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Divergent Reactivity in the Reaction of β-Oxodithioesters and Hydroxylamine: Access to β-Ketonitriles and Isoxazoles

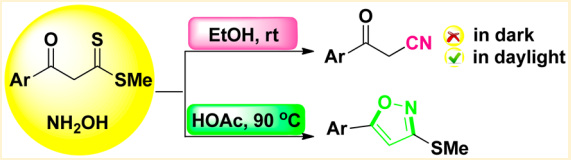
Jiaheng Li,[†] Wei Ma,[†] Wenbo Ming,[†] Cong Xu,[†] Na Wei,[†] and Mang Wang*[,†,‡]

[†]Department of Chemistry, Northeast Normal University, Changchun 130024, P. R. China

[‡]State Key Laboratory of Polymer Physics and Chemistry, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, P. R. China

Supporting Information

ABSTRACT: Starting from β-oxodithioesters and hydroxylamine, two completely different transformations afford either β-ketonitriles or isoxazoles with high chemoselectivity depending on the reaction conditions. The reaction of β-oxodithioesters with hydroxylamine in EtOH at room temperature in daylight gave β-ketonitriles in high yields. On the other hand, 3-methylthio-isoxazoles were efficiently obtained as the final products by heating the mixture of β-oxodithioesters and hydroxylamine in HOAc at 90 °C.



The achievement of complete chemoselectivity in the reactions of multifunctional molecules is a major issue in synthetic organic chemistry.[1] β-Oxodithioesters are a kind of important organic intermediate, having polyfunctional groups with multireactive sites.[2] They have been widely applied in the construction of various classes of heterocycles with interesting properties,[3−7] for example, in the synthesis of thiophenes,[3] pyrroles,[4] thiazoles,[5] 1,2,3-thiadiazoles,[6] dihydropyrimidones,[7] as well as chromene-2-thiones.[8] Taking advantage of easy preparation, versatile reactivity, and high efficiency in the applications of organic synthesis and drug design,[2−8] the synthetic utilization of β-oxodithioesters is still an important task, and those selective transformations based on them are especially desired. Herein, we disclose two completely different transformations of β-oxodithioesters with hydroxylamine which chemoselectively furnish β-ketonitriles and isoxazoles, respectively, under different reaction conditions (Scheme 1A).

During our continuing efforts on the investigations of heterocycle construction from thioorganic intermediates, mainly by using of ketene dithioacetals,[9,10] we were aware that the synthesis of isoxazoles by the reaction of β-oxodithioesters and hydroxylamine was possible and might be similar to the reactions with α-oxo ketene dithioacetals and hydroxylamine.[11] However, to our surprise, there is no report for this application until 2013 when Singh and co-workers developed a straightforward and regioselective synthesis of 3-aminoisoxazoles[12] by multicomponent reactions of β-oxodithioesters, primary (and secondary) amines, and hydroxylamine. In their work, β-oxo thioamide intermediates were proven to be involved to take part in the cyclocondensation with hydroxylamine in EtOH (Scheme 1B).

Interestingly, when we treated methyl 3-oxo-3-phenylpropanedithioate **1a** (1.0 equiv) with hydroxylamine hydrochloride (1.2 equiv) and tertiary amine (Et_3N, 1.2 equiv) in EtOH (4.0 mL) at room temperature for 7 h, no isoxazole derivative was isolated, but an unprecedented product, 3-oxo-3-phenylpropanenitrile **2a**, was obtained in 65% isolated yield (Table 1, entry 1). Other tertiary amines, organic or inorganic bases, including DABCO, DBU, *t*BuOK, NaOH, NaOAc, K_2CO_3, and NaH (entries 2−8), were selected toward the process during screening the reaction conditions. All the reactions afforded **2a** in good yields. Among them, NaOH was the best one. Higher temperature (50 °C) made the reaction messy, and **2a** was obtained only in 25% yield (entry 9). Other solvents were also investigated (entries 1, 10−14), and EtOH was proven to be super.

