This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
DBU-mediated metal-free oxidative cyanation of α-amino carbonyl compounds: using molecular oxygen as the oxidant

Lei Li, a Qian Wang, a Pei Liu, a Hua Meng, b Xing-Lan Kan, a Qun Liu, a and Yu-Long Zhao,* a

a Department of Chemistry, Northeast Normal University, Changchun, 130024, P. R. China
b Zhejiang Sucon Silicone Co., Ltd., Shaoxing, 312088, P. R. China

A novel DBU-mediated oxidative cyanation of α-amino carbonyl compounds by using air as the sole oxidant was developed under mild metal-free conditions for the first time. The reaction involves a tandem oxidation/Strecker reaction/oxidation process and provides a new and efficient method for the construction of α-iminonitriles in good to high yields in a single step.

Introduction

α-Aminonitriles are an important class of versatile intermediates for a wide range of natural products, pharmaceuticals, functional materials, and agricultural chemicals. 1 In addition, nucleophilic additions to the nitrile group can provide access to valuable α-amino aldehydes, ketones, and alcohols, as well as 1,2-diamines. 2 Accordingly, the development of novel and efficient synthetic methods for α-amino nitriles has been a major topic in synthetic organic chemistry. Among the different methods available for the preparation of these compounds, 3-7 the oxidative cyanation of sp 3 C–H bonds adjacent to nitrogen atom represents one of the most straightforward and convenient methods for the synthesis of α-aminonitriles. 4-7 However, in all these reactions reported except the electrochemical methods, 5 transition metal (TM) catalysts/mediators, chemical oxidants (Ox), photosensitizers (PS, in light induced reaction) and/or radical initiators are generally required (Scheme 1, a). 6 Recently, Seidel and co-workers developed a conceptually new strategy for the direct α-cyanation of amines in redox-neutral fashion, but the reaction was carried out under microwave conditions at rather high temperature (200 °C, Scheme 1, b). 7 Obviously, the development of oxidative cyanation of sp 3 C–H bonds adjacent to nitrogen atom in the absence of transition metals, chemical oxidants, photosensitizers and radical initiators under very mild reactions remains a formidable challenge. Herein, we report the first DBU-mediated oxidative cyanation of sp 3 C–H bonds adjacent to nitrogen atom.
C–H bonds adjacent to nitrogen atom without using any redox-active catalysts, chemical oxidants, photosensitizers and radical initiators (Scheme 1, c). Moreover, the reaction takes place under rather mild conditions with molecular oxygen as a green oxidant and provides a new and efficient method for the construction of functionalized α-iminonitriles in a single step.

Results and discussion

In addition, α-amino carbonyl compounds are ubiquitous subunits in biologically active natural products, biomolecules and therapeutic agents. Thus, it is reasonable that considerable efforts have been devoted to the development of novel methods for their assembly. In this field, α-C–H functionalization of the preexisting α-amino carbonyl structures has attracted considerable attention due to its direction and site-specificity. Among these reactions, the generation of electrophilic iminium intermediates through oxidation of sp³ C–H bonds adjacent to nitrogen atom of α-amino carbonyl compounds, followed by attack of various nucleophiles, has recently been recognized as a powerful mean for preparation of α-amino carbonyl compounds. To the best of our knowledge, however, the direct oxidative α-cyanation of α-amino carbonyl compounds has not been exploited. As part of our continuing research on the formation of carbon–carbon and carbon–nitrogen bonds based on oxidative coupling reactions, we recently developed an efficient method for C–C formation via a base-promoted intramolecular CDC of α-amino carbonyl compounds under
very mild metal-free conditions. These results and our continuous interest in the carbocyanation reaction prompted us to investigate the α-cyanation of N-aryl α-amino ketones under basic conditions using molecular oxygen as the oxidant under metal-free conditions. As a result, it was found that the oxidative Strecker reaction of N-aryl α'-amino-α,β-unsaturated ketone 1a (0.2 mmol) with trimethylsilyl cyanide (TMSCN) 2a (0.3 mmol) could proceed rapidly to give (1E,3E)-4-(4-chlorophenyl)-2-oxo-N-p-tolylbut-3-enimidoyl cyanide 3a in 72% yield in the presence of DBU (0.3 mmol, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene) in DMF (1.5 mL) at room temperature in open air for only 4 min along with the oxidation product 4a in 5% yield (entry 3). This reaction is highly chemoselective leaving the cinnamoyl moiety of 1a intact.

