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Photoinduced 1,2-Hydro(cyanomethylation) of Alkenes with a Cyanomethylphosphonium Ylide

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Abstract An efficient method has been developed for the 1,2-hydro(cyanomethylation) of alkenes, in which a cyanomethyl radical species is generated from a cyanomethylphosphonium ylide by irradiation with visible light in the presence of an iridium complex, a thiol, and ascorbic acid. The cyanomethyl radical species then adds across the C=C double bond of an alkene to form an elongated alkyl radical species that accepts a hydrogen atom from the thiol to produce an elongated aliphatic nitrile. The ascorbic acid acts as the reductant to complete the catalytic cycle.

Key words alkenes, nitriles, photocatalysis, radicals, phosphonium ylides, hydro(cyanomethylation)

Radical chemistry has undergone a renaissance since the introduction of photoredox catalysis,1 and a wide variety of reagents are now available as competent precursors to radical species. We recently reported that an ester-stabilized phosphonium ylide2 can act as a precursor to an (alkoxycarbonyl)ethyl radical species3 when irradiated with visible light in the presence of an iridium catalyst, a thiol, and ascorbic acid.4 The radical species, substituted by an electron-withdrawing alkoxycarbonyl group, adds across the C=C double bond of an alkene to generate an elongated aliphatic ester.5

We also examined the use of a cyanomethylphosphonium ylide instead of an ester-stabilized phosphonium ylide. The former act as the precursor of a cyanomethyl radical species7–10 that, due to the electron-withdrawing nature of the cyano group, is sufficiently electrophilic to attach to a C=C double bond of an alkene, as in the case of an (alkoxycarbonyl)methyl radical.3,4 The appended alkyl radical species is not as electrophilic as the original cyanomethyl radical, and can therefore abstract a hydrogen atom from a sulfanyl radical5 to form an elongated aliphatic nitrile.

Initially, we applied the conditions optimized for the reaction of an ester-stabilized phosphonium ylide4 to the reaction of the cyanomethylphosphonium ylide 2 with 4-phenylbut-1-ene (1a), and we obtained 6-phenylhexanenitrile (3a) as expected. The yield, however, was moderate (43% by NMR), which led us to adapt the reaction conditions slightly to fit the ylide 2. The elongated nitrile 3a was produced in 94% NMR yield and 80% isolated yield when 1a (0.50 mmol) was treated with 2 (1.0 mmol, 2.0 equiv) in 1:1 CH3CN/H2O (0.1 M) under irradiation by blue light-emitting diodes (LEDs; 470 nm, 23 W) in the presence of fac-Ir(ppy)3 (1.0 mol%; ppy = 2-phenylpyridinato), C6F5SH (20 mol%), ascorbic acid (10 equiv), and KHSO4 (3.0 equiv) at room temperature for 40 hours (Scheme 1). No product resulting from 1,2-addition in the opposite direction was observable within the detection limits of 1H NMR (400 MHz). A larger-scale experiment using 925 mg (7.0 mmol) of 1a also gave a comparable yield of 3a (83% isolated yield), indicating the scalability of the present reaction.

Scheme 1 1,2-Hydro(cyanomethylation) of alkene 1a with phosphonium ylide 2

The formation of the product 3a can be reasonably explained by assuming the radical mechanism depicted in Scheme 2, which is similar to that proposed in the case of ester-stabilized phosphonium ylides.4 First, an acid/base...
reaction of 2 (pKa = 6.9)\textsuperscript{11} with ascorbic acid (Asch\textsubscript{2}; pKa = 4.0)\textsuperscript{12} generates the phosphonium ascorbate [Ph,PCH\textsubscript{2}CN][Asch\textsuperscript{+}] (4). This has an energetically low-lying σ\textsuperscript{+} orbital for the C–P linkage. The Ir catalyst [fac-Ir(ppy)\textsubscript{3}][Ir(III)] is photoexcited by visible light to form the excited species [Ir(III)]\textsuperscript{*}. This then transfers a single electron to the σ\textsuperscript{+} orbital of the phosphonium ascorbate 4, giving rise to the cyanomethyl radical species 5, along with PPh\textsubscript{3} and [Ir(IV)]\textsuperscript{+}[Asch\textsuperscript{–}]. Electrophilic addition of 5 to the C=C double bond of alkene 1a affords the elongated secondary alkyl radical species 6, which is less electrophilic than 5. Hydrogen-atom transfer from C\textsubscript{6}F\textsubscript{5}S\textsubscript{H} to 6 produces 3a and a thyl radical (C\textsubscript{6}F\textsubscript{5}S\textsuperscript{•}).\textsuperscript{5} The [Ir(IV)]\textsuperscript{+} species and C\textsubscript{6}F\textsubscript{5}S\textsuperscript{•} are reduced back to the [Ir(III)] species and C\textsubscript{6}F\textsubscript{5}S\textsubscript{H}, respectively, by the action of the ascorbate anion [Asch\textsuperscript{–}],\textsuperscript{13,14} which ultimately produces dehydroascorbic acid (DHA).\textsuperscript{15} The additive KHSO\textsubscript{4} might act by suppressing undesirable formation of a thiolate anion (C\textsubscript{6}F\textsubscript{5}S\textsuperscript{–}) from C\textsubscript{6}F\textsubscript{5}S\textsubscript{H}.

