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Umpolung Strategy for Synthesis of β-Ketonitriles through Hypervalent Iodine-Promoted Cyanation of Silyl Enol Ethers

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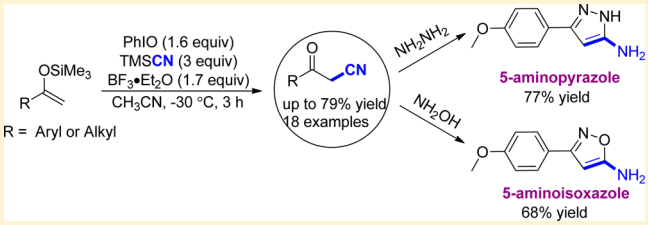
Supporting Information

ABSTRACT: An efficient method to synthesize β-ketonitriles from silyl enol ethers by an umploung hypervalent iodine(III)−CN species generated *in situ* from $PhIO/BF_3{\cdot}Et_2O$/TMSCN has been developed for the first time. This method can be applied to structurally diverse aromatic and aliphatic substrates and further extended to preparation of bioactive compounds like 5-aminopyrazole and 5-aminoisoxazole.

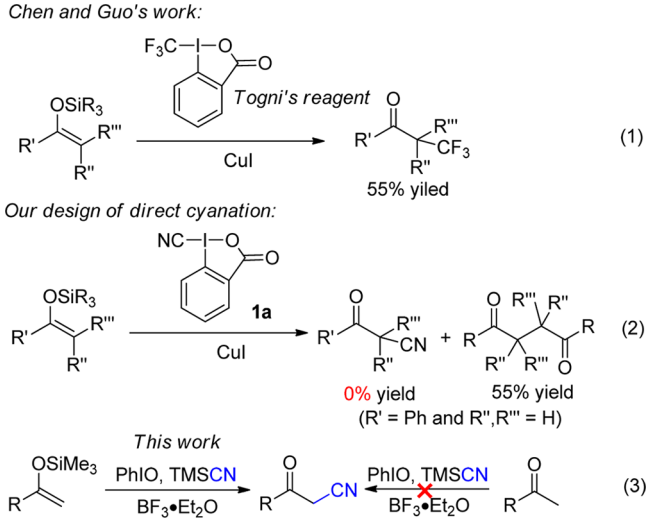


INTRODUCTION

β-Ketonitriles are important intermediates to synthesize different biologically and pharmacologically active heterocycles including aminopyrazoles,[1] aminoisoxazoles,[2] imidazoles,[3] furans,[4] thiophenes,[5] 2-pyridones,[6] and triazoles.[7] Owing to their importance, a variety of methods have been developed to access β-ketonitriles, such as coupling of acetonitriles with esters,[8] cyanide displacement reaction with α-bromo ketones,[9] C-arylation of resin-bound cyanoacetates,[10] indium-mediated coupling of bromoacetonitriles with aromatic acyl cyanides,[11] Pd-catalyzed carbonylation of aryl iodides with trimethylsilylacetonitrile,[12] transformation of enaminones via isoxazoles,[13] and kinetic cyanations of ketone enolates using *p*-toluenesulfonyl cyanide (TsCN).[14] Regardless of this progress, the development of direct α-cyanation of ketones and their reactive enolates is still highly expected.[15,16]

Tautomerism of carbonyl compounds to more reactive enolates and their derivatives such as silyl enol ethers made them preferable to serve as versatile nucleophiles to react with different electrophiles.[17] Recently, hypervalent iodine reagents have received much attention owing to their low toxicity, commercial availability, and environmental friendliness.[18] Chen et al. reported trifluoromethylation of silyl enol ethers using Togni's reagent through a free radical addition in 2014 (eq 1, Scheme 1).[19] This inspired us to design cyanobenziodoxole (**1a**)-promoted cyanation to synthesize β-ketonitriles from silyl enol ethers. However, **1a** resulted in the failure of direct cyanation companied with generation of 1,4-diketone (55% yield, R′ = Ph, and R″, R‴ = H) through oxidative α-C self-coupling of ketone (eq 2). After much literature review, we found that hypervalent iodine reagents have been already used to achieve umpolung of silyl enol ethers, on the basis of their high electrophilicity.[20] Umpolung or polarity inversion of silyl enol ethers exactly provides an alternative way to get target molecules that are hardly synthesized using routine methods (Figure 1).[21] The combination of trimethylsilyl cyanide

Scheme 1. Design of Cyanation for Synthesis of β-Ketonitriles



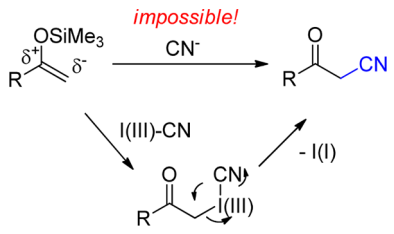


Figure 1. Pathways of cyanation to β-ketonitrile.

