# One-Pot Synthesis of 2-Oxazolines from Ethyl α-Cyanocinnamate Derivatives with *N*-Bromoacetamide

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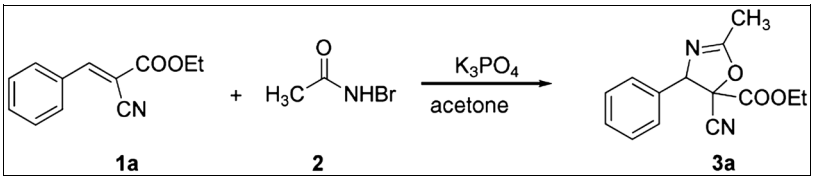


An efficient method for the one-pot synthesis of 2-oxazolines from ethyl α-cyanocinnamate derivatives with *N*-bromoacetamide in the presence of $K_3PO_4$ has been developed. The reaction performed smoothly and cleanly to give 2-oxazolines in good to excellent yields (up to 98%) within 4.5 h in acetone at room temperature without protection of inert gases. A total of 13 examples have been investigated. A possible nucleophilic addition reaction mechanism is proposed.

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## INTRODUCTION

2-Oxazoline belongs to an important class of heterocyclic compound and a versatile intermediate in organic synthesis because it can be easily converted into numerous useful functional derivatives via regioselective and stereoselective ring-opening process.[1] Many of the synthetic compounds and natural products possess the 2-oxazoline unit that exhibit potent biological activity.[2] Furthermore, the chiral 2-oxazolines as the ligand were also used in the many catalytic asymmetric synthesis process.[3] Because of its important applications in the various regions mentioned earlier, many organic chemists and biologists have paid attention to the synthesis of 2-oxazolines for a long time.[1–4] In the past two decades, numerous reports had described their synthesis including condensation of carboxylic acids,[5] esters,[6] nitriles,[7] aldehydes,[8] imino-ether hydrochlorides,[9] Vilsmeier reagent with vicinal amino alcohols,[10] and cyclization of *β*-hydroxy amides.[11] However, each method has its disadvantages in any given situation, such as harsh reaction condition, longer reaction time, and harmful to the environment. Thus, the efficient and the one-pot method for the synthesis of the multifunctional group's 2-oxazolines from new substrates under mild reaction conditions are still desired.

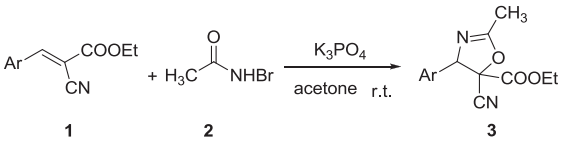
Although 2-oxazolines were also directly synthesized from olefins, the substrates were limited in a certain range, and the available substrates were mainly simple olefins. [12] When electron-deficient olefins reacted with MeCN and 4-$TsNCl_2$ or 2-$NsNCl_2$, the imidazoline products were obtained.[13] Ethyl α-cyanocinnamates are believed to be the useful substrates in organic synthesis.[14] However, the successful one-pot synthesis of 2-oxazolines from ethyl α-cyanocinnamate derivatives has not been reported so far. On the basis of the effort of many scientist and our group to study the aminobromination for the electron-deficient olefins,[15] we discovered that the *N*-bromoacetamide (NBA) could expediently converted the ethyl α-cyanocinnamates (electron-deficient olefins) into the corresponding 2-oxazoline in the presence of base. Under optimized reaction conditions, a very simple and efficient one-pot synthesis of 2-oxazolines from ethyl α-cyanocinnamate derivatives with NBA in the presence of $K_3PO_4$ has been developed. The reaction was performed handily in acetone at room temperature without protection of inert gases and gave the corresponding products in good to excellent yields (up to 98%, Scheme 1). Herein, we wish to report the detailed study of the reaction.