Further increasing the amounts of DBU leads to lower yield of 3a (entry 4). Other bases such as DBN (1,5-diazabicyclo[4.3.0]non-5-ene), NaOH, DABCO (1,4-diazabicyclo[2.2.2]octane), Et3N and Cs2CO3, were less (entries 5 and 6) or not effective (entries 7-9). The solvent, DMF, was a much better choice than other solvents examined, including CH3CN, THF, CH2Cl2 and toluene (entries 10-13). The structure of 3a was determined based on its spectroscopic and analytical data and confirmed by X-ray crystal structure analysis (Fig. 1).

Table 1 Optimization of Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv)</th>
<th>Solvent</th>
<th>Time (min)</th>
<th>Yield (3a) (%)</th>
<th>Yield (4a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DBU (0.5)</td>
<td>DMF</td>
<td>5</td>
<td>38</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>DBU (1.0)</td>
<td>DMF</td>
<td>4</td>
<td>65</td>
<td>10</td>
</tr>
<tr>
<td>3*</td>
<td>DBU (1.5)</td>
<td>DMF</td>
<td>4</td>
<td>72</td>
<td>5</td>
</tr>
<tr>
<td>4*</td>
<td>DBU (2.0)</td>
<td>DMF</td>
<td>4</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>DBN (2.0)</td>
<td>DMF</td>
<td>4</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>NaOH (1.5)</td>
<td>DMF</td>
<td>8</td>
<td>41</td>
<td>7</td>
</tr>
<tr>
<td>7*</td>
<td>DABCO (1.5)</td>
<td>DMF</td>
<td>30</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>8*</td>
<td>Et3N (1.5)</td>
<td>DMF</td>
<td>30</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>9*</td>
<td>Cs2CO3 (1.5)</td>
<td>DMF</td>
<td>30</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>10</td>
<td>DBU (1.5)</td>
<td>MeCN</td>
<td>5</td>
<td>64</td>
<td>12</td>
</tr>
<tr>
<td>11</td>
<td>DBU (1.5)</td>
<td>THF</td>
<td>8</td>
<td>61</td>
<td>15</td>
</tr>
<tr>
<td>12</td>
<td>DBU (1.5)</td>
<td>CH2Cl2</td>
<td>8</td>
<td>35</td>
<td>18</td>
</tr>
<tr>
<td>13</td>
<td>DBU (1.5)</td>
<td>Toluene</td>
<td>6</td>
<td>61</td>
<td>17</td>
</tr>
</tbody>
</table>

* Reaction conditions: 1a (0.2 mmol), 2a (0.3 mmol), base (0.1-0.4 mmol), solvent (1.5 mL), at room temperature for 4-30 min. * Estimated by 1H NMR spectroscopy using dimethyl phthalate as an internal standard. * Isolated yield. * Complex mixture was obtained.
Scheme 2 DBU-Promoted oxidative cyanation of 1 with 2

\[ \text{R}^+ \text{N}^{\text{Ar}} + \text{TMSCN} \rightarrow \text{ROCN}^{\text{Ar}} \]

DBU (1.5 equiv)  
DMF, rt, 4-10 min

\[ \text{R}^+ \text{N}^{\text{Ar}} \quad 1 \quad \text{2} \quad \text{3} \]

\[ \text{3a} \quad (72\%, 4 \text{ min}) \quad \text{3b} \quad (50\%, 8 \text{ min}) \quad \text{3c} \quad (60\%, 5 \text{ min}) \]

\[ \text{3d} \quad (62\%, 5 \text{ min}) \quad \text{3e} \quad (60\%, 4 \text{ min}) \quad \text{3f} \quad (62\%, 4 \text{ min}) \]

\[ \text{3g} \quad (71\%, 4 \text{ min}) \quad \text{3h} \quad (76\%, 5 \text{ min}) \quad \text{3i} \quad (65\%, 5 \text{ min}) \]

\[ \text{3j} \quad (75\%, 10 \text{ min}) \quad \text{3k} \quad (60\%, 8 \text{ min}) \quad \text{3l} \quad (56\%, 4 \text{ min}) \]

\[ \text{3m} \quad (57\%, 5 \text{ min}) \quad \text{3n} \quad (63\%, 5 \text{ min}) \quad \text{3o} \quad (0\%, 6 \text{ h}) \]

\[ \text{3p} \quad (0\%, 6 \text{ h}) \quad \text{3q} \quad (1 \text{ h}) \quad \text{3r} \quad (1 \text{ h}) \]