(TMSCN) with bis(trifluoroacetoxy)iodobenzene (PIFA) or iodosobenzene (PhIO) has been reported about *in situ*

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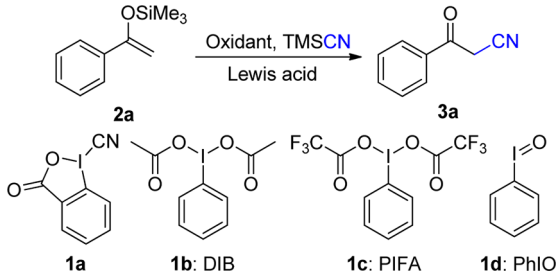
prepared hypervalent iodine(III)−CN intermediates, which were already utilized to accomplish cyanation of heteroaromatics.[22] So we further attempted PIFA/TMSCN and PhIO/TMSCN systems to (β-styryloxy)trimethylsilane, and fortunately as envisioned, 3-oxo-3-phenylpropanenitrile was assembled. It was also observed that direct α-cyanation of acetophenone failed in our studies (eq 3).

RESULTS AND DISCUSSION

The optimization studies for cyanation were initiated by using (β-styryloxy)trimethylsilane as model substrate, which was prepared freshly from the corresponding ketone in the presence of trimethylsilyl chloride, sodium iodide, and triethylamine, and trimethylsilyl cyanide (TMSCN) as cyanide source along with hypervalent iodine reagents **1a**−**d** as oxidants in $CHCl_3$. As shown in Table 1, the efficiencies of various hypervalent iodine

Table 1. Screening Oxidants and Solvents[a]



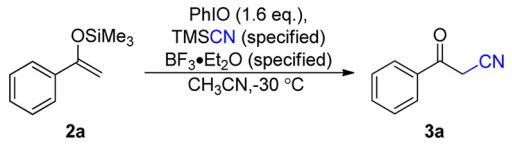
entry	solvent	$BF_3{\cdot}Et_2O$ (equiv)	oxidant/amt (equiv)	TMSCN (equiv)	yield (%)[b]
1	DMF	0	**1a**/1.2		0[c]
2	$CHCl_3$	2	**1b**/1.2	3	0
3	$CHCl_3$	2	**1c**/1.2	3	trace
4	$CHCl_3$	2	**1d**/1.2	3	43
5	$CHCl_3$	0	**1d**/1.2	3	0
6	$CHCl_3$	2	**1d**/1.6	3	60
7	$CHCl_3$	2	**1d**/2.0	3	50
8	CH_2Cl_2	2	**1d**/1.6	3	48
9	DCE	2	**1d**/1.6	3	56
10	THF	2	**1d**/1.6	3	19
11	**CH_3CN**	**2**	**1d/1.6**	**3**	**78**
12	DMF	2	**1d**/1.6	3	48

[a]Reaction conditions: (β-styryloxy)trimethylsilane (0.5 mmol), oxidant (specified), TMSCN (specified), $BF_3{\cdot}Et_2O$ (specified), and solvent (3.0 mL) at −30 °C for 3 h. DCE = 1,2-dichloroethane. [b]Isolated yields. [c]$BF_3{\cdot}Et_2O$ was replaced by CuI at rt for 3 h, the same conditions for trifluoromethylation referred to ref 19.

reagents were first examined, cyanobenziodoxole **1a** and (diacetoxyiodo)benzene **1b** did not furnish the desired product (entries 1 and 2), while iodosobenzene **1d** proved to be most effective and bis(trifluoracetoxy)iodobenzene **1c** only gave a trace of desired product (entries 3 and 4), where hypervalent iodines (except **1a**) were premixed with $BF_3{\cdot}Et_2O$ and TMSCN for preactivation of 40 min before adding (β-styryloxy)-trimethylsilane. Without $BF_3{\cdot}Et_2O$, **1d** was disabled to this transformation (entry 5). Different amounts of **1d** were then investigated, and as a result, 1.6 equiv was found to be the most suitable (entries 6−7). The reaction was also found to be sensitive to the solvent, and CH_3CN afforded better results than others, including $CHCl_3$, CH_2Cl_2, DCE, THF, and DMF (entries 8−12).

Other influencing factors of the reaction such as amounts of TMSCN and $BF_3{\cdot}Et_2O$, preacitivation time, and reaction concentration were then examined, with results depicted in Table 2. Fixing 2.0 equiv of $BF_3{\cdot}Et_2O$, different amounts of

Table 2. Optimization of Reaction Conditions[a]

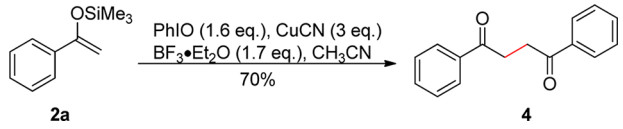


entry	$BF_3{\cdot}Et_2O$ (equiv)	TMSCN (equiv)	yield (%)[b]
1	2	3	78
2	2	2.5	56
3	2	3.5	78
4	**1.7**	**3**	**79**
5	1.5	3	65
6	1.7	3	56[c]
7	1.7	3	77[d]
8	1.7	3	60[e]
9	1.7	3	70[f]
10	1.7	3	69[g]
11	1.7	3	77[h]

[a]Reaction conditions: (β-styryloxy)trimethylsilane (0.5 mmol), PhIO (0.8 mmol), TMSCN (specified), $BF_3{\cdot}Et_2O$ (specified), and CH_3CN (3.0 mL) at −30 °C for 3 h. [b]Isolated yields. [c]Preactivation for 0 h. [d]Preactivation for 1 h. [e]4 h of reaction time. [f]2 h of reaction time. [g]4 mL of CH_3CN. [h]2 mL of CH_3CN.

