet oxygen. Herein we report singlet oxygen oxidation of a variety of benzylic amines to imines with practical interest and the development of an oxidative Ugi-type reaction featuring the oxidation of secondary amines with singlet oxygen.

Initially, we treated dibenzylamine **1a** (10 mg) with oxygen in the presence of 1.0 mol % of sensitizer [Ru^{II}(TDCPP)(CO)] (H_2TDCPP = *meso*-tetrakis(2,6-dichlorophenyl)porphyrin) under light irradiation using a 300-W tungsten filament lamp. The reaction gave imine **2a** in >99% NMR yield within 8 h (Table 1, entry 1).

Table 1. Oxidation of **1a** to **2a** with Various Photosensitizers[a]



entry	sensitizer (mol %)	*t* (h)	yield (%)
1	[Ru^{II}(TDCPP)(CO)] (1.0)	8	>99
2[b]	[Ru^{II}(TDCPP)(CO)] (1.0)	8	trace
3[c]	[Ru^{II}(TDCPP)(CO)] (1.0)	8	trace
4		8	no reaction
5	[Ru^{II}(TDCPP)(CO)] (0.01)	71	>99
6	H_2TPP (0.01)	71	>99
7	H_2TDCPP (0.01)	71	>99
8	methylene blue (0.01)	71	10
9[d]	H_2TPP (0.1)	14	98[e]

[a] Reaction conditions: **1a** (10 mg), CH_2Cl_2 (1.0 mL), rt; yields were determined by ^1H NMR except for entry 9. [b] Under N_2 instead of O_2. [c] Without light source. [d] Reaction conditions: **1a** (200 mg), CH_2Cl_2 (2 mL), 4 Å MS (500 mg). [e] Yield of isolated product.

Control experiments (Table 1, entries 2−4) revealed that oxygen, light source, and the sensitizer are all required for this reaction. Lowering the loading of [Ru^{II}(TDCPP)(CO)] to 0.01 mol % lengthened the reaction time to 71 h (Table 1, entry 5); under the same conditions, similar results were obtained by using H_2TPP or H_2TDCPP as the sensitizer (Table 1, entries 6 and 7), but only 10% yield of **2a** was formed when the sensitizer was methylene blue (Table 1, entry 8). The oxidation of **1a** to **2a** was insensitive to solvent, as similar product yields were found for the reactions conducted in CH_2Cl_2, CH_3CN, CS_2, THF, and ethyl acetate (EA). When the reaction was scaled up from 10 mg to 200 mg of **1a**, a complex mixture of products was found. Interestingly, in the presence of 4 Å MS (500 mg), the 200 mg-scale reaction for 14 h with H_2TPP (0.1 mol %) as sensitizer resulted in the isolation of **2a** in 98% yield (Table 1, entry 9) by removal of the solvent after filtration; the imine product was subsequently used for Ugi-type reactions without further purification (see below), and no adverse effect was observed.

With H_2TPP (0.1 mol %) as sensitizer and in the presence of 4 Å MS, secondary amines **1b**−***l*** were oxidized by singlet oxygen to afford imines **2b**−***l*** in 90% to >99% yields (Table 2). These light-induced amine oxidations by singlet oxygen were remarkably clean, as the imine products were not contaminated by *N*-oxide or nitrone. The oxidation is regioselective, occurring at the less substituted position for the unsymmetric dibenzylamines **1d**,**e** (Table 2, entries 3 and 4). In the oxidation

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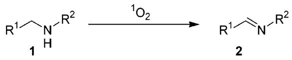
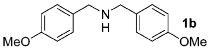
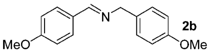
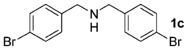
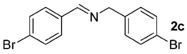
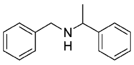
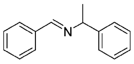
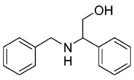
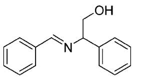
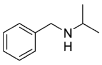
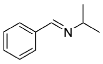
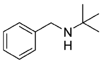
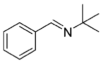
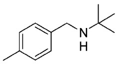
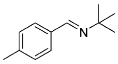
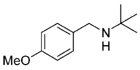
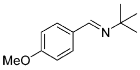
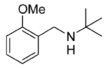
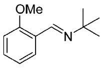
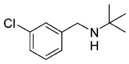
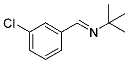
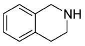
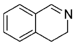
Table 2. Oxidation of **1b**−***l*** to **2b**−***l*** with Singlet Oxygen[a]



entry	substrate	product	*t* (h)	yield (%)[b]
1	 **1b**	 **2b**	14	>99
2	 **1c**	 **2c**	14	>99
3	 **1d**	 **2d**	14	96
4	 **1e**	 **2e**	8	96
5	 **1f**	 **2f**	9	92
6	 **1g**	 **2g**	14	94
7	 **1h**	 **2h**	14	96
8	 **1i**	 **2i**	14	97
9	 **1j**	 **2j**	14	90
10	 **1k**	 **2k**	14	98
11	 **1l**	 **2l**	8	97