Various alkenes 1 were subjected to the 1,2-hydro(cyanomethylation) reaction with 2 (Table 1). A wide range of functional groups were tolerated to afford the corresponding elongated aliphatic nitriles 3b\textsuperscript{–}–g in yields ranging from 74 to 88% (Table 1, entries 1–6). Not only monosubstituted alkenes, but also polysubstituted alkenes, participated in the reaction. Geminally disubstituted alkenes 1h and 1i were suitable substrates (entries 7 and 8). Cyclic disubstituted alkenes 1j and 1k afforded the corresponding products 3j and 3k in yields of 59 and 79%, respectively (entries 9 and 10). The reaction of the acyclic vicinally disubstituted alkenes (Z)- and (E)-11 was sluggish, and the reason for the low yield of product 3l is unclear (entries 11 and 12). In the case of trisubstituted alkene 1m, a mixture of diastereomers of 3m was formed through nonstereoselective transfer of a hydrogen atom to an intermediate tertiary radical species (entry 13). Even the tetrasubstituted alkene 1n underwent the reaction (entry 14). The 1,2-adduct 3o was obtained in 18% NMR yield from styrene (1o), and the final reaction mixture contained various products, probably as a result of the high reactivity of the benzylic radical intermediates (entry 15).\textsuperscript{16}

### Table 1 1,2-Hydro(cyanomethylation) of Various Alkenes 1 with Phosphorus Ylide 2\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene 1</th>
<th>Product 3</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HO\textsubscript{2}C–CH=CH\textsubscript{2}</td>
<td>3b</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>NC\textsubscript{5}H\textsubscript{4}–C\textsubscript{5}H\textsubscript{5}CN</td>
<td>3c</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>NC\textsubscript{5}H\textsubscript{4}–CH\textsubscript{3}CN</td>
<td>3d</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>HO\textsubscript{2}C–CH\textsubscript{3}</td>
<td>3e</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>Ph\textsubscript{2}C=CH\textsubscript{2}</td>
<td>1f</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>Cl–CH\textsubscript{2}–CH=CH\textsubscript{2}</td>
<td>3f</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>C\textsubscript{6}H\textsubscript{11}</td>
<td>3g</td>
<td>73</td>
</tr>
<tr>
<td>8</td>
<td>C\textsubscript{6}H\textsubscript{11}CN</td>
<td>3i</td>
<td>77</td>
</tr>
<tr>
<td>9</td>
<td>CH\textsubscript{3}–CH=CH\textsubscript{2}</td>
<td>3j</td>
<td>59</td>
</tr>
<tr>
<td>10</td>
<td>C\textsubscript{6}H\textsubscript{11}–CH\textsubscript{3}</td>
<td>3k</td>
<td>79</td>
</tr>
<tr>
<td>11</td>
<td>n-Pr–CH\textsubscript{3}</td>
<td>3l</td>
<td>28</td>
</tr>
<tr>
<td>12</td>
<td>n-Pr–CH\textsubscript{3}</td>
<td>3l</td>
<td>29\textsuperscript{f}</td>
</tr>
<tr>
<td>13</td>
<td>n-Pr–CH\textsubscript{3}</td>
<td>3m</td>
<td>45</td>
</tr>
<tr>
<td>14</td>
<td>CH\textsubscript{3}–CH=CH\textsubscript{2}</td>
<td>3n</td>
<td>56\textsuperscript{f}</td>
</tr>
<tr>
<td>15</td>
<td>PH\textsubscript{2}C=CH\textsubscript{2}</td>
<td>1o</td>
<td>18\textsuperscript{f}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: 1 (0.50 mmol), 2 (1.0 mmol), fac-Ir(ppy)\textsubscript{3} (1.0 mol%), C\textsubscript{6}F\textsubscript{5}S\textsubscript{H} (20 mol%), ascorbic acid (5.0 mmol), KHSO\textsubscript{4} (1.5 mmol), 1:1 CH\textsubscript{3}CN/H\textsubscript{2}O (5.0 mL), r.t., 40 h, blue LEDs (470 nm, 23 W).