Scheme 1. Reactions of β-Oxodithioesters and Hydroxylamine

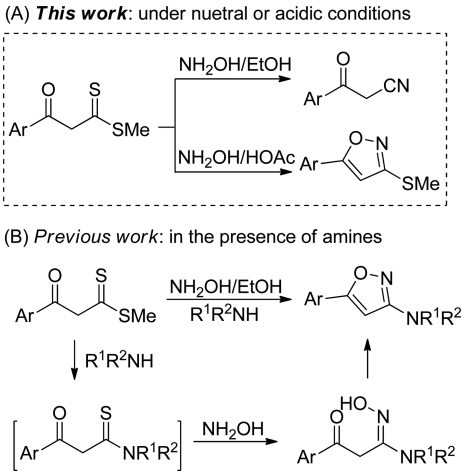


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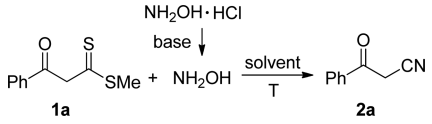
Table 1. Optimization for the Conversion of β-Oxodithioesters into β-Ketonitriles[a]



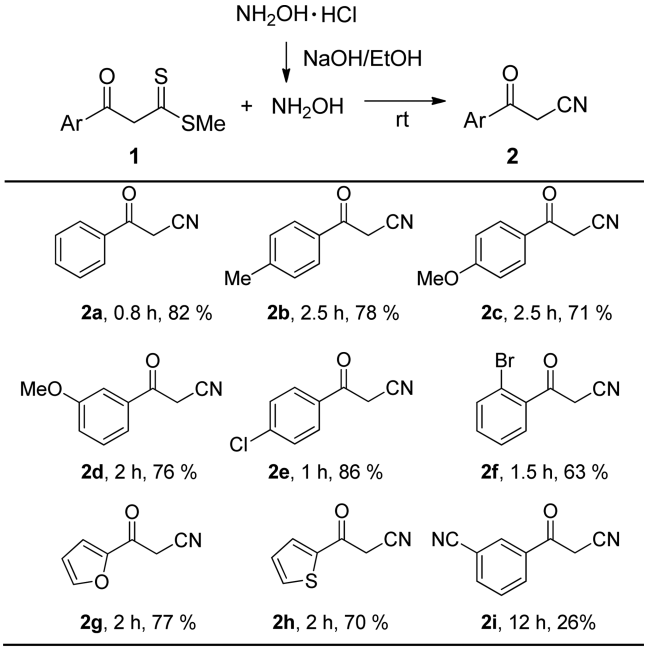
entry	base	T (°C)	solvent	time (h)	yield (%)[b]
1	Et_3N	rt	EtOH	7	65
2	DABCO	rt	EtOH	5	68
3	DBU	rt	EtOH	7	65
4	*t*BuOK	rt	EtOH	4	73
5	**NaOH**	**rt**	**EtOH**	**0.8**	**82**
6	NaOAc	rt	EtOH	5.5	72
7	K_2CO_3	rt	EtOH	5	73
8	NaH	rt	EtOH	4	76
9	NaOH	50	EtOH	0.5	25[c]
10	NaOH	rt	DMF	10	61
11	NaOH	rt	THF	11	67
12	NaOH	rt	CH_2Cl_2	10	48
13	NaOH	rt	MeCN	12	62
14	NaOH	rt	H_2O[d]	10	42[c]

[a]Reaction conditions: **1a** (0.5 mmol), $NH_2OH·HCl$ (0.6 mmol), base (0.6 mmol), solvent (4 mL). [b]Isolated yields. [c]Messy. [d]0.1 equiv TBAB was added.

β-Ketonitriles are versatile synthetic intermediates[13] which have been widely applied in the synthesis of various useful heterocycles.[14] The above reaction sequence indicates for the first time that the reaction of β-oxodithioesters with hydroxylamine may serve as an efficient route to β-ketonitriles.[13,15] Thus, the scope of the reaction was investigated by choosing β-oxodithioesters **1b−i** with different aryl substituents as substrates under the optimized conditions (Table 1, entry 5). As shown in Table 2, the selected substrates **1** bearing both electron-donating and electron-withdrawing aryl groups could efficiently afford the corresponding β-ketonitrile products **2b−h** at room temperature in good yields. By comparison, β-oxodithioester with a strong electron-withdrawing CN at phenyl ring gave **2i** in low yield even by prolonging reaction time. Complex mixture was often obtained when *S*-methyl 3-oxo-3-(pyridin-4-yl)propanethioate was selected toward the identical reaction conditions.