\(^a\) Reaction conditions: 1 (0.2 mmol), 2 (0.30 mmol), DBU (0.30 mmol), DMF (1.5 mL), rt, 4-10 min. \(^b\) Isolated yield. \(^c\) 1o and 1p were recovered in 95% and 94% yields, respectively. \(^d\) A complex mixture was produced.
Under the optimal conditions (Table 1, entry 3), the scope and generality of the reaction was next examined. As described in Scheme 2, all of selected N-aryl α'-amino-α,β-unsaturated ketone substrates 1a-i, bearing phenyl, electron-deficient and electron-rich aryl, heteroaryl and 2-naphthyl groups at the β-position of the enone moiety, reacted smoothly with trimethylsilyl cyanide 2 to give the corresponding (1E,3E)-2-oxo-N,4-diarylbut-3-enimidoyl cyanides 3a-i in good to high yields at room temperature in open air for 4-10 min. In addition, the reaction of substrate 1j bearing a (E)-phenylvinyl group (R) gave the desired product 3j in 75% yield (Scheme 2). On the other hand, various N-aryl groups of 1 were also well-tolerated and the corresponding (1E,3E)-2-oxo-N,4-diarylbut-3-enimidoyl cyanides 3k-n were prepared in good to high yields (Scheme 2). No reaction was observed when α-amino carbonyl compounds 1o and 1p were used as substrates (Scheme 2). In addition, the reaction of α-amino carbonyl compound 1q or 1r with trimethylsilyl cyanide 2 led to a complex mixture under the identical conditions as above (Scheme 2), which may be due to the lower pKa value of the hydrogen at the nitrogen.

To further probe the mechanisms for formation of 3, some control experiments were designed and investigated. As a result, it was found that the yield of product 3a decreased greatly from 72 to 16% under the standard condition when TEMPO (1.0 equiv.; TEMPO = 2,2,6,6-tetramethylpiperidinoxy) was used as a radical inhibitor (Scheme 3, a). No desired product 3a was produced when the reaction of 1a with TMSCN 2 was carried out under nitrogen atmosphere (Scheme 3, b). These results indicate that molecular oxygen as oxidant (from air) is necessary for the oxidative cyanation reaction and a radical mechanism may be involved in this oxidative coupling process. No reaction was observed under otherwise identical conditions but in the absence of DBU (Scheme 3, c), which demonstrates that DBU is also crucial for the above oxidative cyanation reaction. In addition, the imine 5a could be formed in 11% yield (along with a complex mixture) in the absence of TMSCN under otherwise identical conditions as above (Scheme 3, d). According to the results of this transformation, we predicted that the imine 5a may be a key intermediate in the reaction. Therefore, the reaction of imine 5a with TMSCN 2 was further investigated.
As expected, under otherwise identical conditions as above, the Strecker reaction of imine 5a with TMSCN 2 can smoothly proceed to give the product 3a in 60% yield (Scheme 3, c).

Based on above experimental results and related report, a possible mechanism for the formation of 3 is proposed (Scheme 4). Initially, the deprotonation of 1 into enolate anion I followed by a single-electron transfer (SET) process between I and triplet oxygen forms the superoxide anion radical and the radical intermediate II/III. Then, the intermediate IV, generated by the reaction of intermediate III with superoxide anion radical, undergoes an elimination of hydroperoxide anion to give the imine intermediate V, which rapidly reacts with trimethylsilyl cyanide 2 to generate the intermediate VI. Finally, (1E,3E)-2-oxo-N,4-diarylbut-3-enimidoyl cyanide 3 was produced via a sequential deprotonation, oxidation and elimination of TMS-peroxide anion process (VI→3, Scheme 4).
In order to explore the synthetic potential of these functionalized (1E,3E)-2-oxo-N,4-diarylbut-3-enimidoyl cyanides, the cyclization reaction of 3 with benzene-1,2-diamine was examined (Scheme 5). It was found that the cyclization reaction of 3a (0.2 mmol) with benzene-1,2-diamine (0.24 mmol) could easily proceed to give 2-cyano quinoxaline 6a in 92% yield in AcOH (2.0 mL) at 120 °C for 10 min in the presence of NaOAc (0.24 mmol). Similarly, 2-cyano quinoxaline derivatives 6f and 6h were obtained in 91% and 95% yields from (1E,3E)-2-oxo-N,4-diarylbut-3-enimidoyl cyanides 3f and 3h, respectively (Scheme 5).
Conclusions

