Photooxidative Cyanation

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Continuous-Flow Oxidative Cyanation of Primary and Secondary Amines Using Singlet Oxygen**

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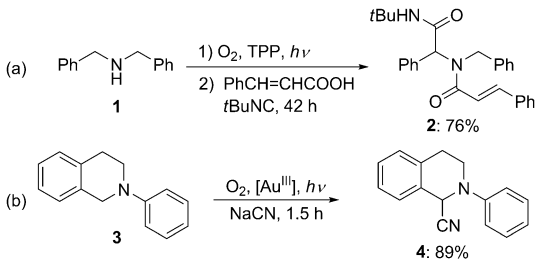
Abstract: *Primary and secondary amines can be rapidly and quantitatively oxidized to the corresponding imines by singlet oxygen. This reactive form of oxygen was produced using a variable-temperature continuous-flow LED-photoreactor with a catalytic amount of tetraphenylporphyrin as the sensitizer. α-Aminonitriles were obtained in good to excellent yields when trimethylsilyl cyanide served as an in situ imine trap. At 25°C, primary amines were found to undergo oxidative coupling prior to cyanide addition and yielded secondary α-aminonitriles. Primary α-aminonitriles were synthesized from the corresponding primary amines for the first time, by an oxidative Strecker reaction at –50 °C. This atom-economic and protecting-group-free pathway provides a route to racemic amino acids, which was exemplified by the synthesis of tert-leucine hydrochloride from neopentylamine.*

Imines are versatile and valuable building blocks for organic synthesis, particularly because of the prevalence of nitrogen-containing biologically active compounds.[1] Whereas they are classically prepared by the condensation of carbonyl compounds and amines, the selective oxidation of amines to imines provides a more elegant pathway. Direct oxidation is, however, generally limited to the use of benzylamines, expensive stoichiometric oxidants,[2] biocatalysts,[3] or complex metal catalysts.[4–6] Singlet oxygen is an attractive oxidant because it is inexpensive and a highly atom-economic reagent,[7,8] although it is difficult to generate and handle, resulting in its rare use for the formation of imines.[9] Che et al. have reported the efficient oxidation of secondary benzylamines to the corresponding imines by singlet oxygen in a batch reactor in 8–14 h (Scheme 1 a), which was followed by stepwise Ugi-type reactions.[10] An organogold(III) complex[11] with a long-lived and highly emissive triplet excited state is also suitable for the activation of singlet oxygen. Oxidative cyanation of tetrahydroisoquinolines with this catalyst and using sunlight to generate singlet oxygen resulted in α-aminonitriles in high yields and shorter reaction times (1.5 h; Scheme 1 b).



Scheme 1. Previous work by Che et al.:[10,11] a) $^1O_2$ oxidation of benzylic amines to imines and subsequent trapping in an Ugi-type reaction; b) oxidative cyanation of tetrahydroisoquinoline derivatives.

We have recently developed a variable-temperature flow photoreactor for the efficient generation of $^1O_2$,[7] which was later improved to operate more efficiently using a low-energy LED lamp (420 nm)[12] and tetraphenylporphyrin (TPP) as the photosensitizer.[13] This set-up was key to the continuous synthesis of the anti-malarial drug artemisinin.[13] Herein, we report the utilization of our photooxidation module for the highly efficient and rapid continuous aerobic oxidative cyanation of amines, a process that is not limited to the use of activated benzylic C–H bonds and allows for the oxidative cyanation of primary amines without oxidative coupling for the first time.

Initially, we focused on the oxidation step in the flow system. A 0.5 M solution of dibenzylamine (**1**) and TPP (0.1 mol%) in dichloromethane (0.5 mL min^{-1}) was mixed with oxygen gas (5 mL min^{-1}) with the help of a T-mixer, prior to entering a continuous-flow photooxidation module (3.5 mL; Figure 1). Subsequent evaporation of the solvent revealed clean and quantitative conversion into *N*-benzylidene-1-phenylmethanamine (**5**). By-products, such as nitriles, nitrones, amides, or carbonyl compounds, that usually accompany the oxidative synthesis of imines were not observed. Whereas the use of a medium-pressure mercury lamp gave