TMSCN were screened, and as a result, 3.0 equiv of TMSCN was proven to be most beneficial (Table 2, entries 1−3). With 3.0 equiv of TMSCN, further decreasing the amount of $BF_3{\cdot}Et_2O$ to 1.7 equiv provided the best yield of 79% (Table 2, entries 4−5). Preactivation time of **1d** with $BF_3{\cdot}Et_2O$ and TMSCN and reaction time were also investigated, the results showed that either prolonging or shortening preactivation and reaction time was unbeneficial to this reaction (entries 6−9). Increase or decrease of the concentration through adjusting the amount of CH_3CN was found to be detrimental to this cyanation (entries 10−11). Moreover, a coupling product 1,4-diketone **4** was generated when using CuCN as cyanide source, where the yield is higher than the reported (Scheme 2).[20a]

Scheme 2. An Approach to 1,4-Diketone



With the optimal conditions in hand, we then generalized the protocol developed for the oxidative cyanation. As described in Table 3, the reactions of different silyl enol ethers bearing either electron-donating substituents, such as methyl and methoxyl, or electron-withdrawing substituents, like halogen and ester, on aromatic ring gave the corresponding cyanated products in moderate to good isolated yields (**3a**−**l**). *Meta*-substituents and *para*-substituents were found to be more favorable than *ortho*-substituents (**3b,c** vs **3d**, **3i,j** vs **3k**) and the electron-withdrawing ability of groups did not influence the reaction with regularity (**3f**−**i**). In addition, heteroaryl-containing compounds were converted into the corresponding β-

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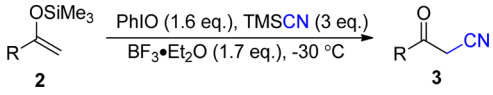
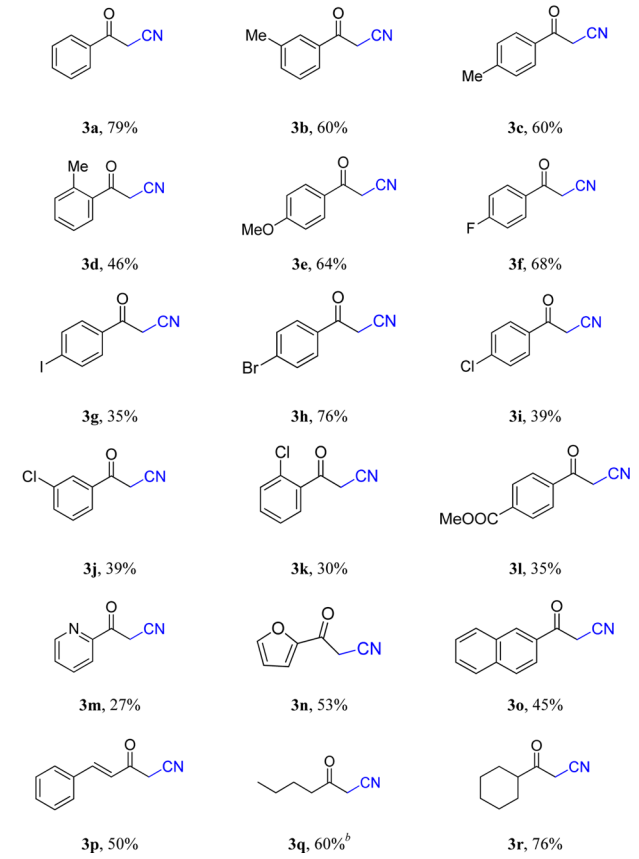
Table 3. Substrate Scope[a]

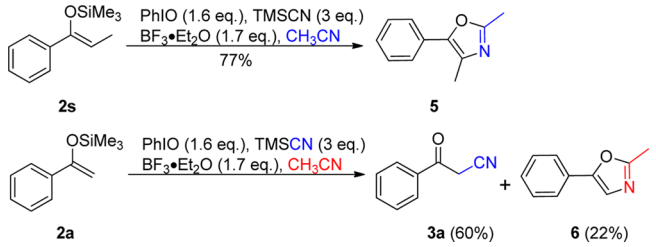




[a]Reaction conditions: silyl enol ether (0.5 mmol), PhIO (0.8 mmol), TMSCN (1.5 mmol), $BF_3{\cdot}Et_2O$ (0.85 mmol), and CH_3CN (3.0 mL) at −30 °C for 3 h. Isolated yields. [b]The yield was based on portion of terminal ene.