Different from Singh's work, in which primary or secondary amines took part in the multicomponent reactions,[12] tertiary amines were only used as the base in our experiments to neutralize $NH_2OH·HCl$ for the reaction with β-oxodithioesters. It was reported that nitriles could be produced from thiohydroxamic acids by a thermodynamic dehydrosulfurization.[16,17] Based on these results, the conversion of **1** into **2** may involve a thiohydroxamic acid intermediate **A** and then **A′**, which was generated from the nucleophilic substitution of **1** by NH_2OH (Scheme 2, path a). Compared to the work on the decomposition of thiohydroxamic acids into nitriles which usually occurred at high temperature,[16] **A′** easily afforded nitriles **2** at ambient conditions in our work. Accordingly, a photolytic process was supposed and has been proven by a controlled experiment in which no **2a** was detected when the reaction of **1a** and NH_2OH was performed in dark under the standard conditions. The suspended sulfur could be observed during the reaction. Additionally, a route involving thiazirene intermediate **C** via **B** was not ruled out at the present (Scheme 2, path a′).

Table 2. Synthesis of β-Ketonitriles by the Reaction of β-Oxodithioesters with Hydroxylamine[a]



[a]Reaction conditions: **1** (0.5 mmol), $NH_2OH·HCl$ (0.6 mmol), NaOH (0.6 mmol), EtOH (4 mL), rt. Isolated yields.

Further studies on the influence of the wavelength and intensity of the light and the concentration on the process were carried out. Although no photocatalyst was used, the wavelength of the light was proven to be key to the transformation of β-oxodithioesters into β-ketonitrile. Upon treatment of **1f** with hydroxylamine under the irradiation of blue light (450−480 nm), no desired β-ketonitrile **2f** was detected after 2.5 h along with the recovery of **1f** in 82% yield. On the contrary, **2f** could be isolated in good yield when the reaction was exposed to green, red, as well as white light. Green light showed a slightly higher efficiency. In addition, the intensity of the light made no difference to the reaction, but dilute solution gave inferior results (for details, see SI).

As described in Scheme 2, the reaction path b also presents a reasonable route for the synthesis of isoxazoles from β-oxodithioesters and hydroxylamine as we initially expected.[11,12] Aiming to investigate the possibility of path b, we further screened the reaction conditions including base, temperature, and solvent for the reaction. To our delight, 3-(methylthio)-5-phenylisoxazole **3a** could be isolated in 17% yield (Scheme 3, entry 1) when treating methyl 3-oxo-3-phenylpropanedithioate **1a** with neutral hydroxylamine (1.2 equiv, preneutralized by NaOAc (1.2 equiv) in water) in HOAc at room temperature. The yield of **3a** was able to be dramatically increased to 84% yield by heating the reaction mixture at 90 °C (entry 3). NH_4OAc was also proved to be an efficient base for the preneutralization of hydroxylamine hydrochloride (entry 4). It was found that the pretreatment of hydroxylamine hydrochloride with a base was required and that no reaction occurred without this neutralization (entry 5). Moreover, we did not detect isoxazole isomer which resulted from the reaction of **1a** with hydroxylamine by primary attack of hydroxylamine at its oxo moiety. It should be due to the predominant attack of softer nucleophilic nitrogen of hydroxylamine at softer electrophilic thiocarbonyl of **1a**.

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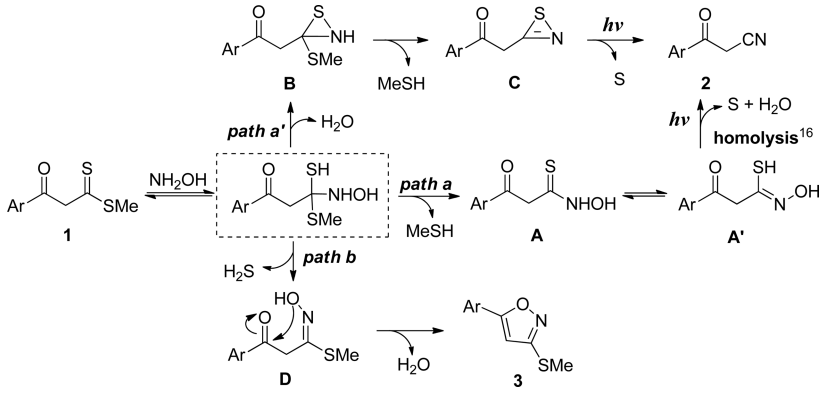
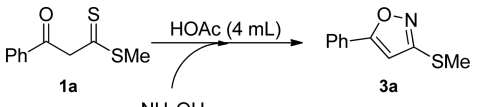
Scheme 2. Proposed Reaction Mechanism



Scheme 3. Optimization for Preparing Corresponding Isoxazoles



entry	base	T/°C	t/h	yield[a]
1	NaOAc	r.t.	15	17%
2	NaOAc	50	10	63%
3	NaOAc	90	5	84%
4	NH_4OAc	90	7	82%
5	-	90	15	trace

[a]Isolated yield.