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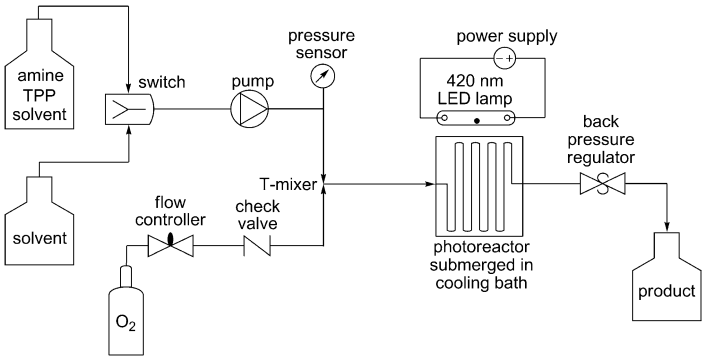
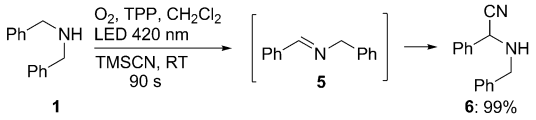


Figure 1. Aerobic oxidation of amines in a continuous-flow photoreactor.

similar results, the use of methylene blue with a red LED lamp (660 nm) resulted in only 2% conversion.

Having established suitable oxidation conditions, we next sought to subject the imine that was formed in situ to a subsequent nucleophilic addition. Owing to the utility of α-aminonitriles for the synthesis of both α-amino acids and 1,2-diamines, trimethylsilyl cyanide (TMSCN) was chosen as a trapping agent.[14] α-Aminonitriles can also be found in a variety of drug motifs,[15] for example, vildagliptin,[16] an oral anti-hyperglycemic agent. We first explored the oxidative cyanation[17,18] of dibenzylamine (**1**). TMSCN (1.1 equiv) and TPP (0.3 mol%) were dissolved in CH_2Cl_2 (0.5 M) with **1** and exposed to the oxidation conditions described above. The corresponding α-aminonitrile **6** was obtained in quantitative yield in 90 seconds (Scheme 2).[19]



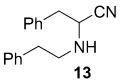
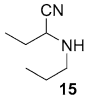
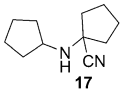
Scheme 2. Oxidative cyanation of dibenzylamine (**1**).

Pyrrolidine and piperidine gave good yields of the corresponding monomeric α-aminonitriles (Table 1, entries 2 and 3); however, side products were formed that resulted from di- and trimerization of the corresponding imines.[20–23] Primary amines, in contrast, were found to undergo oxidative coupling to the corresponding N-substituted imines, which were subsequently trapped to yield the corresponding nitriles. Both activated (entry 4) and unactivated primary amines (entries 5–7) were transformed in good to excellent yields.

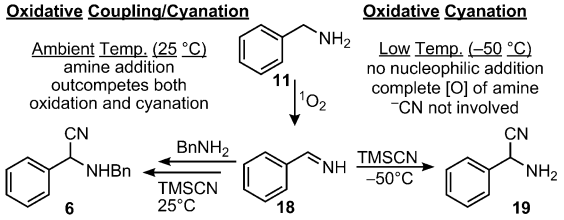
The formation of α-aminonitriles from primary amines without oxidative coupling would be a valuable transformation that provides access to a vast pool of natural and unnatural amino acids. However, no examples of this transformation have been reported to date. We hypothesized that the formation of the oxidative coupling products was due to a significantly higher rate for nucleophilic addition of benzylamine (**7**) than for that of cyanide (from TMSCN) at the primary aldimine **18** formed in situ, which results in exclusive formation of the coupling products **5** and **6** (Table 2, entry 1). Whereas high dilution favored oxidative coupling (entry 2),[24] small amounts of the primary amine **19** were detected in a more concentrated THF solution (entry 3). Even with a 10-fold excess of TMSCN, the desired monomeric product **19** was obtained in only 23% yield (entry 4).

As oxidations with singlet oxygen are known to occur at low temperatures,[25] we sought to decrease the rate of all nucleophilic additions by cooling the photooxidation, thereby allowing complete oxidation of the amine (Scheme 3). Warming of the solution that contains fully oxidized amine in the presence of TMSCN was expected to afford the desired primary α-aminonitrile. Indeed, when the irradiation chamber was cooled to −50 °C in a reactor with a volume of 7.5 mL, a 3:1 mixture of the monomeric and dimeric products was obtained in both CH_2Cl_2 and THF (entries 7 and 9, respectively).

Table 1: Oxidative cyanation of primary and secondary amines with singlet oxygen.