In conclusion, we have developed a novel DBU-mediated oxidative cyanation of \( \alpha \)-amino carbonyl compounds by using air as the sole oxidant under metal-free conditions for the first time. The reaction involves a tandem oxidation/Strecker reaction/oxidation process and provides a new and efficient method for the construction of \( \alpha \)-imino nitriles in a single step. The advantages of those methods include: (1) mild reaction conditions and short reaction time; (2) simplicity and safety of operation; (3) any transition metals, synthetic oxidants, photosensitizers and radical initiators are not required and only cheap DBU and air are necessary. These advantages make this protocol very practical. Further studies are in progress.

Financial supports of this research by the National Natural Sciences Foundation of China (21472017 and 21172032), Natural Sciences Foundation of Jilin Province (20150101065JC) and Fundamental Research Funds for the Central Universities are greatly acknowledged.

Experimental

General methods

All reagents were commercial and were used without further purification. Chromatography was carried on flash silica gel (300-400 mesh). All reactions were monitored by TLC, which was performed on precoated aluminum sheets of silica gel 60 (F254). Unless noted, the \( ^1 \)H NMR spectra were recorded at 400 MHz and 500 MHz in CDCl\(_3\) and the \( ^{13} \)C NMR spectra were recorded at 125 MHz in CDCl\(_3\) with TMS as internal standard. All coupling constants (\( J \) values) were reported in Hertz (Hz). High-resolution mass spectra (HRMS) were obtained using a Bruker microTOF II focus spectrometer (ESI).

General Procedure for the Preparation of 3 (3a as Example).

To a solution of \((E)\)-4-(4-chlorophenyl)-1-(\(p\)-tolylamino)but-3-en-2-one 1a (0.2 mmol, 57.1 mg) and TMSCN 2 (0.30 mmol, 0.040 mL) in DMF (1.5 mL) was added DBU (0.3 mmol, 0.045 mL). Then the
reaction mixture was stirred at room temperature in open air for 5 min. After 1a was consumed (monitored by TLC), the reaction mixture was poured into water (50 mL) and extracted with CH₂Cl₂ (10 mL × 3). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to yield the corresponding crude product, which was purified by chromatography (silica gel, petroleum ether/acetone = 10/1, v/v) to give 3a (44.4 mg, 72%) as a yellow solid.

**1E,3E-4-(4-Chlorophenyl)-2-oxo-N-(p-tolyl)but-3-enimidoyl cyanide (3a).** Yellow solid; m.p. 107-109 °C; ¹H NMR (CDCl₃, 500 MHz) δ: 7.91 (d, J = 16.0 Hz, 1H), 7.83 (d, J = 16.0 Hz, 1H), 7.63 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 2.45 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ: 183.5, 145.4, 143.3, 142.2, 137.4, 135.8, 132.8, 130.3, 130.2, 129.4, 123.0, 118.4, 110.6, 21.6; IR (KBr) ν: 2921, 2215, 1618, 1600, 1556, 1445, 1319, 1108, 1060 cm⁻¹; HRMS (ESI-TOF)calcd for C₁₃H₁₃ClN₂O⁺([M + Na]⁺): 331.0609, found: 331.0620.

**1E,3E-2-Oxo-N-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)but-3-enimidoyl cyanide (3b).** Yellow solid; m.p. 135-137 °C; ¹H NMR (500 MHz, CDCl₃) δ: 7.94 (d, J = 4.0 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 2.46 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ: 183.5, 144.7, 143.2, 142.5, 137.6, 135.4, 132.6 (q, J₁₁ = 32.7 Hz), 130.3, 129.1, 126.0 (q, J₁₂ = 3.6 Hz), 123.7 (q, J₁₁ = 270.7 Hz), 123.2, 120.2, 110.6, 21.6; IR (KBr) ν: 2926, 2211, 1608, 1550, 1324, 1117, 1066 cm⁻¹; HRMS (ESI-TOF)calcd for C₁₉H₁₄F₃N₂O⁺([M + H]⁺): 343.1053, found: 343.1049.

