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## Consecutive oxygen-based oxidations convert amines to α-cyanoepoxides<sup>†</sup>

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Tri- or tetrasubstituted  $\alpha$ -cyanoepoxides can be rapidly prepared from unactivated amines and malononitrile or methyl cyanoacetate when singlet oxygen, produced in a continuous-flow photoreactor, serves as an oxidant and *in situ* peroxide source. The hydrogen peroxide generated in amine oxidation epoxidizes an electron deficient olefin intermediate, formed by deaminative Mannich coupling. The corresponding  $\alpha,\alpha$ -dicyano- or  $\alpha$ -cyano- $\alpha$ -esterepoxides were obtained in good yields (43–82%).

 $\alpha$ -Cyanoepoxides have found many applications in organic chemistry, for example 1,3-dipolar cycloadditions,<sup>1</sup> regioselective nucleophilic additions,<sup>2</sup> and as bielectrophile reagents for the synthesis of a variety of heterocyclic compounds.<sup>2a,3</sup> These valuable intermediates are generally prepared *via* a two step process; the formation of an electron deficient alkene by Knoevenagel condensation<sup>4</sup> between an aldehyde and an ethanenitrile derivative at elevated temperature followed by hypochloride-mediated epoxidation<sup>5</sup> (Scheme 1).

However, the formation of the key olefin intermediate by a deaminative Mannich-type reaction is significantly less common,<sup>6</sup> as an additional step is required for imine formation by condensation of a carbonyl and an amine. Recently, Tian and coworkers<sup>7</sup> circumvented the condensation step, trapping *N*-Ph secondary imines formed under metal-free oxidative C–H activation conditions with carbon nucleophiles to generate *gem*-dicyano olefins. We hypothesized that if singlet oxygen were utilized for amine oxidation,<sup>8</sup> the photooxidation byproduct, hydrogen peroxide, could serve as a subsequent oxidant to epoxidize the electron-deficient alkene intermediate (Scheme 1, bottom) in a "boomerang"-type oxidation.<sup>9</sup>



Scheme 1 Strategies to prepare α-cyanoepoxides

Singlet oxygen can be efficiently generated<sup>10</sup> in a variable temperature continuous flow photoreactor<sup>11</sup> and has been previously utilized for the rapid oxidation of primary and secondary amines.<sup>12</sup> The resultant imines can be efficiently trapped by *in situ* trimethylsilyl cyanide to yield a series of  $\alpha$ -aminonitriles.<sup>13</sup>

Here, we describe that modification of this synthetic platform yields an expedianted synthesis of a variety of substituted  $\alpha$ -cyanoepoxides. When an ethanenitrile derivative is used as a nucleophilic trap of <sup>1</sup>O<sub>2</sub>-generated *N*-substituted/unsubstituted imines, an efficient deaminative Mannich-type reaction occurs. The resultant olefin is immediately epoxidized by *in situ*-formed hydrogen peroxide to yield  $\alpha, \alpha$ -dicyano- and  $\alpha$ -cyano- $\alpha$ -esterepoxides in 43–82% (Fig. 1).



Fig. 1 Formation of α-dicyanoepoxide by photooxidation of benzylamine.

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**Table 1** Transformation of amines to  $\alpha$ -dicyanoepoxides<sup>a</sup>

Entry	Amine	Product	Yield <sup><math>b</math></sup> (%)
1	Ph NH <sub>2</sub> 1	NC CN O Ph 3	74
2	Ph N TMS H 6	NC CN O Ph 3	69 <sup>c</sup>
3	NH <sub>2</sub> 7		$56^d$

<sup>a</sup> For detailed experimental conditions see ESI; 0.1 M amine solution in THF; TPP 0.2 mol%; -60 °C; residence time in photoreactor 2.5 min; malononitrile 1.7 equiv. <sup>*b*</sup> Isolated yields. <sup>*c*</sup> Oxidation run at room temperature. <sup>*d*</sup> Amide byproduct was isolated in 28%.

When a phenylaldimine (2) solution exiting the photooxidation module was treated with 1.7 equivalents of malononitrile and concentrated under reduced pressure at 30 °C, α-dicyanoepoxide 3 was obtained in 74% yield, along with two minor byproducts, the Knoevenagel-type olefin 5 and epoxy amide 4 (Fig. 1).<sup>14</sup>

N-Trimethylsilyl benzylamine 6 gave the corresponding  $\alpha$ -dicyanoepoxide 3 in good yield (Table 1, entry 2). While TMS-protection allows for aldimine formation at room temperature without formation of the oxidative coupling product,<sup>13</sup> we wished to avoid protecting groups and utilize unprotected amines. Neopentylamine 7 gave the product 8 only in moderate yield (Table 1, entry 3), with an increased amount of amide byproduct (28%).