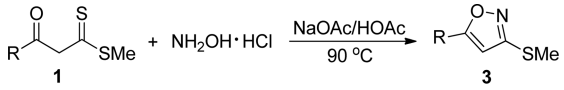
Isoxazoles are one of classes of heterocyclic compounds with widely biological and pharmacological activities and agrochemical properties.[18] Functionalized isoxazoles have also been demonstrated to be versatile building blocks in organic synthesis.[19] Thus, the scope of the above reaction was investigated. As described in Table 3, this reaction could be carried with a series of substituted β-oxodithioesters affording the corresponding products **3**. **1** with both electron-donating and electron-withdrawing groups can afford isoxazoles **3a**−**h** in good yields. Those substrates containing heteroaryls are also suitable for the reaction, providing the corresponding isoxazole derivatives **3i**−**l** in 63−89% yields. However, β-oxodithioester bearing CN at phenyl ring gave **3m** in 27% yield.

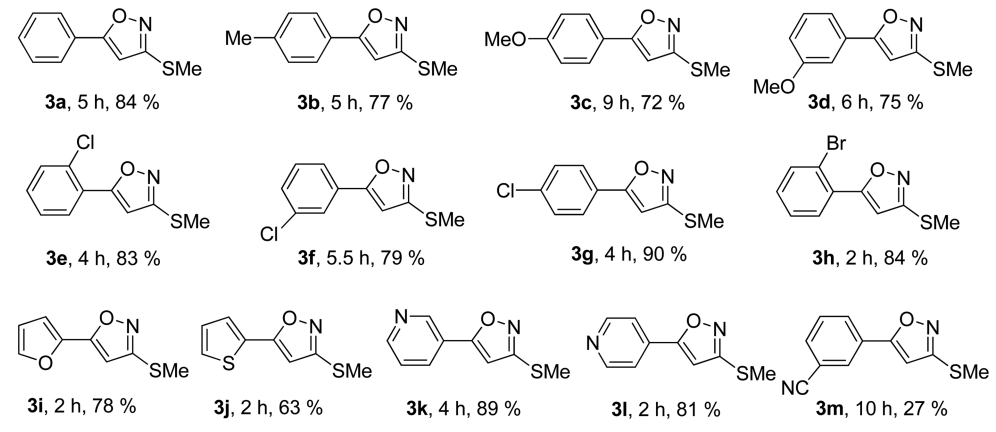
In conclusion, two well-controlled transformations of β-oxodithioesters with hydroxylamine are described to afford β-ketonitriles and isoxazoles, respectively, under different reaction conditions. The reaction of β-oxodithioesters with hydroxylamine in EtOH at room temperature in daylight gave β-ketonitriles in high yields via thiohydroxamic acid intermediate followed by homolysis. On the other hand, 3-methylthioisoxazoles were efficiently obtained through a cyclocondensation of β-oxodithioesters and hydroxylamine by heating the mixture in HOAc at 90 °C. The simple execution, readily available substrates, mild conditions, good yields, and, in particular, the good chemoselectivity of the reactions make the protocol very attractive for practical applications.

EXPERIMENTAL SECTION

General. All commercially available compounds were used as received unless otherwise noted. Reactions were monitored through thin layer chromatography (TLC, silica gel 60 F254). Subsequent to elution, spots were visualized using UV radiation (254 nm). Flash column chromatography was performed on silica gel 60 (particle size 200−400 mesh). ^{1}H NMR and ^{13}C NMR were recorded at 25 °C on a

Table 3. Substrate Scope for the Synthesis of Isoxazoles[a]





[a]Reaction conditions: **1** (0.5 mmol), NH_2OH·HCl (0.6 mmol), NaOAc (0.6 mmol), H_2O (0.5 mL), HOAc (4 mL), 90 °C. Isolated yields.