**1E,3E-4-(2-Chlorophenyl)-2-oxo-N-(p-tolyl)but-3-enimidoyl cyanide (3c).** Yellow solid; m.p. 118-120 °C; ¹H NMR (500 MHz, CDCl₃) δ: 8.39 (d, J = 16.0 Hz, 1H), 7.85-7.81 (m, 2H), 7.50 (d, J = 8.5 Hz, 2H), 7.46 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 7.39-7.32 (m, 4H), 2.45 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ: 183.4, 143.2, 142.5, 136.2, 136.5, 132.5, 132.0, 130.4, 130.3, 128.0, 127.1, 123.0, 120.3, 110.6, 21.5; IR (KBr) ν: 3032, 2217, 1663, 1595, 1328, 1272, 1208 cm⁻¹; HRMS (ESI-TOF)calcd for C₁₉H₁₄ClN₂O⁺([M + H]⁺): 309.0789, found: 309.0798.

**1E,3E-2-Oxo-N,4-dip-tolylbut-3-enimidoyl cyanide (3d).** Yellow solid; m.p. 133-135 °C; ¹H NMR (500 MHz, CDCl₃) δ: 7.96 (d, J = 16.0 Hz, 1H), 7.81 (d, J = 16.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 2.45 (s, 3H), 2.41 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ: 183.6, 147.2, 143.5, 142.3, 141.8, 136.2, 131.6, 130.2, 129.8, 129.2,
122.8, 116.8, 110.7, 21.7, 21.5; HRMS (ESI-TOF) calcd for C_{16}H_{17}N_{2}O_{4} (\text{[M + H]^{+}}): 289.1335, found: 289.1337.

\((1E,3E)-4-(4-Methoxyphenyl)-2-oxo-N-p-tolylbut-3-enimidoyl cyanide (3e).\) Yellow solid; m.p. 112-114 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.94 (d, \(J = 16.0\) Hz, 1H), 7.72 (d, \(J = 16.0\) Hz, 1H), 7.66 (d, \(J = 8.5\) Hz, 2H), 7.46 (d, \(J = 8.5\) Hz, 2H), 7.34 (d, \(J = 8.0\) Hz, 2H), 6.95 (d, \(J = 9.0\) Hz, 2H), 3.87 (s, 3H), 2.44 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 183.4, 162.4, 146.9, 143.5, 141.7, 136.4, 131.1, 130.2, 127.1, 122.7, 115.4, 114.5, 110.7, 55.5, 21.5; IR (KBr) \(v\): 2960, 2930, 2217, 1730, 1663, 1258, 1170, 1020 cm\(^{-1}\); HRMS (ESI-TOF) calcd for C_{16}H_{17}N_{2}O_{4} (\text{[M + H]^{+}}): 305.1285, found: 305.1286.

\((1E,3E)-2-Oxo-4-phenyl-N-(p-tolyl)but-3-enimidoyl cyanide (3f).\) Yellow solid; m.p. 90-92 °C; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\): 7.97 (d, \(J = 16.0\) Hz, 1H), 7.85 (d, \(J = 16.0\) Hz, 1H), 7.69 (d, \(J = 7.5\) Hz, 2H), 7.50 (d, \(J = 8.0\) Hz, 2H), 7.44-7.46 (m, 3H), 7.34 (d, \(J = 8.0\) Hz, 2H), 2.45 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\): 183.6, 146.9, 143.4, 142.0, 135.9, 134.3, 131.4, 130.2, 129.0, 129.0, 122.9, 117.9, 110.6, 21.5; IR (KBr) \(v\): 2962, 2938, 2218, 1738, 1670, 1261, 1176, 1032 cm\(^{-1}\); HRMS (ESI-TOF) calcd for C_{16}H_{17}N_{2}O_{4} (\text{[M + H]^{+}}): 275.1179, found: 275.1179.