\textsuperscript{b} Isolated yield.

\textsuperscript{c} NMR yield with 1,1,2,2-tetrachloroethane as internal standard.
In the case of 1-benzofuran (7), the cyanomethyl radical species added regioselectively to form a benzylic radical species, giving the 2-substituted 2,3-dihydro-1-benzofuran 8 (Scheme 3).

![Scheme 3](image)

Scheme 3 The addition reaction to 1-benzofuran (7)

Notably, even a branched α-cyanoethyl group was attached to the C=C double bond of 1a when α-cyanoethylphosphonium ylide 9 was employed (Scheme 4).

![Scheme 4](image)

Scheme 4 The reaction with the α-cyanoethylphosphonium ylide 9

A similar reaction to form elongated aliphatic nitriles from alkenes has been reported, in which a cyanomethyl radical species is generated from CH3CN by using an excess of dicumyl peroxide at a high temperature; these potentially hazardous conditions significantly limit the synthetic value of the method. The present reaction uses cyanomethylphosphonium ylide, which is stable and easily accessible, as the radical source, thereby providing a convenient method for synthesizing elongated aliphatic nitriles from alkenes.17

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612230.

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(16) The reactions of terminal alkynes such as 4-phenylbut-1-yne gave complex mixtures of products, in which the corresponding 1,2-hydro(cyanomethylation) product (a β,γ-unsaturated nitrile) was present in ~10% yield as a 1:1 mixture of E- and Z-isomers.

(17) 6-Phenylhexanenitrile (3a); Typical Procedure

A vial (2–5 mL; Biotage, Fisher Scientific) equipped with a stirrer bar was charged with the phosphorus ylide 2 (302 mg, 1.00 mmol), fac-Ir(ppy)₃ (3.30 mg, 0.005 mmol, 1.0 mol%), ascorbic acid (882 mg, 5.00 mmol), and KHSO₄ (207 mg, 1.52 mmol). The vial was then flushed with argon gas and quickly capped with a Teflon septum. 4-Phenylbut-1-ene (1a, 67.6 mg, 0.51 mmol), C₆F₅SH (20.0 mg, 0.100 mmol, 20 mol%), distilled CH₂CN (2.5 mL), and H₂O (2.5 mL; degassed with argon gas for 30 min) were added from a syringe, and the mixture was stirred vigorously for 40 h under blue LED lights (470 nm, 23 W) while the vial was cooled with a fan. The mixture was then diluted with brine (25 mL) and extracted with CH₂Cl₂ (3 × 25 mL). The organic phase was dried (Na₂SO₄), filtered, and concentrated under reduced pressure to give a residue that was purified by column chromatography [silica gel, hexane/EtOAc (9:1)] to give a colorless oil; yield: 70.7 mg (0.41 mmol, 80%).

IR (ATR): 2936, 2245, 1454 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 1.45–1.53 (m, 2 H), 1.63–1.73 (m, 4 H), 2.33 (t, J = 7.2 Hz, 2 H), 2.63 (t, J = 7.6 Hz, 2 H), 7.16–7.21 (m, 3 H), 7.26–7.31 (m, 2 H). ¹³C NMR (100 MHz, CDCl₃): δ = 17.1, 25.3, 28.3, 30.5, 35.5, 119.7, 125.8, 128.3, 141.9. HRMS (EI⁺): m/z [M⁺] calcld for C₁₂H₁₅N: 173.1204; found: 173.1205.