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500 and 125 MHz spectrometer, respectively, by using TMS as internal standard. High-resolution mass spectra (HRMS) were obtained using a microTOF II focus spectrometer (ESI). Melting points were uncorrected. β-Oxodithioesters **1** were prepared by the method reported in the literature.[20]

General Procedure for the Synthesis of 2 (2a was selected as an example). Hydroxylamine hydrochloride (0.6 mmol) was stirred with NaOH (0.6 mmol) in 4 mL of EtOH for 10 min at room temperature. Then, 3-oxo-3-phenylpropanedithioate **1a** (0.5 mmol) was added, and the reaction mixture was stirred at ambient conditions for 50 min to consume **1a** (monitored by TLC). The reaction was quenched by saturated aqueous NaCl, and extracted with dichloromethane (10 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated to afford the crude product, which was purified by column chromatography on silica gel (eluent, petroleum ether/ethyl acetate, 9:1) to give β-ketonitrile **2a** (59.5 mg, 82%) as a white solid.

General Procedure for the Synthesis of 3 (3a was selected as an example). Hydroxylamine hydrochloride (0.6 mmol) was first preneutralized by NaOAc (0.6 mmol) in 0.5 mL of water. Then, HOAc (4 mL) and 3-oxo-3-phenylpropanedithioate **1a** (0.5 mmol) were added to the above mixture (0.6 mmol). After stirring at 90 °C for 5 h to consume **1a** (monitored by TLC), the reaction was quenched by saturated aqueous NaCl, neutralized by aqueous $NaHCO_3$, and extracted with dichloromethane (10 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated to afford the crude product, which was purified by column chromatography on silica gel (eluent, petroleum ether/ethyl acetate, 20:1) to give isoxazole **3a** (80.3 mg, 84%) as a white solid.

*3-Oxo-3-phenylpropanenitrile (**2a**).* White solid (59.5 mg, 82%). Mp 87−88 °C (lit.[15a] Mp 81 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.11 (s, 2H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.4, 113.8, 128.4 (2C), 129.1 (2C), 134.2, 134.8, 187.1. HRMS (ESI-TOF): Calcd for $[M + Na]^+$ C_9H_7NNaO, 168.0420; found, 168.0426.

*3-Oxo-3-(p-tolyl)propanenitrile (**2b**).* White solid (62.1 mg, 78%). Mp 103−105 °C (lit.[15b] Mp 94−96 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.44 (s, 3H), 4.09 (s, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8, 29.3, 114.1, 128.6 (2C), 129.8 (2C), 131.8, 146.0, 186.8. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_{10}H_{10}NO$, 160.0757; found, 160.0759.

*3-(4-Methoxyphenyl)-3-oxopropanenitrile (**2c**).* White solid (62.2 mg, 71%). Mp 132−133 °C (lit.[14c] Mp 132−137 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.90 (s, 3H), 4.05 (s, 2H), 6.98 (dd, *J* = 1.5, 7.0 Hz, 2H), 7.90 (dd, *J* = 2.0, 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.0, 55.6, 114.1 (2C), 114.3, 127.2, 130.9 (2C), 164.7, 185.5. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_{10}H_{10}NO_2$, 176.0706; found, 176.0710.

*3-(3-Methoxyphenyl)-3-oxopropanenitrile (**2d**).* White solid (66.6 mg, 76%). Mp 127−128 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.86 (s, 3H), 4.10 (s, 2H), 7.19−7.21 (m, 1H), 7.41−7.48 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.4, 55.4, 112.4, 113.6, 120.8, 121.1, 123.0, 135.3, 159.9, 186.8. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_{10}H_{10}NO_2$, 176.0706; found, 176.0716.

*3-(4-Chlorophenyl)-3-oxopropanenitrile (**2e**).*[14b] White solid (77.2 mg, 86%). Mp 138−139 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.06 (s, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.4, 113.4, 129.6 (2C), 129.8 (2C), 132.5, 141.5, 185.9. HRMS (ESI-TOF): Calcd for $[M + H]^+$ C_9H_7ClNO, 180.0211; found, 180.0213.

*3-(2-Bromophenyl)-3-oxopropanenitrile (**2f**).* Light yellow oil (70.6 mg, 63%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.14 (s, 2H), 7.41−7.47 (m, 2H), 7.53 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.67 (dd, *J* = 1.0, 7.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 32.2, 113.1, 119.0, 127.7, 129.5, 133.2, 133.9, 137.644, 190.2. HRMS (ESI-TOF): Calcd for $[M + H]^+$ C_9H_7BrNO, 223.9706; found, 223.9686.