\((1E,3E)-4-(Furan-2-yl)-2-oxo-N-(p-tolyl)but-3-enimidoyl cyanide (3g).\) Yellow solid; m.p. 146-148 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.70 (s, 2H), 7.58 (s, 1H), 7.49 (d, \(J = 8.5\) Hz, 2H), 7.34 (d, \(J = 8.5\) Hz, 2H), 6.84 (d, \(J = 3.5\) Hz, 1H), 6.56 (dd, \(J = 3.5, 1.6\) Hz, 1H), 2.44 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 183.5, 151.4, 146.0, 143.4, 141.9, 135.8, 132.2, 130.2, 122.9, 118.3, 115.5, 113.1, 110.7, 21.5; HRMS (ESI-TOF) calcd for C_{16}H_{17}N_{2}O_{4} (\text{[M + H]^{+}}): 265.0972, found: 265.0977.

\((1E,3E)-2-Oxo-4-(thiophen-2-yl)-N-(p-tolyl)but-3-enimidoyl cyanide (3h).\) Yellow solid; m.p. 133-135 °C; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\): 2.44 (s, 3H), 7.12 (dd, \(J = 3.5, 5.0\) Hz, 1H), 7.34 (d, \(J = 8.0\) Hz, 2H), 7.45 (d, \(J = 2.0\) Hz, 1H), 7.48 (d, \(J = 8.5\) Hz, 2H), 7.50 (d, \(J = 5.0\) Hz, 1H), 7.60 (d, \(J = 16.0\) Hz, 1H), 8.07 (d, \(J = 15.5\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\): 183.2, 143.4, 141.9, 140.0, 139.1, 135.9, 133.5, 130.2, 128.6, 122.9, 116.8, 110.7, 21.5; IR (KBr) \(v\): 2962, 2214, 1665, 1582, 1420, 1213, 1001 cm\(^{-1}\); HRMS (ESI-TOF) calcd for C_{16}H_{17}N_{2}O_{4}S (\text{[M + H]^{+}}): 281.0743, found: 281.0743.

\((1E,3E)-4-(Naphthalen-2-yl)-2-oxo-N-p-tolylbut-3-enimidoyl cyanide (3i).\) Yellow solid; m.p. 176-178 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 8.13 (d, \(J = 15.5\) Hz, 1H), 8.09 (s, 1H), 7.95 (d, \(J = 16.0\) Hz, 1H), 7.92-7.82 (m, 4H), 7.57-7.53 (m, 2H), 7.51 (d, \(J = 8.5\) Hz, 2H), 7.35 (d, \(J = 8.0\) Hz, 2H), 2.45
(1E,3E,5E)-2-Oxo-6-phenyl-N-(p-tolyl)hexa-3,5-dienimidoyl cyanide (3j). Yellow solid; m.p. 160-162 °C; 1H NMR (500 MHz, CDCl₃) δ: 7.74 (dd, J = 15.5, 11.0 Hz, 1H), 7.52 (d, J = 7.5 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.41-7.35 (m, 4H), 7.33 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 15.5 Hz, 1H), 7.07-7.02 (m, 1H), 2.44 (s, 3H); 13C NMR (125 MHz, CDCl₃) δ: 183.6, 146.9, 144.3, 143.4, 141.9, 135.9, 135.7, 130.2, 129.8, 128.9, 127.6, 126.7, 122.9, 121.3, 110.7, 21.5; HRMS (ESI-TOF) calcld for C₂₀H₁₃N₅O⁺ ([M + H]⁺): 301.1335, found: 301.1336.

(1E,3E)-N,4-Bis(4-chlorophenyl)-2-oxobut-3-enimidoyl cyanide (3k). Yellow solid; m.p. 148-150 °C; 1H NMR (CDCl₃, 500 MHz) δ: 7.42 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 16.0 Hz, 1H), 7.92 (d, J = 16.0 Hz, 1H); 13C NMR (CDCl₃, 125 MHz) δ: 183.0, 146.0, 144.2, 137.7, 137.6, 136.8, 132.6, 130.2, 129.9, 129.2, 123.7, 118.0, 110.0; IR (KBr) ν: 2923, 2208, 1668, 1607, 1487, 1335, 1092 cm⁻¹; HRMS (ESI-TOF) calcld for C₁₇H₁₂Cl₃N₅O⁺ ([M + H]⁺): 329.0243, found: 329.0257.