## RESULT AND DISCUSSION

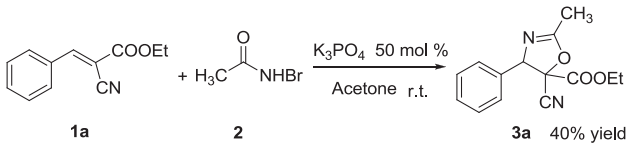
The initial experiment was carried out by using the ethyl α-cyanocinnamate **1a** as model substrate and NBA as a reagent in the presence of 50% anhydrous $K_3PO_4$ in acetone. When a mixture of ethyl α-cyanocinnamate (1.0 equiv), NBA (1.1 equiv), and $K_3PO_4$ (0.5 equiv) was stirred at room temperature for 24 h, to our delight, the reaction proceeded smoothly, and the reaction afforded the corresponding product **3a** in 40% yield (Scheme 2).

Encouraged by this result, a systematic study was undertaken for the optimization of the reaction conditions. Firstly, the category and amount of base were investigated, and the results are listed in Table 1. As shown in the Table 1, anhydrous $K_3PO_4$ is an efficient base for this reaction. When the loading of $K_3PO_4$ was increased, the yield of corresponding product was improved (Table 1, entries 1–3). However, when the loading of $K_3PO_4$ was increased up to 2.0 equiv,

**Scheme 1.** One-pot synthesis of 2-oxazolines from ethyl α-cyanocinnamate derivatives with *N*-bromoacetamide (NBA).




**Scheme 2.** One-pot synthesis of 2-oxazoline (**3a**) from ethyl α-cyanocinnamate (**1a**) in the present of 50 mol% $K_3PO_4$.




the yield of corresponding product was decreased although the starting material was consumed in short period (Table 1, entry 4). It was discovered that anhydrous $K_2CO_3$ was also an efficient base for this reaction (Table 1, entry 5). However, when the stronger bases were subjected to this reaction, such as KOH and NaOH, the reactions did not work well (Table 1, entries 6 and 7). These outcomes indicate that stronger bases are not suitable promoting reagents for this reaction. The anhydrous NaOAc was discovered to be not an effective reagent, too, even though reaction time was prolonged up to 48 h (Table 1, entry 8). It is worthy to note that the reaction failed to give any product in the absence of base that indicates that the base is a key role for this reaction (Table 1, entry 9). For the $K_3PO_4$, the best base was chosen; a little excess of stoichiometric loading was found to be necessary for ensuring the reaction to work well.

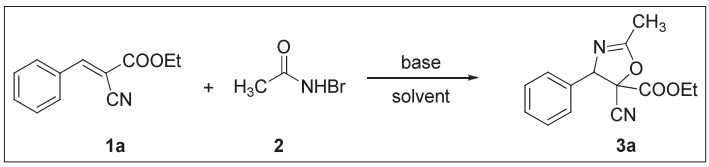
Further study showed that the solvent affected this reaction, too. As shown in Table 1 (entries 1–15), acetone is a best solvent for the reaction among the investigated solvents. Besides acetone, THF and toluene were also found to be efficient solvents for this reaction (entries 10 and 11). However, DMF, $CHCl_3$, $CH_2Cl_2$, and $CH_3CN$ were less efficient (Table 1, entries 12–15).

It was discovered that the mole ratio of the substrate, reagent, and $K_3PO_4$ also affected the yield of the product, and the outcomes are listed in Table 2. As shown in Table 2, the most reasonable mole ratio of the substrate, NBA, and $K_3PO_4$ is **1a**:NBA:$K_3PO_4$ = 1.0:1.5:1.2 (mol) in which the highest chemical yield (96%) was achieved when the reaction was carried out at room temperature in acetone within 2.5 h (Table 2, entry 6).

To explore the scope and the limitation of the one-pot synthesis of 2-oxazolines from ethyl α-cnayocinnamate derivatives and gain an insight into the reaction mechanism, a series of the ethyl α-cyanocinnamate derivatives bearing electron-donating groups (EDG) and/or electron-withdrawing groups (EWG) on the benzene ring have been investigated. The results are summarized in Table 3.