*3-(Furan-2-yl)-3-oxopropanenitrile (**2g**).* White solid (52.0 mg, 77%). Mp 91−92 °C (lit.[15b] Mp 76−78 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.98 (s, 2H), 6.65 (dd, *J* = 1.5, 3.5 Hz, 1H), 7.40 (d, *J* = 1.0 Hz, 1H), 7.67 (dd, *J* = 1.0, 1.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.8, 113.3, 113.3, 119.3, 147.7, 150.4, 175.7. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_7H_6NO_2$, 136.0393; found, 136.0398.

*3-Oxo-3-(thiophen-2-yl)propanenitrile (**2h**).* White solid (52.9 mg, 70%). Mp 130−131 °C (lit.[15b] Mp 124−126 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.03 (s, 2H), 7.21 (t, *J* = 4.5 Hz, 1H), 7.80 (dd, *J* = 5.0, 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.5, 113.4, 128.7, 133.7, 136.2, 140.8, 179.5. HRMS (ESI-TOF): Calcd for $[M + H]^+$ C_7H_6NOS, 152.0165; found, 152.0166.

*3-(2-Cyanoacetyl)benzonitrile (**2i**).* Light yellow solid (13.3 mg, 26%). Mp 189−190 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12 (s, 2H), 7.71 (dd, *J* = 7.6, 8 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 8.17 (d, *J* = 8 Hz, 1H), 8.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.5, 112.8, 113.9, 117.2, 130.2, 132.0, 132.2, 134.9, 137.4, 185.3. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_{10}H_7N_2O$, 171.0553; found, 171.0565.

*3-(Methylthio)-5-phenylisoxazole (**3a**).* White solid (80.3 mg, 84%). Mp 51−52 °C (lit.[11] Mp 56−57 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.55 (s, 3H), 6.32 (s, 1H), 7.35−7.38 (m, 3H), 7.64−7.66 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 99.0, 125.7 (2C), 127.1, 128.9 (2C), 130.2, 160.9, 169.8. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_{10}H_{10}NOS$, 192.0478; found, 192.0478.

*3-(Methylthio)-5-(p-tolyl)isoxazole (**3b**).* Yellow solid (79.0 mg, 77%). Mp 65−66 °C (lit.[11] Mp 64−65 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.55 (s, 3H), 6.27 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 21.5, 98.4, 124.4, 125.7 (2C), 129.6 (2C), 140.6, 160.8, 170.1. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_{11}H_{12}NOS$, 206.0634; found, 206.0633.

*5-(4-Methoxyphenyl)-3-(methylthio)isoxazole (**3c**).* White solid (79.7 mg, 72%). Mp 88−89 °C (lit.[11] Mp 74−75 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.62 (s, 3H), 3.84 (s, 3H), 6.28 (s, 1H), 6.95 (d, *J* = 12.0 Hz, 2H), 7.63 (d, *J* = 12.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 55.4, 97.7, 114.3 (2C), 119.9, 127.4 (2C), 160.8, 161.2, 169.9. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_{11}H_{12}NO_2S$, 222.0583; found, 222.0585.

*5-(3-Methoxyphenyl)-3-(methylthio)isoxazole (**3d**).* White solid (83.0 mg, 75%). Mp 80−81 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.63 (s, 3H), 3.86 (s, 3H), 6.40 (s, 1H), 6.98 (dd, *J* = 1.5, 8.5 Hz, 1H), 7.27 (d, *J* = 1.5 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 55.4, 99.3, 110.9, 116.2, 118.3, 128.3, 130.1, 159.9.1, 160.9, 169.7. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_{11}H_{12}NO_2S$, 222.0583; found, 222.0588.

*5-(2-Chlorophenyl)-3-(methylthio)isoxazole (**3e**).* Yellow semisolid (93.7 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.64 (s, 3H), 6.83 (s, 1H), 7.36−7.38 (m, 2H), 7.49 (dd, *J* = 2.0, 7.0 Hz, 1H), 7.89−7.91 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 103.9, 125.9, 127.2, 129.4, 130.8, 130.9, 131.7, 160.9, 166.0. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_{10}H_9ClNOS$, 226.0088; found, 226.0092.