Other C-H acids such as TMS-acetylene, diethylmalonate,15 and nitromethane failed to react under these conditions, presumably due to their lower acidity in comparison to malononitrile.<sup>16</sup> However, when methyl cyanoacetate was used as a nucleophilic trap for benzylideneamine 2,  $\alpha$ -cyano- $\alpha$ -methylesterepoxide 9 was obtained as a single diastereomer in 71% yield (Table 2, entry 1). Excellent diastereoselectivity in the Knoevenagel condensation, providing only E-isomers, has been observed previously.17 In contrast to malononitrile, good yields were obtained for aliphatic substrates, generating tri- and tetrasubstituted epoxides (entries 3, 4, 7-9), as well as the spiro compound 14 (entry 5). The imine resulting from asymmetrical methylbenzylamine 15 gave a diastereomeric mixture of epoxides in a 1.7:1 ratio with a combined yield of 72% (entry 6).

Diisopropyl- and diethylamine both gave the corresponding  $\alpha$ -cyano- $\alpha$ -methylesterepoxide in good yields (entries 8, 9). However, when dibenzylamine was exposed to the reaction conditions, amide 23 was obtained as the sole product in 71% yield (entry 10). Benzylamine, liberated upon Mannich coupling, attacks the ester following epoxidation. The lack of amide products observed for the other secondary amine substrates is presumably due to the lower boiling points of the eliminated amine. To test this notion, a crude solution of **10** (product in entry 3) was re-suspended in THF with one equivalent of benzylamine. Upon concentration, the corresponding N-benzyl amide was formed in 63% yield, representing a formal insertion of a two carbon unit into a C-N bond.

The proposed mechanism begins with singlet oxygen mediated photooxidation of the amine to the corresponding imine to form **Table 2** Transformation of amines to  $\alpha$ -cyano- $\alpha$ -methylesterepoxides<sup>a</sup>

Entry	Amine	Product	Yield <sup>b</sup> (%)
1	Ph NH <sub>2</sub> 1	NC, CO <sub>2</sub> Me O Ph <sup>H</sup> <b>9</b>	71
2	Ph N <sup>TMS</sup> H 6	NC, CO <sub>2</sub> Me O Ph H 9	72
3	NH <sub>2</sub> 7	NC, CO <sub>2</sub> Me	82
4	Ph H <sub>2</sub> N 11	Ph NC, ,,CO <sub>2</sub> Me	70
5		NC CO <sub>2</sub> Me	69
6	Ph NH <sub>2</sub> 15	NC CO <sub>2</sub> Me O Ph <sup>roten</sup> 16	72 <sup>c</sup>
7	→	NC CO <sub>2</sub> Me	43
8		NC CO <sub>2</sub> Me	75
9	∕_N∕ H20	NC, ,,CO <sub>2</sub> Me	76
10	Ph <sup>^N</sup> Ph <sup>H</sup> 22	NC NC O H Ph H 23	71

<sup>a</sup> For detailed experimental conditions see ESI; 0.1 M amine solution in THF; TPP 0.2 mol%; r.t. or -60 °C; residence time in photoreactor 2.5 min; methyl cyanoacetate 1.2 equiv. <sup>b</sup> Isolated yields. <sup>c</sup> D.r. 1.7:1.

hydrogen peroxide (Scheme 2).<sup>18</sup> A subsequent Mannich-type reaction<sup>19</sup> is followed by deamination, resulting in an electrondeficient alkene. Epoxidation by H2O2<sup>20</sup> occurs slowly in solution as monitored by TLC, with traces of alkene observed after 72 h. However, immediate evaporation upon trapping with methyl cyanoacetate results in full conversion to the corresponding epoxide.

The Mannich-type deamination is not dependent on peroxides, as evidenced by the immediate formation of the alkene upon reaction of methyl cyanoacetate with N-benzylidene-1-phenylmethanamine, prepared by classical condensation (see ESI<sup>†</sup>). Crude



Scheme 2 Proposed mechanism for the formation of α-cyanoepoxides from amines.

proton NMR revealed an imine: alkene ratio of 0.7:1.0, which did not change with extended reaction times. We hypothesize that the deamination, under these reaction conditions, exists in equilibrium and the alkene is irreversibly trapped by the peroxide, thus driving the reaction to completion.

We have demonstrated that synthetically valuable intermediates,  $\alpha$ -dicyano- or  $\alpha$ -cyano- $\alpha$ -esterepoxides, can be rapidly and efficiently generated in a continuous manner by trapping of ketimines and aldimines, formed upon photooxidation of the corresponding amine by singlet oxygen, with malononitrile or methyl cyanoacetate. The epoxidation occurs by hydrogen peroxide, a waste product of  ${}^{1}O_{2}$ -oxidation of amines and requires no additional acids, bases, or oxidants. This rapid increase in molecular complexity is not limited to activated amines and is not sensitive to substitution in the alpha position. Further studies in this area are currently underway.

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