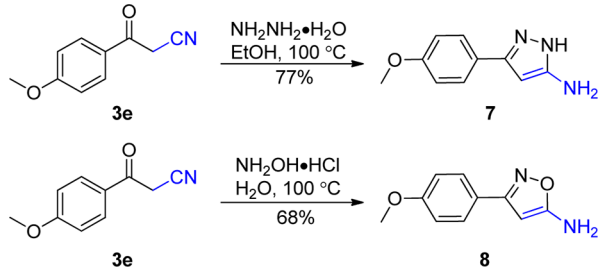
ketonitriles in moderate yields (**3m**,**n**), and naphthalene-containing substrate also led to 45% yield (**3o**). It is worth noting that cinnamyl-containing and aliphatic substrates smoothly afforded the cyanation products with up to 76% yield (**3p**−**r**), and only terminal cyano products were detected (also see Scheme 3). Likewise, silyl enol ether of propiophenone, **2s**, did not gave the desired cyanation product using this method, whereas a highly substituted oxazole was produced when switching the feeding order, namely, adding TMSCN immediately after the mixture of PhIO, $BF_3{\cdot}Et_2O$, and silyl enol ether in sequence, where the solvent CH_3CN was involved into the reaction.[23] However, the same procedure with **2a** generated **3a** in 60% yield as a major product with relatively small amounts of oxazole **6** in 22%, which suggested the early interaction of hypervalent iodine and solvent CH_3CN before TMSCN (Scheme 4).

Scheme 4. Approach to Synthesis of Oxazoles



We next moved toward applications of *β*-ketonitrile to prepare two important intermediates, namely, 5-aminopyrazole and 5-aminoisoxazole, which can be further converted into a variety of biologically active products.[1,2] As shown in Scheme 5,

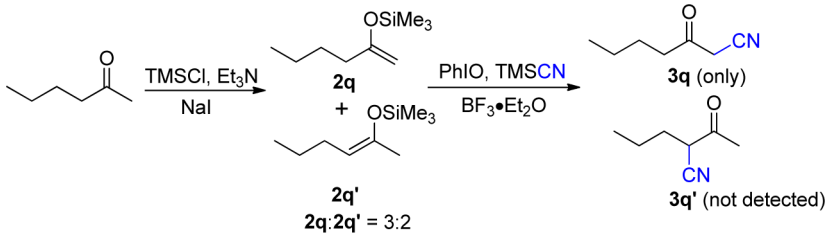
Scheme 5. Applications of *β*-Ketonitrile



the reactions of 4-methoxybenzoylacetonitrile with hydrazine hydrate[30] and hydroxylamine hydrochloride[2b] can easily give 5-aminopyrazole and 5-aminoisoxazole with the good yields of 77% and 68%, respectively.

Based on our experimental results, a plausible mechanistic pathway for the synthesis of *β*-ketonitriles was proposed to interpret the obsevered reactivities (Figure 2). Active hypervalent iodine(III)−CH_2CN species is first formed *in situ* from the mixture of PhIO/$BF_3{\cdot}Et_2O$/CH_3CN. Then silyl enol ether **2** is oxidized by hypervalent iodine(III)−CH_2CN species to achieve umpolung and give intermediate **A**. The CH_2CN moiety in **A** is exchanged by CN^- in the presence of TMSCN to reach **B**. Through an intramolecular S_N2 reaction and an electron transfer in a three-membered ring transition state **TS1**, cyanation product **3a** is furnished, accompanied by the release of iodobenzene. Alternatively, intermediate **A** can be converted into a five-membered ring transition state **TS2** through nitrogen attack of cyano group and an oxazole **5** or **6** is

Scheme 3. Regioselectivity of the Method



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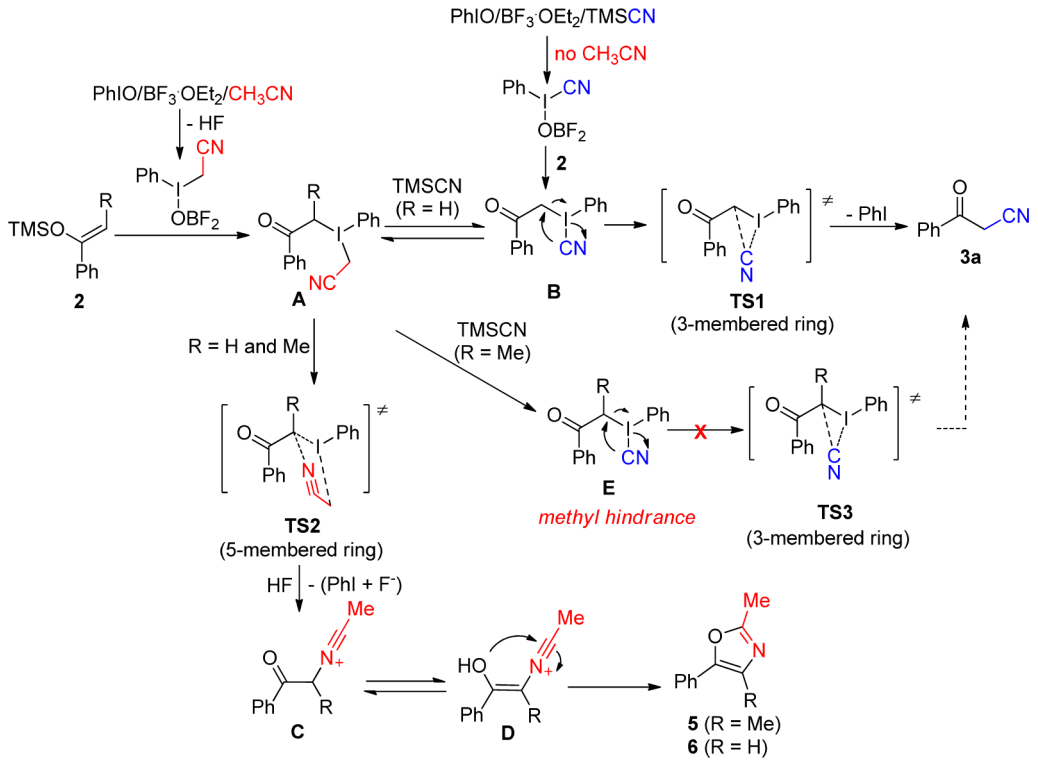