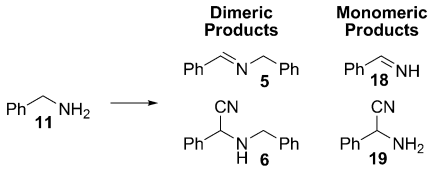
Entry[a]	Substrate	Product	Yield[b] [%]
1	 **1**	 **6**	99
2	 **7**	 **8**	71
3	 **9**	 **10**	76
4	 **11**	 **6**	97
5	 **12**	 **13**	86[c]
6	 **14**	 **15**	94
7[d]	 **16**	 **17**	84

[a] For detailed reaction conditions, see the Supporting Information; amine (0.3–0.5 M), TMSCN (1.1 equiv), TPP (0.1 mol%), CH_2Cl_2, RT, residence time: 1.5–3 min. [b] Yields of isolated products. [c] The primary aminonitrile was isolated in 9% yield. [d] THF was used as the solvent.



Scheme 3. Effective control of the nucleophilic addition by temperature, to exclusively yield either the product of oxidative coupling or that of cyanation. Bn = Benzyl.

Table 2: Oxidative cyanation of benzylamine (**11**).[a]



Entry	*C* [M]	TMSCN [equiv]	Solvent	*T* [°C]	Yield[b] [%]		
					11	**5+6**	**18+19**
1	0.5	1.1	CH_2Cl_2	20	0	97	0
2	0.01	1.1	CH_2Cl_2	20	0	98	0
3	1.0	1.1	CH_2Cl_2	20	36	56	5
4	0.1	10	CH_2Cl_2	20	0	73	23
5	0.1	10	CH_2Cl_2	−40	0	49	49
6	0.1	10	CH_2Cl_2	−70	0	61	36
7[c]	0.1	10	CH_2Cl_2	−50	0	25	71
8[c]	0.1	5	CH_2Cl_2	−50	0	84	13
9[c]	0.1	10	THF	−50	0	21	74
10[c]	0.1	5	THF	−50	0	27	65
11[c,d]	**0.1**	**5**	**THF**	**−50**	**0**	**0**	**99**
12[c,d]	0.1	5	THF	−25	complex mixture		
13[c,d]	**0.1**	**2.5**	**THF**	**−50**	**0**	**4**	**91**
14[c,d]	0.1	1.5	THF	−50	complex mixture		
15[c,d]	0.3	1.5	THF	−50	0	20	74
16[c]	0.1	5	wet THF	−50	0	53	45

[a] For detailed reaction conditions, see the Supporting Information; TPP (0.1 mol%), residence time: 1.5–3 min. [b] Yields determined by NMR spectroscopy. [c] A photoreactor with a volume of 7.5 mL was used. [d] TBAF (4 mol%, based on TMSCN) was used.

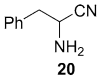
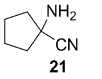
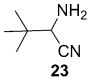
Although TMSCN serves as a convenient and effective cyanide source, it is nevertheless relatively expensive and toxic. However, a lower loading of the nucleophile resulted in a moderate to severe drop in the yield of the oxidized monomer that depended on the solvent (entries 8 and 10). TBAF is known to activate TMSCN,[26] and the addition of 4 mol% of TBAF (based on TMSCN)[27] was sufficient to yield quantitative conversion into the desired α-aminonitrile **19** in THF (entry 11). Decreasing the amount of TMSCN from 5 to 2.5 equiv resulted in good yields of the primary amine **19**; nevertheless, traces of dimer **6** were observed (entry 13). A further decrease in the amount of TMSCN led to a complex mixture (entry 14); however, acceptable yields could be obtained at higher concentrations (entry 15). The addition of water to the reaction mixture resulted in increased selectivity towards secondary amines (entry 16). This reaction outcome can be explained by the hydrolysis of primary aldimine **18** to benzaldehyde and its subsequent reaction with benzylamine (**7**), which results in the formation of **5**. The development of this process was greatly accelerated by the use of flow techniques, as a large number of reaction conditions could be screened using the same reaction set-up (flow photooxidation module) in a short amount of time.

Under the optimized conditions (entry 11), a longer reaction time (1 h) was necessary for full conversion in a batch reactor. As opposed to the flow system, a mixture of products was obtained, with the desired nitrile **19** being isolated in poor yield (24%).[28]

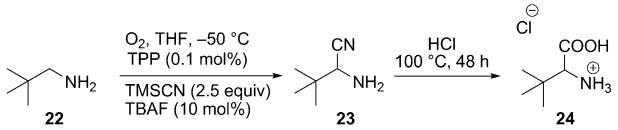
Using these optimized conditions (Table 2, entry 13), primary α-aminonitriles were easily and rapidly prepared in good to excellent yields (Table 3). Relatively inexpensive neopentylamine (**22**) was converted into the corresponding nitrile **23** in high yield (Entry 4), which gave the significantly more valuable D,L-*tert*-leucine hydrochloride (**24**) upon hydrolysis in conc. HCl in a yield of 87% over three steps (Scheme 4). The synthesis of the non-proteinogenic amino acid D,L-*tert*-leucine serves as a proof of principle that essential components of pharmaceutically active peptides and templates for asymmetric synthesis[29] can be efficiently generated using the described process.