(1E,3E)-4-(4-Chlorophenyl)-2-oxo-N-phenylbut-3-enimidoyl cyanide (3l). Yellow solid; m.p. 165-167 °C; 1H NMR (CDCl₃, 500 MHz) δ: 7.93 (d, J = 16.0 Hz, 1H), 7.82 (d, J = 16.0 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.57-7.54 (m, 2H), 7.50-7.47 (m, 3H), 7.42 (d, J = 8.5 Hz, 2H); 13C NMR (CDCl₃, 125 MHz) δ: 183.2, 146.0, 145.8, 137.6, 137.5, 132.6, 130.6, 130.2, 129.6, 129.4, 122.0, 118.1, 110.1; IR (KBr) ν: 2220, 1728, 1674, 1604, 1564, 1332.67, 1208, 993 cm⁻¹; HRMS (ESI-TOF) calcld for C₁₃H₁₂Cl₃N₅O⁺ ([M + H]⁺): 295.0633, found: 295.0626.

(1E,3E)-4-(4-Chlorophenyl)-2-oxo-N-(m-tolyl)but-3-enimidoyl cyanide (3m). Yellow solid; m.p. 132-134 °C; 1H NMR (500 MHz, CDCl₃) δ: 7.92 (d, J = 16.0 Hz, 1H), 7.81 (d, J = 16.0 Hz, 1H), 7.63 (d, J = 8.5 Hz, 2H), 7.45-7.40 (m, 3H), 7.29 (d, J = 5.5 Hz, 3H), 2.45 (s, 3H); 13C NMR (125 MHz, CDCl₃) δ: 183.3, 146.0, 145.7, 139.7, 137.5, 137.2, 132.7, 131.5, 130.2, 129.4, 129.3, 122.8, 118.9, 118.2, 110.2, 21.3; IR (KBr) ν: 2922, 2217, 1667, 1598, 1563, 1329, 994 cm⁻¹; HRMS (ESI-TOF) calcld for C₁₃H₁₄Cl₂N₅O⁺ ([M + H]⁺): 309.0789, found: 309.0791.
(1E,3E)-4-(4-Chlorophenyl)-N-(4-methoxyphenyl)-2-oxobut-3-enimidoyl cyanide (3n). Yellow solid; m.p. 153-155 °C; 1H NMR (500 MHz, CDCl₃) δ: 7.88 (d, J = 16.0 Hz, 1H), 7.84 (d, J = 16.0 Hz, 1H), 7.79 (d, J = 9.0 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 3.92 (s, 3H); 13C NMR (125 MHz, CDCl₃) δ: 150.5, 142.7, 140.8, 139.9, 135.3, 133.4, 130.7, 130.0, 129.5, 129.3, 129.2, 129.1, 128.9, 128.0, 120.2, 115.6; IR (KBr) ν: 2917, 2208, 1667, 1608, 1535, 1312, 1271, 1167, 993 cm⁻¹; HRMS (ESI-TOF) calcd for C₁₅H₁₄ClN₂O₄⁺ ([M + H]+): 325.0738, found: 325.0733.

**General Procedure for the Preparation of 6 (6a as Example).**

To a solution of (1E,3E)-4-(4-chlorophenyl)-2-oxo-N-(p-tolyl)but-3-enimidoyl cyanide 3a (0.20 mmol, 61.6 mg) in AcOH (2 mL) was added benzene-1,2-diamine (0.24 mmol, 25.9 mg) and NaOAc (0.24 mmol, 19.7 mg). Then the reaction mixture was stirred at 120 °C for 10 min. After 3a was consumed (monitored by TLC), the reaction mixture was poured into water (50 mL) and extracted with CH₂Cl₂ (10 mL x 3). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to yield the corresponding crude product, which was purified by chromatography (silica gel, petroleum ether/acetone = 10/2, v/v) to give 6a (53.5 mg, 92%) as a yellow solid.

**(E)-3-(4-Chlorostyril)quinoxaline-2-carbonitrile (6a).** Yellow solid; m.p. 173-175 °C; 1H NMR (500 MHz, CDCl₃) δ: 8.13 (d, J = 15.5 Hz, 1H), 8.08 (t, J = 8.5 Hz, 2H), 7.89 (t, J = 8.0 Hz, 1H), 7.79 (t, J = 8.0 Hz, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 15.5 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H); 13C NMR (125 MHz, CDCl₃) δ: 150.2, 142.7, 140.9, 138.4, 135.8, 133.8, 133.5, 130.9, 129.6, 129.3, 129.2, 129.1, 128.6, 115.6; IR (KBr) ν: 2221, 1615, 1535, 1456, 1355, 1228, 951, 860, 750, 718 cm⁻¹; HRMS (ESI-TOF) calcd for C₁₇H₁₅ClN₂⁺ ([M + H]+): 292.0636, found: 292.0636.