Figure 2. Proposed reaction mechanisms.

formed eventually through a decomposition of **TS2**, tautomerism of ketone **C** to enol **D** and nucleophilic addition of hydroxyl. From our studies on cyantion of (Z)-trimethyl(1-phenylprop-1-enyloxy)silane **2s** where no cyanation product was generated, we speculated rationally that methyl hindered the attack of CN in intermediate **E** to form **TS3**.

In conclusion, we have developed a direct cyanation method of silyl enol ethers to synthesize *β*-ketonitriles through an umpolung strategy in the $PhIO/BF_3{\cdot}Et_2O/TMSCN$ system, in which diversely substituted aromatic, heteroaromatic, and aliphatic substrates worked well. Further studies about the synthetic utility of this versatile oxidative system and more mechanistic details are presently pursued in our laboratories.

EXPERIMENTAL SECTION

General Information. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a 500 spectrometer (500 MHz for ^1H, 125 MHz for ^{13}C) at 20−25 °C. ^1H NMR spectra were reported in parts per million using tetramethylsilane TMS (δ = 0.00 ppm) as an internal standard. The data of ^1H NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), coupling constants (*J*, Hz), and integration. ^{13}C NMR spectra were reported in parts per million using solvent $CDCl_3$ (δ = 77.2 ppm) or DMSO-d_6 (δ = 39.5 ppm) as an internal standard, The data of ^{13}C NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), and coupling constants (*J*, Hz). High-resolution mass spectra (HRMS) electrospray ionization (ESI) was carried out on a UPLC-Q-ToF MS spectrometer. Reactions were monitored by TLC, and column chromatography was performed using silica gel. All solvents were purified by conventional methods, distilled before use. Commercially available reagents were used without further purification unless otherwise specified.

Procedure for Synthesis of Cyanobenziodoxole (1a). Compound **1a** was synthesized according to the reported method:[24] 1-acetoxy-1,2-benziodoxol-3(1*H*)-one (4.58 g, 15.0 mmol) was dissolved in dry dry CH_2Cl_2 (40 mL) under Ar atmosphere. After the addition of Me_3SiCN (4.3 mL, 30 mmol), the mixture was stirred for 24 h at room temperature. The crude product was filtered off, washed with CH_2Cl_2, and dried at 40 °C under vacuum to give white solid cyanobenziodoxole **1a**; 70% yield, 2.82 g. NMR data were in complete agreement with the reported ones.[24]

Procedure for Synthesis of Iodosylbenzene, PhIO. PhIO was synthesized according to the reported method:[25] To (diacetoxyiodo)-benzene (3.2 g, 10 mmol) in a 100 mL Erlenmeyer flask was added 54 mL of sodium hydroxide solution (1.88 M) dropwise at room temperature. The light yellow suspension appeared slowly, and the resulting mixture was stirred for 3 h at room temperature. The precipitate was filtered under high vacuum and washed with water until the washing water became neutral to afford the slightly yellow solid, which was dried in the air and then mortared into fine powder for use.

General Procedure for Preparation of Silyl Enol Ether. Silyl enol ethers were synthesized according to the reported method:[26] The 100 mL three-necked flask loaded with a mixture of ketone (25 mmol) and sodium iodide (4.5 g, 30 mmol) was evacuated and filled with argon three times; then dry acetonitrile (30 mL) was added. The resulting solution was stirred for 5 min at room temperature, and triethylamine (4.2 mL, 30 mmol) was added, followed by chlorotrimethylsilane (3.82 mL, 30 mmol). The reaction mixture was then stirred at 40 °C overnight. The reaction was quenched with cold pentane (50 mL) and ice water (50 mL). The organic phase was separated, and the aqueous layer was extracted with pentane (30 mL × 2). The combined organics were washed with brine and then dried over anhydrous $MgSO_4$. The solvent was removed first in vacuo by rotatory evaporator, and the residue was distilled under reduced pressure to provide pure silyl enol ether **2**.

General Procedure for Preparation of *β*-Ketonitriles. For a sealed 50 mL two-necked bottle filled with PhIO (176 mg, 0.8 mmol), argon replacement was executed three times in 1 h, and the bottle was cooled to −30 °C. Dry solvent (3 mL), $BF_3{\cdot}Et_2O$ (0.11 mL, 0.85 mmol), and TMSCN (0.19 mL, 1.5 mmol) were then added successively under stirring conditions. After 40 min for preactivation, silyl enol ether **2** (0.5 mmol) was added to the mixture slowly and

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reacted at −30 °C for 3 h. The reaction was quenched with saturated sodium bicarbonate, sodium thiosulfate solution, and ethyl acetate. The organic phase was separated, and the aqueous layer was extracted with EtOAc (8 mL × 3). The organic extract was combined, dried with $MgSO_4$, and filtered to get a clear organic solution. The solvents were removed under reduced pressure. The resulting residue was purified by column chromatography using EtOAc−petroleum ether as eluent to give desired product **3**.