*5-(3-Chlorophenyl)-3-(methylthio)isoxazole (**3f**).* White solid (89.1 mg, 79%). Mp 89−90 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.64 (s, 3H), 6.43 (s, 1H), 7.27−7.41 (m, 2H), 7.61−7.63 (m, 1H), 7.72 (t, *J* = 1.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 99.8, 123.9, 125.8, 128.7, 130.3, 130.3, 135.0, 161.1, 168.3. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_{10}H_9ClNOS$, 226.0088; found, 226.0090.

*5-(4-Chlorophenyl)-3-(methylthio)isoxazole (**3g**).* White solid (101.6 mg, 90%). Mp 111−112 °C (lit.[11] Mp 107−108 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.63 (s, 3H), 6.40 (s, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 99.3, 125.5, 128.0 (2C), 129.3 (2C), 136.4, 161.1, 168.7. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_{10}H_9ClNOS$, 226.0088; found, 226.0094.

*5-(2-Bromophenyl)-3-(methylthio)isoxazole (**3h**).* Light yellow semisolid (113.5 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.55 (s, 3H), 6.76 (s, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 103.8, 121.1, 127.7, 128.0, 130.0, 131.1, 134.1, 160.6, 167.4. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_{10}H_9BrNOS$, 269.9583; found, 269.9596.

*5-(Furan-2-yl)-3-(methylthio)isoxazole (**3i**).* Yellow solid (70.7 mg, 78%). Mp 55−56 °C (lit.[11] Mp 56−57 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.62 (s, 3H), 6.33 (s, 1H), 6.53 (dd, *J* = 1.5, 3.5 Hz, 1H),

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6.89 (d, J = 8.5 Hz, 1H), 7.53 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 98.5, 110.7, 111.8, 142.8, 144.1, 160.7, 161.5. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_8H_8NO_2S$, 182.0270; found, 182.0271.

*3-(Methylthio)-5-(thiophen-2-yl)isoxazole (**3j**).* Yellow solid (62.1 mg, 63%). Mp 65−66 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.62 (s, 3H), 6.28 (s, 1H), 7.12 (dd, J = 4.0, 5.0 Hz, 1H), 7.46 (dd, J = 1.0, 5.0 Hz, 1H), 7.49 (d, J = 1.0, 3.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 98.7, 127.2, 128.0, 128.2, 128.8, 161.0, 164.8. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_8H_8NOS_2$, 198.0042; found, 198.0044.

*3-(Methylthio)-5-(pyridin-3-yl)isoxazole (**3k**).* Yellow solid (85.5 mg, 89%). Mp 107−108 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.65 (s, 3H), 6.51 (s, 1H), 7.42 (dd, J = 1.0, 5.0 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 8.68 (dd, J = 1.5, 4.5 Hz, 1H), 8.99 (d, J = 2.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 100.0, 123.4, 123.7, 132.9, 147.0, 151.0, 161.3, 167.0. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_9H_9N_2OS$, 193.0430; found, 193.0435.

*3-(Methylthio)-5-(pyridin-4-yl)isoxazole (**3l**).* White solid (77.9 mg, 81%). Mp 108−109 °C (lit.[11] Mp 96−97 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.65 (s, 3H), 6.59 (s, 1H), 7.60 (dd, J = 1.5, 4.5 Hz, 2H), 8.75 (t, J = 1.0, 5.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 101.6, 119.4 (2C), 133.8, 150.7 (2C), 161.4, 167.1. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_9H_9N_2OS$, 193.0430; found, 193.0432.

*3-(3-(Methylthio)isoxazol-5-yl)benzonitrile (**3m**).* White solid (17.5 mg, 27%). Mp: 141−142 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.65 (s, 3H), 6.50 (s, 1H), 7.61 (t, J = 6.0 Hz, 1H), 7.73 (d, J = 6.4 Hz, 1H), 7.97 (d, J = 6.4 Hz, 1H), 8.02 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 100.5, 113.6, 117.9, 128.4, 129.2, 129.7, 130.0, 133.4, 161.4, 167.3. HRMS (ESI-TOF): Calcd for $[M + H]^+$ $C_{11}H_9N_2OS$, 217.0430; found, 217.0441.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01869.

Study on the influence of the light on the formation of β-ketonitriles, study on the influence of the concentration on the formation of β-ketonitriles, and copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wangm452@nenu.edu.cn.

Notes

The authors declare no competing financial interest.

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