**Table 1**

The influence of base and solvent to the reaction.[a]

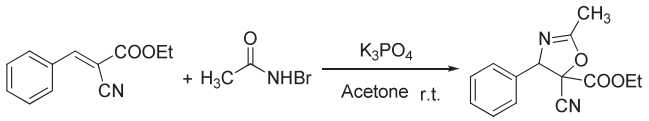



| Entry | Substrate | Product | Solvent | Base (mol%) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **1a** | **3a** | Acetone | $K_3PO_4$(50) | 24 | 40 |
| 2 | **1a** | **3a** | Acetone | $K_3PO_4$(70) | 18 | 80 |
| 3 | **1a** | **3a** | Acetone | $K_3PO_4$(110) | 2.0 | 93 |
| 4 | **1a** | **3a** | Acetone | $K_3PO_4$(200) | 0.5 | 84 |
| 5 | **1a** | **3a** | Acetone | $K_2CO_3$(110) | 5.5 | 90 |
| 6 | **1a** | **3a** | Acetone | KOH(110) | 10 | 20 |
| 7 | **1a** | **3a** | Acetone | NaOH(110) | 48 | Trace |
| 8 | **1a** | **3a** | Acetone | NaOAc(110) | 48 | Trace |
| 9 | **1a** | **3a** | Acetone | 0 | 48 | 0 |
| 10 | **1a** | **3a** | THF | $K_3PO_4$(110) | 4.5 | 90 |
| 11 | **1a** | **3a** | Toluene | $K_3PO_4$(110) | 24 | 83 |
| 12 | **1a** | **3a** | DMF | $K_3PO_4$(110) | 48 | Trace |
| 13 | **1a** | **3a** | $CHCl_3$ | $K_3PO_4$(110) | 48 | Trace |
| 14 | **1a** | **3a** | $CH_2Cl_2$ | $K_3PO_4$(110) | 24 | 25 |
| 15 | **1a** | **3a** | $CH_3CN$ | $K_3PO_4$(110) | 10 | 57 |

[a]Conditions: substrate (2.0 mmol), NBA (2.2 mmol), solvent (10 mL), at room temperature. [b]Isolated yield.

**Table 2**

The influence of mol ratio of the starting material, reagent, and $K_3PO_4$ to reaction.[a]




**1a** **NBA** **3a**

| Entry | Substrate | Product | **1a**:NBA:$K_3PO_4$ (mole ratio) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **1a** | **3a** | 1:1.1:1.1 | 2.0 | 93 |
| 2 | **1a** | **3a** | 1:1.5:1.1 | 5.5 | 95 |
| 3 | **1a** | **3a** | 1:2.0:1.1 | 12 | 88 |
| 4 | **1a** | **3a** | 1:1.5:0.5 | 24 | 39 |
| 5 | **1a** | **3a** | 1:1.5:0.7 | 24 | 61 |
| 6 | **1a** | **3a** | 1:1.5:1.2 | 2.5 | 96 |
| 7 | **1a** | **3a** | 1:1.5:1.5 | 1.5 | 90 |
| 8 | **1a** | **3a** | 1:1.5:2.0 | 0.5 | 86 |

[a]Conditions: substrate **1a** (2.0 mmol), acetone (10 mL), at room temperature. [b]Isolated yield.