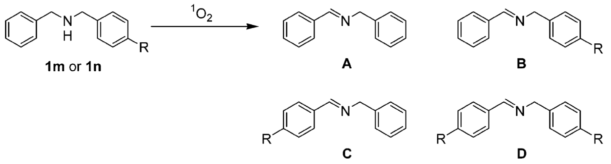
[a] Reaction conditions: **1** (1.0 mmol), H_2TPP (0.1 mol %), EA (2.0 mL), 4 Å MS (500 mg), O_2 (1 atm), 300 W tungsten lamp, rt. [b] Yield of isolated product.

of *N*-isopropylbenzylamine (**1f**), a selective formation of *N*-benzylidene rather than *N*-isopropylidene moiety was observed (Table 2, entry 5). 1,2,3,4-Tetrahydroisoquinoline (**1*l***) was oxidized to **2*l*** in 97% yield (Table 2, entry 11); the latter is an important precursor for the synthesis of isoquinoline alkaloids.

We also examined the oxidation of unsymmetric dibenzylamines **1m**,**n**; the results are depicted in Table 3 (entries 1 and 3). In each case, a mixture of four products were detected, with both the total yield (94−99%) and product ratio being comparable to those reported by Nicolaou and co-workers for the oxidation of the same substrates by IBX (Table 3, entries 2 and 4).[3b] This suggests involvement of an imine hydrolysis/cross-condensation mechanism in the amine oxidation by singlet oxygen, similar to that by IBX.[3b]

The singlet oxygen oxidation of secondary benzylic amines to imines can be scaled up to gram-scale without appreciable decrease in product yields. Treatment of **1a** (4.0 g, 20.3 mmol) in EA (10 mL) with H_2TPP (0.1 mol %) and 4 Å MS (10 g) at room temperature under oxygen with light irradiation for 14 h afforded **2a** in 97% yield. Under the same conditions, **2*l*** was prepared in 97% yield from the oxidation of **1*l*** (2.24 g, 16.8 mmol).

Table 3. Oxidation of Unsymmetric Dibenzylamines **1m**,**n** with Singlet Oxygen[a]

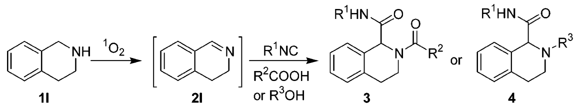


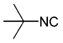
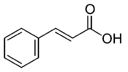
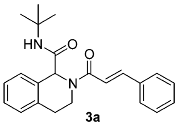
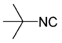
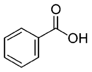
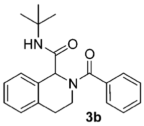
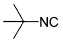
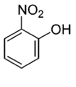
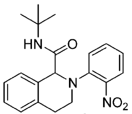
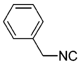
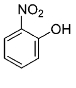
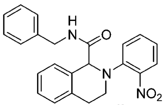
entry	R	substrate	product ratio[b] A	B	C	D	yield (%)[c]
1	Br	**1m**	1.0	2.0	1.7	1.0	94
2[d]	Br	**1m**	1.0	0.8	1.7	1.2	99
3	OMe	**1n**	1.0	1.1	0.7	0.9	99
4[d]	OMe	**1n**	1.0	1.6	0.7	1.0	99

[a] Reaction conditions: **1m** or **1n** (1.0 mmol), H_2TPP (0.1 mol %), EA (2 mL), 4 Å MS (500 mg), O_2 (1 atm), rt, 14 h. [b] Determined by ^{1}H NMR. [c] Yield of isolated product. [d] Data from ref 3b.