**(E)-3-Styrylquinoxaline-2-carbonitrile (6f).** Yellow solid; m.p. 172-174 °C; 1H NMR (500 MHz, CDCl₃) δ: 8.18 (d, J = 15.5 Hz, 1H), 8.08 (q, J = 8.5 Hz, 2H), 7.88 (t, J = 8.0 Hz, 1H), 7.77 (t, J = 7.5 Hz, 1H), 7.69 (d, J = 7.5 Hz, 2H), 7.64 (d, J = 16.0 Hz, 1H), 7.44-7.37 (m, 3H); 13C NMR (125 MHz, CDCl₃) δ: 150.5, 142.7, 140.8, 139.9, 135.3, 133.4, 130.7, 130.0, 129.5, 129.2, 129.1, 128.9, 128.0, 120.2, 115.6; HRMS (ESI-TOF) calcd for C₁₇H₁₂N₂⁺ ([M + H]+): 258.1026, found: 258.1031.

**(E)-3-(2-(Thiophen-2-yl)vinyl)quinoxaline-2-carbonitrile (6h).** Yellow solid; m.p. 184-186 °C; 1H NMR (500 MHz, CDCl₃) δ: 8.28 (d, J = 15.0 Hz, 1H), 8.04 (d, J = 9.0 Hz, 2H), 7.85 (t, J = 7.5 Hz, 1H),
7.75 (t, J = 7.5 Hz, 1H), 7.39 (d, J = 15.0 Hz, 1H), 7.39-7.36 (m, 2H), 7.09 (t, J = 4.0 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ: 150.4, 142.8, 140.9, 140.7, 133.4, 132.3, 130.6, 130.4, 129.5, 129.1, 128.8, 128.2, 119.2, 115.5; IR (KBr) ν: 2219, 1606, 1510.40, 1355, 1203, 958, 864, 756, 708 cm$^{-1}$; HRMS (ESI-TOF) calcd for C$_{15}$H$_{10}$N$_2$S$^+$ ([M + H]$^+$): 264.0590, found: 264.0591.

Notes and references


2011, 13, 3852; (q) Y. Pan, S. Wang, C. W. Kee, E. Dubuisson, Y. Yang, K. P. Loh and C.-H. Tan, Green

7 (a) L. Ma, W. Chen and D. Seidel, J. Am. Chem. Soc., 2012, 134, 15305; (b) D. Das, M. T. Richers, L. Ma and D.

Res., 2007, 40, 1367; (c) Chemistry and Biochemistry of the Amino Acids, (Ed.: G. C. Barrett), Chapman and

9 For selected reviews and papers on the arylation reaction: (a) F. Bellina and R. Rossi, Chem. Rev., 2010, 110,
1082; (b) D. A. Culkin and J. F. Hartwig, Acc. Chem. Res., 2003, 36, 234; (c) M. Miura and M. Nomura, Top.
Curr. Chem., 2002, 219, 211; (d) J.-C. Wu, R.-J. Song, Z.-Q. Wang, X.-C. Huang, Y.-X. Xie and J.-H. Li,

10 For selected reviews on the alkylation reaction using alkyl halides, see: (a) T. Hashimoto and K. Maruoka, Chem.

11 For selected reports, see: (a) L. Zhao and C.-J. Li, Angew. Chem. Int. Ed., 2008, 47, 7075; (b) K. Li, G. Tan, J.
15, 5024.

12 For selected recent reports, see: (a) Y.-J. Li, X. Li, S.-X. Zhang, Y.-L. Zhao and Q. Liu, Chem. Commun., 2015,
51, 11564; (b) Y. Dong, B. Liu, P. Chen, Q. Liu and M. Wang, Angew. Chem. Int. Ed., 2014, 53, 3442; (c) H.
Xiong, Y. Li, X. Zhou, K. Sun, Q. Liu and Q. Zhang, Angew. Chem. Int. Ed., 2013, 52, 2529; (e) T. Xiong, Y. Li,


15 CCDC 1028181 (3a) contains the supplementary crystallographic data for this paper. These data can be obtained
free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.