All ethyl α-cyanocinnamate derivatives reacted with NBA successfully to give the corresponding 2-oxazolines in good to excellent yields (72–98%). Both EDG and EWG on the phenyl ring were compatible to the reaction system. As shown in Table 3, the reaction activity of ethyl α-cyanocinnamate derivatives depends greatly on the substituent groups of benzene ring, especially those on the 4-position of the phenyl ring. For the ethyl α-cyanocinnamate derivatives that bearing stronger EDGs or no any substituent group on the benzene ring (Table 3, **1a–1e**), the reaction gave the expected products in high yields up to 90–98% (Table 3, entries 1–5). However, when the ethyl α-cyanocinnamate derivatives bearing stronger EWGs on the phenyl ring (**1g–1j**), the reaction afforded the corresponding products in slightly lower yields of 79–85% (Table 3, entries 7–10). Other substrates such as **1k** and **1l** could give the expected products in the excellent yields of 90% and 93%, respectively (entries 11 and 12). Herein, the substrates of **1f** and **1m** also afforded the corresponding products in good yields of 85% and 72%, respectively (Table 3, entries 6 and 13). The results mentioned earlier indicate that the EDGs and EWGs on the phenyl ring could affect the reaction activity of substrates.

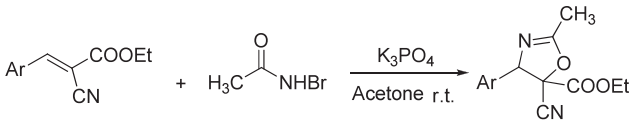
We realized that the formation process of 2-oxazoline was via an aminobrominated intermediate. To confirm the hypothesis of the 2-oxazoline formation from an aminobrominated intermediate, the following experiment was carried out: Ethyl α-cyanocinnamate **1a** was reacted with NBA in acetone promoted by $K_3PO_4$ at room temperature. When the substrate **1a** was justly consumed, the reaction was stopped and the solvent was concentrated under reduced pressure to give a mixture. The reaction mixture was analyzed by $^1$H NMR. The aminobrominated intermediate (ethyl β-acetamide-β-benzyl-α-bromo-α-cyanopropionate) as well as corresponding 2-oxazoline **3a** were simultaneously observed (shown in Fig. 1). Furthermore, the HRMS analysis of the mixture indicated that the aminobrominated intermediate and the product **3a** were clearly identified. HRMS-ESI (*m/z*): Calcd for $C_{14}H_{15}BrNaN_2O_3[M+Na]^+$ 361.0164 (aminobrominated intermediate), found 361.0195; Calcd for $C_{14}H_{14}NaN_2O_3$ $[M+Na]^+$ 281.0897 (**3a**), found 281.0892. Indeed, during the course of our reaction, a phenomenon was obviously observed that the spot of aminobrominated intermediate was disappeared when the reaction time was extended for a while monitored by TLC.

We found that the reaction has high regiospecificity. To further seek the evidence of regiospecificity of the reaction, a single crystal of one product, 5-cyano-5-ethoxyformacyl-2-methyl-4-(naphthalen-1-yl)-4,5-dihydrooxazole **3l**, was cultured. The regiospecificity of this 2-oxazoline was confirmed by its X-ray crystallographic analysis (Fig. 2, CCDC-873424). The result showed that the nitrogen atom in 2-oxazoline ring is connected to β-carbon of the substrate.

On the basis of the very electron deficient property of the substrates, the presence of the intermediate of aminobrominated product during reaction progress monitored by $^1$H NMR analysis and the evidence of regiospecificity of the reaction, the plausible reaction mechanism involving the aminobromination and the cyclization reaction processes is proposed (Scheme 3). The first step was a deprotonation reaction of NBA by $K_3PO_4$ to generate a Hofmann species $AcNBr^-$ (**Hs**), which in turn attacks the benzylic position of ethyl α-cyanocinnamate to generate a Michael intermediate (**G**). A carbanion in this

**Table 3**

The reaction results of various ethyl α-cyanocinnamate derivatives with *N*-bromoacetamide.[a]