In summary, we have developed a continuous-flow process for the oxidation of both activated (benzylic) and unactivated primary and secondary amines to the corresponding secondary imines by singlet oxygen. Subsequent in situ cyanation using TMSCN afforded α-aminonitriles in high yields. By lowering the temperature and adding a sub-stoichiometric amount of TBAF, we have provided the first example of primary amines undergoing clean oxidative cyanation to primary α-aminonitriles in good to excellent yields. This novel transformation could serve as

Table 3: Oxidative cyanation of primary amines with singlet oxygen.

Entry[a]	Substrate	Product	Yield[b] [%]
1	 **11**	 **19**	90
2	 **12**	 **20**	73
3	 **16**	 **21**	81
4	 **22**	 **23**	92

[a] For detailed reaction conditions, see the Supporting Information; amine (0.1 M), TMSCN (2.5 equiv), TPP (0.1 mol%), THF, −50°C, residence time: 1.5–3 min, TBAF (4 mol%, based on TMSCN). [b] Yields of isolated products.



Scheme 4. Synthesis of D,L-*tert*-leucine hydrochloride (**24**) from neopentylamine (**22**).

a more attractive route for the synthesis of unprotected amino acids, as it exhibits excellent step-[30] and atom-economy[31] and does not require protecting groups.[32] Studies on other reactions of imines, as well as on the enantioselective synthesis of α-amino nitriles, are currently underway.

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[21] For NMR data of the dimer, see: B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2004**, *126*, 13244 – 13246.

[22] For NMR data of the trimer, see Ref. [23d,h].

[23] Several approaches to 1-pyrroline from pyrrolidine have been described; by catalytic dehydrogenation: a) M. M. Robison, *J. Am. Chem. Soc.* **1958**, *80*, 6254 – 6257; b) S. Kamiguchi, A. Nakamura, A. Suzuki, M. Kodomari, M. Nomura, Y. Iwasawa, T. Chihara, *J. Catal.* **2005**, *230*, 204 – 213; reaction with *tert*-butyl hypochlorite followed by base: c) D. B. Rubinov, I. L. Rubinova, *Russ. J. Org. Chem.* **2004**, *40*, 1187 – 1189; treatment with $Na_2S_2O_8$, NaOH, and catalytic $AgNO_3$: d) K. Ogawa, Y. Nomura, Y. Takeuchi, S. Tomoda, *J. Chem. Soc. Perkin Trans. 1* **1982**, 3031 – 3035; reaction with *N*-chlorosuccinimide, followed by base: e) J.-C. Guillemin, J.-M. Denis, M.-C. Lasne, J.-L. Ripoil, *Tetrahedron* **1988**, *44*, 4447 – 4455; f) J. Quick, R. Oterson, *Synthesis* **1976**, 745 – 746; g) H. Bock, R. Dammel, *Chem. Ber.* **1987**, *120*, 1971 – 1985; treatment with iodosoben-

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[24] It was found that cyanide addition to imines proceeded very slowly in highly diluted solutions (Table 2, entry 2). Therefore, yields of nitriles and imines are given as a sum in Table 2. With more concentrated solutions, only traces of imines were observed. Corresponding peaks in the ^{1}H NMR spectrum completely disappeared after concentration in vacuo.

[25] We recently reported that the outcome of the photooxidation strongly depends on the reaction temperature; for an example, see Ref. [13a].

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[27] Contains 5 % water. Other TBAF loadings (100, 50, 1 mol %) as well as other activators, such as hexamethylphosphoric triamide (HMPA), Et_3N, 1,4-diazabicyclo[2.2.2]octane (DABCO), and *N*-methylmorpholine-*N*-oxide (NMO), were studied; however, their application was not successful.

[28] A greater amount of the dimeric products was also observed in the batch process.

[29] a) A. S. Bommarius, M. Schwarm, K. Stingl, M. Kottenhahn, K. Huthmacher, K. Drauz, *Tetrahedron: Asymmetry* **1995**, *6*, 2851 – 2888; b) A. S. Bommarius, M. Schwarm, K. Drauz, *J. Mol. Catal. B* **1998**, *5*, 1 – 11.

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[32] I. S. Young, P. S. Baran, *Nat. Chem.* **2009**, *1*, 193 – 205.