*3-Oxo-3-phenylpropanenitrile (**3a**).*[12a] Pale yellow solid; 79% yield, 57.5 mg; mp 68−70 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz,, 2H), 7.68 (tt, J = 7.5, 1.0 Hz, 1H), 7.54 (t, J = 7.5 Hz, 2H), 4.10 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.2, 134.9, 134.4, 129.3, 128.7, 113.9, 29.6. HRMS (ESI) calcd for C_9H_7NO $[M + H]^+$ 146.0599, found 146.0597.

*3-Oxo-3-m-tolylpropanenitrile (**3b**).*[12a] Pale yellow solid; 60% yield, 47.6 mg; mp 65−67 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.47 (d, J = 7.0 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 4.09 (s, 2H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.5, 139.3, 135.7, 134.4, 129.1, 129.0, 125.8, 114.1, 29.6, 21.4. HRMS (ESI) calcd for $C_{10}H_9NO$ $[M + H]^+$ 160.0757, found 160.0758.

*3-Oxo-3-p-tolylpropanenitrile (**3c**).*[12a] Pale yellow solid; 60% yield, 47.4 mg; mp 94−96 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 4.05 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.8, 146.2, 132.0, 130.0, 128.8, 114.0, 29.4, 22.0. HRMS (ESI) calcd for $C_{10}H_9NO$ $[M + H]^+$ 160.0757, found 160.0759.

*3-Oxo-3-o-tolylpropanenitrile (**3d**).*[12a] Pale yellow solid; 46% yield, 36.5 mg; mp 68−70 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 8 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.33−7.31 (m, 2H), 4.05 (s, 2H), 2.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.5, 140.6, 134.0, 133.5, 130.0, 129.4, 126.3, 114.2, 31.6, 22.0. HRMS (ESI) calcd for $C_{10}H_9NO$ $[M + H]^+$ 160.0757, found 160.0761.

*3-(4-Methoxyphenyl)-3-oxopropanenitrile (**3e**).*[12a] Pale yellow solid; 64% yield, 55.8 mg; mp 119−121 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 7.5 Hz, 2H), 6.98 (d, J = 8 Hz, 2H), 4.03 (s, 2H), 3.90 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.6, 164.9, 131.1, 127.5, 114.5, 114.3, 55.9, 29.2. HRMS (ESI) calcd for $C_{10}H_9NO_2$ $[M + H]^+$ 176.0706, found 176.0713.

*3-(4-Fluorophenyl)-3-oxopropanenitrile (**3f**).*[12a] Pale yellow solid; 68% yield, 55.6 mg; mp 75−77 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (t, J = 6.5 Hz, 2H), 7.21 (t, J = 7.5 Hz, 2H), 4.07 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.6, 166.8 (d, J = 262.5 Hz), 131.5 (d, J = 10 Hz), 130.9 (d, J = 2.5 Hz), 116.6 (d, J = 22.5 Hz), 113.7, 29.5. HRMS (ESI) calcd for C_9H_6FNO $[M + H]^+$ 164.0506, found 164.0506.

*3-(4-Iodophenyl)-3-oxopropanenitrile (**3g**).*[1d] Yellow solid; 35% yield, 47 mg; mp 173−175 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 7.5 Hz, 2H), 7.63 (d, J = 8 Hz, 2H), 4.04 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.5, 138.8, 133.7, 129.8, 113.5, 103.5, 29.5. HRMS (ESI) calcd for C_9H_6INO $[M + H]^+$ 271.9567, found 271.9563.

*3-(4-Bromophenyl)-3-oxopropanenitrile (**3h**).*[12a] Pale yellow solid; 76% yield, 85.4 mg; mp 156−157 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 8.5 Hz, 2H), 4.05 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.3, 133.2, 132.8, 130.5, 130.1, 113.5, 29.5. HRMS (ESI) calcd for C_9H_6BrNO $[M + H]^+$ 223.9706, found 223.9703.

*3-(4-Chlorophenyl)-3-oxopropanenitrile (**3i**).*[12a] Pale yellow solid; 39% yield, 35.4 mg; mp 121−123 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 9 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 4.06 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.1, 141.7, 132.7, 130.0, 129.8, 113.6, 29.6. HRMS (ESI) calcd for C_9H_6ClNO $[M + H]^+$ 180.0211, found 180.0215.

*3-(3-Chlorophenyl)-3-oxopropanenitrile (**3j**).*[27] Pale yellow solid; 39% yield, 35.3 mg; mp 72−73 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91(s, 1H), 7.80 (d, J = 8 Hz, 1H), 7.65 (d, J = 8 Hz, 1H), 7.49 (t, J = 8 Hz, 1H), 4.08 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.2, 135.9, 135.8, 134.9, 130.7, 128.7, 126.7, 113.5, 29.7. HRMS (ESI) calcd for C_9H_6ClNO $[M + H]^+$ 180.0211, found 180.0208.