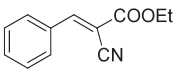
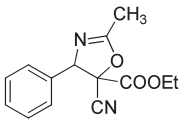
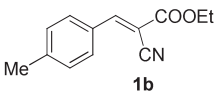
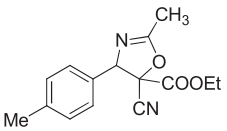
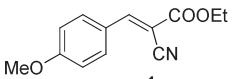
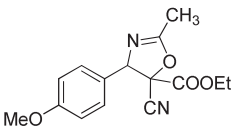
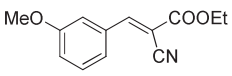
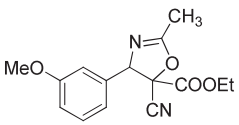
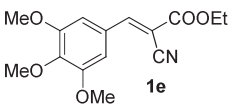
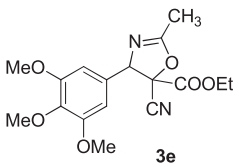
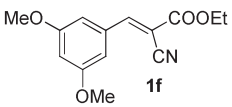
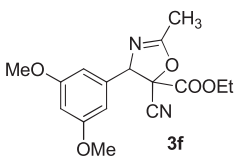

| Entry | Substrate | Product | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  **1a** |  **3a** | 2.5 | 96 |
| 2 |  **1b** |  **3b** | 2.0 | 91 |
| 3 |  **1c** |  **3c** | 2.2 | 98 |
| 4 |  **1d** |  **3d** | 1.5 | 96 |
| 5 |  **1e** |  **3e** | 1.5 | 90 |
| 6 |  **1f** |  **3f** | 4.5 | 85 |

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**Table 3**
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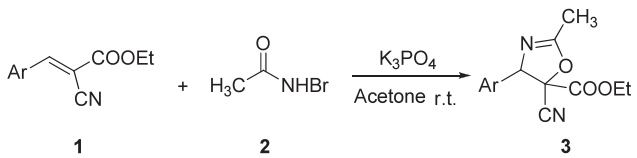
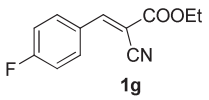
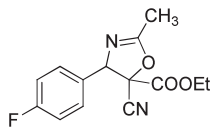
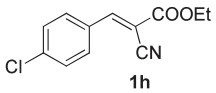
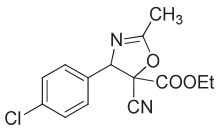
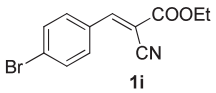
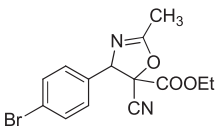
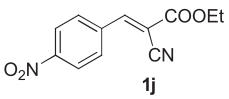
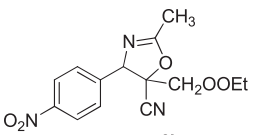
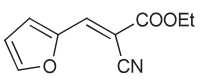
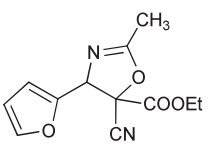
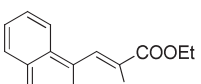
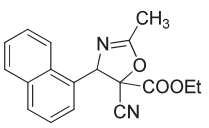
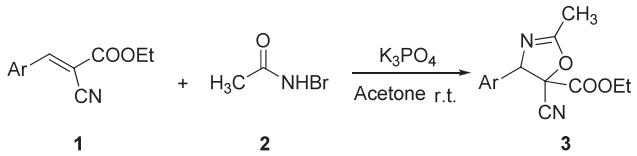
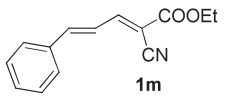
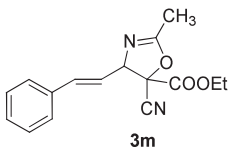



| Entry | Substrate | Product | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 7 |  **1g** |  **3g** | 1.5 | 85 |
| 8 |  **1h** |  **3h** | 1.5 | 82 |
| 9 |  **1i** |  **3i** | 1.4 | 82 |
| 10 |  **1j** |  **3j** | 1.7 | 79 |
| 11 |  **1k** |  **3k** | 2.0 | 93 |
| 12 |  **1l** |  **3l** | 0.5 | 90 |

(*Continued*)

**Table 3**
*(Continued)*




| Entry | Substrate | Product | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 13 |   |   | 4.5 | 72 |

[a]Conditions: substrate (2.0 mmol), NBA (3.0 mmol), $K_3PO_4$ (2.4 mmol), acetone (10 mL), at room temperature.
[b]Isolated yield.