Encouraged by the almost quantitative yields of **2a**,***l*** readily obtained from gram-scale oxidation of **1a**,***l*** with singlet oxygen, we started to explore the feasibility of applying such reaction to the oxidative Ugi-type reaction. In the work by Zhu and co-workers, reaction of **1*l***, isocyanide, and carboxylic acid in the presence of IBX gave Ugi products in 50−99% yields.[15] From oxidation of **1*l*** (134 mg, 1.0 mmol) with singlet oxygen, followed by removal of the solvent and direct addition of ^{t}BuNC

Table 4. Ugi-Type Reaction by Using **1*l*** as Starting Material with Singlet Oxygen as Oxidant[a]



entry	R^1NC	R^2COOH or R^3OH	product	yield (%)[b]
1			 **3a**	89
2			 **3b**	82
3			 **4a**	41
4			 **4b**	62

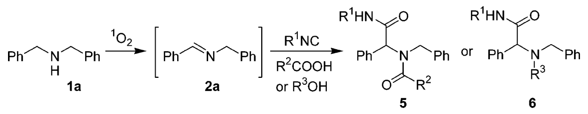
[a] Reaction conditions for the Ugi-type reaction: R^1NC (0.77 mmol), R^2COOH or R^3OH (1.0 mmol), MeOH (5 mL), 60 °C, 46 h. [b] Yield of isolated product.

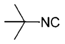
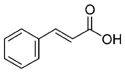
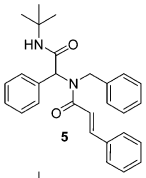
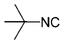
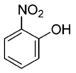
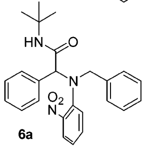
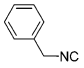
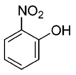
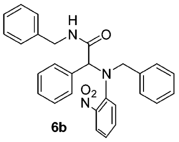
and carboxylic acid PhCH═CHCOOH or PhCOOH, we obtained Ugi products **3a** or **3b** in 89% or 82% yield, respectively (Table 4, entries 1 and 2).

El Kaïm, Grimaud, and co-worker developed a new type of Ugi reaction using nitrophenol instead of acid.[17] We found that the singlet oxygen oxidation of **1*l*** to **2*l*** can be applied to this type of Ugi reaction as well, affording Ugi products **4a** and **4b** in 41% and 62% yields, respectively, upon addition of isocyanide ^{t}BuNC or BnNC and *o*-nitrophenol (Table 4, entries 3 and 4).

For the oxidative Ugi-type reaction based on the IBX oxidation of **1a** to **2a**, the corresponding Ugi product was obtained in 32% yield.[15] Remarkably, upon oxidation of **1a** (197 mg, 1.0 mmol) by singlet oxygen, treatment of the in situ formed **2a** with isocyanide and carboxylic acid or nitrophenol afforded the Ugi products **5** and **6a**,**b** in 72−96% yields (Table 5). The structure of **6a** has been determined by X-ray crystallographic studies (Table S1 in the Supporting Information and Figure 1).

Table 5. Ugi-Type Reaction by Using **1a** as Starting Material with Singlet Oxygen as Oxidant[a]



entry	R^1NC	R^2COOH or R^3OH	product	yield (%)[b]
1			 **5**	96
2			 **6a**	76
3			 **6b**	72

[a] Reaction conditions for the Ugi-type reaction: R^1NC (0.77 mmol), R^2COOH or R^3OH (1.0 mmol), MeOH (5 mL), 60 °C, 42 h. [b] Yield of isolated product.

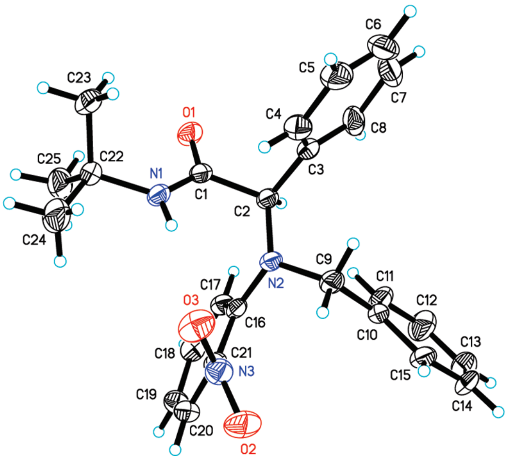


Figure 1. ORTEP drawing for **6a**.

In summary, we have demonstrated a clean oxidation of various secondary benzylic amines to imines by singlet oxygen under mild conditions. Such amine oxidation can be performed on gram-scale with almost quantitative yield. We have also developed oxidative Ugi-type reactions featuring reaction of isocyanide and carboxylic acid/nitrophenol with the imines formed in situ from oxidation of secondary amines by singlet oxygen.

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Supporting Information Available: Experimental procedures, compound characterization data, Table S1, and ^1H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) El Kaïm, L.; Grimaud, L.; Oble, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 7961.