*3-(2-Chlorophenyl)-3-oxopropanenitrile (**3k**).*[27] Pale yellow solid; 30% yield, 27 mg; mp 95−97 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 7.5 Hz, 1H), 7.51−7.47 (m, 2H), 7.41 (t, J = 7.5 Hz, 1H), 4.15 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.6, 135.9, 133.9, 131.9, 131.2, 130.6, 127.7, 113.5, 33.1. HRMS (ESI) calcd for C_9H_6ClNO $[M + H]^+$ 180.0211, found 180.0215.

*Methyl-4-(2-cyanoacetyl)benzoate (**3l**).*[12a] Pale yellow solid; 35% yield, 35.3 mg; mp 163−164 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, J = 8 Hz, 2H), 7.99 (d, J = 8 Hz, 2H), 4.12 (s, 2H), 3.97 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.9, 165.9, 137.5, 135.6, 130.5, 128.6, 113.5, 52.9, 29.9. HRMS (ESI) calcd for $C_{11}H_9NO_3$ $[M + H]^+$ 204.0655, found 204.0662.

*3-(Pyridine-2-yl)-3-oxopropanenitrile (**3m**).*[1c] Pale yellow solid; 27% yield, 19.4 mg; mp 94−96 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, J = 4.5 Hz, 1H), 8.11 (d, J = 8 Hz, 1H), 7.91 (td, J = 7.5, 1.5 Hz, 1H), 7.57 (ddd, J = 7.5, 5.0, 1.0 Hz 1H), 4.40 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.6, 151.0, 149.5, 137.6, 128.7, 122.6, 114.6, 28.7. HRMS (ESI) calcd for $C_8H_6N_2O$ $[M + H]^+$ 147.0553, found 147.0553.

*3-(Furan-2-yl)-3-oxopropanenitrile (**3n**).*[27] Pale yellow solid; 53% yield, 35.9 mg; mp 63−65 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 0.5 Hz, 1H), 7.39 (dd, J = 3.5, 0.5 Hz, 1H), 6.65 (dd, J = 3.5, 1.5 Hz, 1H), 3.97 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 150.7, 147.9, 119.5, 113.6, 113.5, 29.0. HRMS (ESI) calcd for $C_7H_5NO_2$ $[M + H]^+$ 136.0393, found 136.0395.

*3-(Naphthalen-2-yl)-3-oxopropanenitrile (**3o**).*[27] Yellow solid; 45% yield, 43.5 mg; mp 107−108 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.99−7.90 (m, 4H), 7.67 (t, J = 7 Hz, 1H), 7.61 (t, J = 7 Hz, 1H), 4.22 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.2, 136.4, 132.5, 131.8, 130.9, 129.9, 129.7, 129.4, 128.1, 127.6, 123.6, 114.0, 29.6. HRMS (ESI) calcd for $C_{13}H_9NO$ $[M + H]^+$ 196.0757, found 196.0758.

*Cinnamoylacetonitrile (**3p**).*[28] Yellow solid; 50% yield, 43 mg; mp 94−95 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 16 Hz, 1H), 7.59 (d, J = 7 Hz, 2H), 7.47−7.42 (m, 3H), 6.88 (d, J = 16 Hz, 1H), 3.72 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.5, 146.8, 133.6, 131.9, 129.4, 129.0, 122.6, 114.2, 31.0. HRMS (ESI) calcd for $C_{11}H_9NO$ $[M + H]^+$ 172.0757, found 172.0753.

*3-Oxoheptanenitrile (**3q**).*[29] White solid; 60% yield, 37.7 mg; decomposition before melt. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.47 (s, 2H), 2.62 (t, J = 7 Hz, 2H), 1.63−1.59 (m, 2H), 1.37−1.33 (m, 2H), 0.93 (t, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 114.0, 42.1, 32.1, 25.5, 22.2, 13.9. HRMS (ESI) calcd for $C_7H_{11}NO$ $[M + H]^+$ 126.0914, found 126.0919.

*3-Cyclohexyl-3-oxopropionitrile (**3r**).* Pale yellow oil; 76% yield, 57.7 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.51 (s, 2H), 2.55 (tt, J = 11.0, 3.5 Hz, 1H), 1.92−1.89 (m, 2H), 1.83−1.79 (m, 2H), 1.71−1.68 (m, 1H), 1.42−1.20 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 114.1, 50.2, 30.4, 28.3, 25.7, 25.4. HRMS (ESI) calcd for $C_9H_{13}NO$ $[M + H]^+$ 152.1070, found 152.1066.