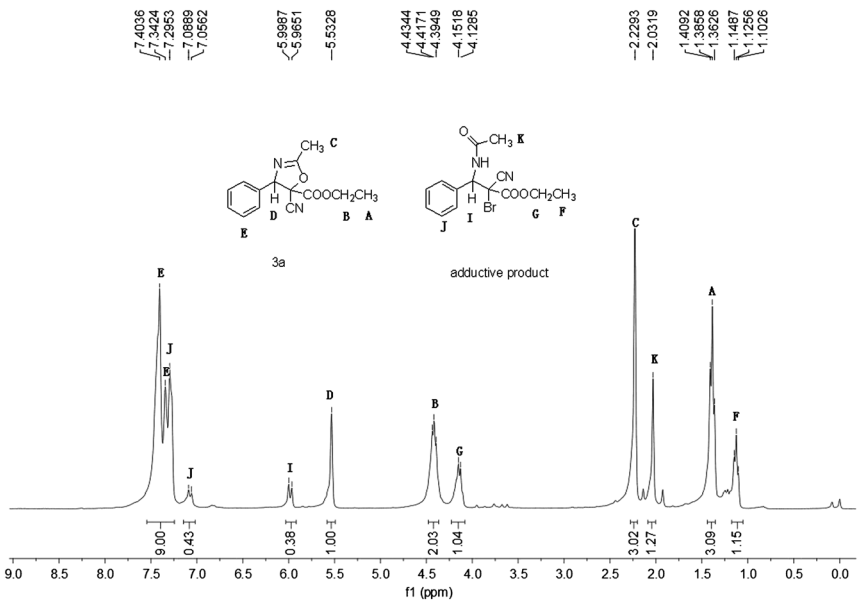



**Figure 1.** The $^1$H NMR spectrum of reaction mixture.

Michael intermediate (**G**) was formed, and it was stabilized by the inductive effect from two EWGs (CN and COOEt). In the second step, $Br^+$ ion migrated to the carbanion from NBr of the amide and then created an acetamido anion (**H**).[15] In this stage, the acetamido anion (**H**) accepted a proton from another NBA molecule and gave a aminobrominated product (**E**) and a new $AcNBr^-$ ion (**Hs**). The latter, as a stronger base than NBA, would participate in the next cycle. Herein, an intermediate **M** was formed via intramolecular rearrangement of compound **E**. The final step was an intramolecular nucleophilic substitution reaction of intermediate **M** that afforded 2-oxazoline **P** with assistance of the base. The regioselectivity could be explained by the fact that the *β*-position of the substrate is loaded more positive charge related to its α-position because of inductive effect from two EWGs (CN and COOEt).

Briefly, the present one-pot synthesis of 2-oxazolines essentially consists of two key reactions: nucleophilic conjugate addition of electron-deficient olefines and intramolecular nucleophilic substitution reaction of intermediate **M**.[15,16]

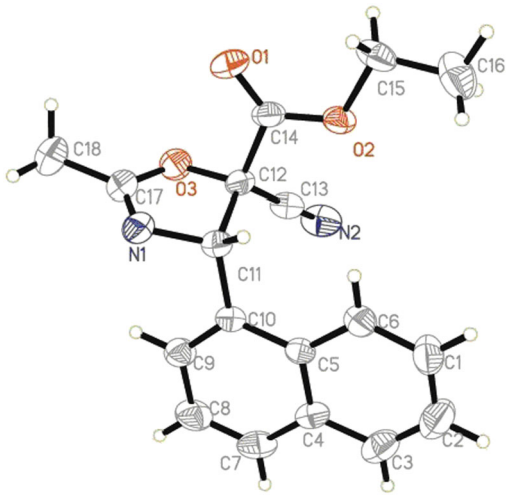
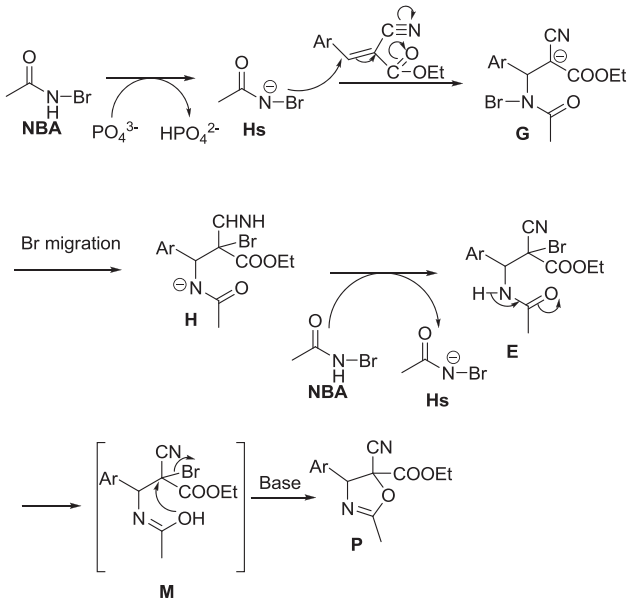



**Figure 2.** X-ray crystal structure of product **3l**.

**Scheme 3.** The plausible reaction mechanism.




## CONCLUSION

A one-pot method for the synthesis of 2-oxazoline derivatives using ethyl α-cyanocinnamate derivatives with NBA in the presence of $K_3PO_4$ has been developed. This new protocol can conveniently and efficiently converts the ethyl α-cyanocinnamate derivatives into 2-oxazolines at room temperature in good to excellent yields with the extensive range of α-cyanocinnamate derivatives. Both EDG and EWG on the phenyl ring are compatible to the reaction system. The proposed plausible reaction mechanism involving aminobromination process and cyclization process can explain well the regiospecificity of the reaction.

## EXPERIMENTAL

**General information.** Unless otherwise stated, all reagents were purchased from commercial sources and without further purification. Reaction progress was monitored by TLC using Merck silica gel 60F-254 with detection by UV. Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. $^1$H (300 MHz) and $^{13}$C (75.5 MHz) NMR spectra were recorded using $CDCl_3$ as a solvent. Chemical shifts (δ) are reported in ppm, using TMS as an internal standard. Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet), coupling constant *J* (Hz), and integration. HRMS was recorded on a commercial apparatus (ESI). The crystal structure was recorded on an X-ray diffraction spectrometer. Melting point was uncorrected.

**Preparation of *N*-bromoacetamide.** *N*-Bromoacetamide was prepared according to the reference with slight modification. [15] Acetamide (5.0 g, 85 mmol) and liquid bromine (13.5 g, 170 mmol) were added into a 150 mL round-bottomed flask immersed in an ice-water bath and stirred electromagnetically at 0–5°C until the solid dissolved completely. The ice-cooled 50% KOH solution (10 mL) was dropped while stirring at 0–5°C, and a large amount of light yellow solid was precipitated. The mixture was allowed to stand in the ice-water bath for 2–3 h to complete the reaction. Upon addition of 10 g of NaCl and 125 mL of $CHCl_3$, the suspension was heated on a hot-water bath to dissolve the precipitate with vigorous stirring. Then, the organic layer was separated and dried with anhydrous $Na_2SO_4$. After the solid was filtrated off, 125 mL of hexane was added to the filtrate and the solution was placed in a refrigerator overnight. The white needles were collected by filtration, and dried in vacuum: yield 5.72 g (49.1%). mp 90.5–91.5°C.