Typical Procedure for Synthesis of 1,4-Diketone 4.[20a] For a sealed 50 mL two-necked bottle filled with PhIO (176 mg, 0.8 mmol), argon replacement was executed three times in 1 h, and the bottle was cooled to −30 °C. Dry CH_3CN (3 mL), $BF_3{\cdot}Et_2O$ (0.11 mL, 0.85 mmol), and CuCN (134 mg, 1.5 mmol) were then added successively under stirring conditions. After 40 min for preactivation, silyl enol ether **2a** (98 mg, 0.5 mmol) was added to the mixture slowly and reacted at −30 °C for 3 h. The reaction was quenched with saturated sodium bicarbonate, sodium thiosulfate solution, and ethyl acetate. The organic phase was separated, and the aqueous layer was extracted with EtOAc (8 mL × 3). The organic extract was combined, dried with $MgSO_4$, and filtered to get a clear organic solution. The solvents were removed under reduced pressure. The resulting residue was purified by column chromatography using EtOAc−petroleum ether as eluent to give white solid 1,4-diphenyl-1,4-butadione **4**; 70% yield, 42 mg; mp 142−143 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 7.5 Hz,, 4H), 7.58 (t, J = 7.5 Hz, 2H), 7.48 (t, J = 8 Hz, 4H), 3.47 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 136.9, 133.3, 128.8, 128.3, 32.7. HRMS (ESI) calcd for $C_{16}H_{14}O_2$ $[M + H]^+$ 239.1067, found 239.1074.

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Typical Procedure for Synthesis of Oxazole 5.[23c] A dry 50 mL two-necked bottle was charged with PhIO (176 mg, 0.8 mmol) and then evacuated and backfilled with argon. After cooling to −30 °C, $BF_3{\cdot}Et_2O$ (0.11 mL, 0.85 mmol), silyl enol ether **2s** (103 mg, 0.5 mmol), and TMSCN (0.19 mL, 1.5 mmol) were added subsequently. The reaction mixture was stirred for 3 h at −30 °C. The reaction mixture was quenched with saturated sodium bicarbonate, sodium thiosulfate solution, and ethyl acetate. The organic phase was separated, and the aqueous layer was extracted with EtOAc (8 mL × 3). The combined organic extract was then concentrated, and the resulting residue was purified by column chromatography on silica gel to get white solid 2,4-dimethyl-5-phenyloxazole, **5**; 77% yield, 67 mg; mp 45−47 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 7.5 Hz, 2H), 7.42 (t, J = 8 Hz, 2H), 7.29 (t, J = 7.5 Hz, 1H), 2.48 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 145.3, 131.8, 129.5, 128.9, 127.5, 125.2, 14.1, 13.4. HRMS (ESI) calcd for $C_{11}H_{11}NO$ $[M + H]^+$ 174.0914, found 174.0907.

Similar Procedure for Synthesis of Oxazole 6. 2-Methyl-5-phenyloxazole (**6**)[23c] was synthesized by a similar method as that for **5**. Pale yellow solid; 22% yield, 17.6 mg; mp 55−58 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 7 Hz, 2H), 7.41 (t, J = 8 Hz, 2H), 7.31 (t, J = 7 Hz, 1H), 7.18 (s, 1H), 2.52 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 151.3, 129.0, 128.3, 124.7, 124.1, 121.9, 14.3. HRMS (ESI) calcd for $C_{10}H_9NO$ $[M + H]^+$ 160.0757, found 160.0750.

Procedure for Preparation of 5-Aminopyrazole 7. Compound **7** was synthesized according to the reported method:[30] To a solution of **3e** (103 mg, 0.5 mmol) in 3 mL of ethanol in a 50 mL round-bottom flask was added hydrazine hydrate (0.08 mL, 2.5 mmol), and the resulting mixture was heated at 100 °C for 6 h. After cooling to rt, the solvents were removed under reduced pressure, and the resulting residue was purified by column chromatography to give white solid 3-(4-methoxyphenyl)-5-amine-1*H*-pyrazol **7**; 77% yield, 72 mg; mp 136−137 °C. ^{1}H NMR (500 MHz, DMSO) δ 11.7 (br s, 1H), 7.60 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.5 Hz, 2H), 5.71 (s, 1H), 4.75 (br s, 2H), 3.78 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 158.6, 126.1, 114.0, 55.1. HRMS (ESI) calcd for $C_{10}H_{11}N_3O$ $[M + H]^+$ 190.0975, found 190.0969.

Procedure for Preparation of 5-Aminoisoxazole 8. Compound **8** was synthesized according to the reported method:[2b] To a stirred solution of compound **3e** (103 mg, 0.5 mmol) and sodium hydroxide (40 mg, 1 mmol) in water (1.5 mL) was added hydroxylamine hydrochloride (34 mg, 0.5 mmol), and the resulting mixture was heated at 100 °C for 2.5 h. After cooling to rt, the mixture was diluted with $CHCl_3$, and the organic layer was separated. The aqueous layer was further extracted with $CHCl_3$, and the combined organic layers were dried over $MgSO_4$ and then concentrated under reduced pressure to afford orange solid 3-(4-methoxyphenyl)-5-amine-isoxazol, **8**; 68% yield, 64 mg; mp 110−113 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 9 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 5.38 (s, 1H), 4.55 (brs, 2H), 3.83 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 163.7, 161.0, 128.2, 122.4, 114.3, 78.2, 55.5. HRMS (ESI) calcd for $C_{10}H_{10}N_2O_2$ $[M + H]^+$ 191.0815, found 191.0818.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra of compounds **3**, **4**, **5**, **6**, **7**, and **8**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01102.

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Notes

The authors declare no competing financial interest.

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