**General experimental procedure.** Into a dried vessel were added substrate (2.0 mmol), NBA (3.0 mmol), anhydrous $K_3PO_4$ (2.4 mmol), and acetone (10 mL). The mixture was stirred at room temperature in air until the reaction was completed. The reaction was monitored by TLC up to the aminobrominated intermediate was disappeared completely. Ethyl acetate (20 mL) was added into the reaction mixture to quench the reaction. The solution was washed with brine (3 × 10 mL) and water (3 × 10 mL). The organic solution was dried by anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give crude product that was purified by column chromatography with silica gel using petroleum ether and EtOAc as eluent to afford the pure product.

***5-Cyano-5-ethoxyformacyl-2-methyl-4-phenyl-4,5-dihydrooxazole (3a).*** Following general experimental procedure, a white solid (495 mg, 96% yield) was obtained. mp: 50–52°C.$^1$H NMR(300 MHz, $CDCl_3$) δ 7.44–7.28 (m, 5H, Ar-H), 5.53 (s, 1H, Ar-CH-), 4.45 (q, 2H, $CH_2CH_3$), 2.25 (s, 3H, $CH_3$), 1.41 (t, $J$ = 7.1 Hz,3H, $CH_2CH_3$); $^{13}$C NMR (75.5 MHz, CDCl3) δ 165.0, 164.1, 135.5, 129.4, 128.9 (2), 127.1 (2), 113.0, 82.1, 79.7, 64.3, 14.0, 13.6; HRMS-ESI (*m/z*): Calcd for $C_{14}H_{14}NaN_2O_3$ $[M+Na]^+$ 281.0897, found: 281.0892.

***5-Cyano-5-ethoxyformacyl-2-methyl-4-(4-methylphenyl)-4, 5-dihydrooxazole (3b).*** Following general experimental procedure, a white solid (469 mg, 91% yield) was obtained. mp: 53–55°C. $^1$H NMR(300 MHz, $CDCl_3$) δ 7.34–7.18 (m, 4H, Ar-H), 5.49 (s, 1H, ArCH), 4.45 (d, $J$ = 2.88 Hz, 2H, $CH_2CH_3$), 2.37 (s, 3H, Ar-$CH_3$), 2.25 (s, 3H, $CH_3$) 1.42 (d, $J$ = 1.17 Hz, 3H, $CH_2CH_3$); $^{13}$C NMR(75.5 MHz, $CDCl_3$) δ 165.0, 163.9, 139.2,

132.6, 129.6 (2), 127.0 (2), 113.1, 82.1, 79.6, 64.2, 21.3, 14.0, 13.5; HRMS-ESI (*m/z*): Calcd for $C_{15}H_{16}NaN_2O_3$ $[M+Na]^+$ 295.1053, found: 295.1054.

***5-Cyano-5-ethoxyformacyl-2-methyl-4-(4-methoxyphenyl)-4,5-di-hydrooxazol (3c).*** Following general experimental procedure, the colorless oil (564 mg, 98% yield) was obtained. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, $J$ = 8.4 Hz, 2H, Ar-H), 6.94 (d, $J$ = 8.5 Hz, 2H, Ar-H), 5.47 (s, 1H, ArCH), 4.44 (q, 2H, $CH_2CH_3$), 3.82 (s, 3H, $OCH_3$), 2.25 (s, 3H, $CH_3$), 1.41 (t, $J$ = 7.1 Hz, 3H, $CH_2CH_3$); $^{13}$C NMR(75.5 MHz, $CDCl_3$) δ 165.0, 163.8, 160.3, 128.4 (2), 127.6, 114.3 (2), 113.2, 82.2, 79.4, 64.2, 55.2, 14.0, 13.5; HRMS-ESI (*m/z*): Calcd for $C_{15}H_{16}NaN_2O_4$ $[M+Na]^+$ 311.1002, found 311.1002.

***5-Cyano-5-ethoxyformacyl-2-methyl-4-(3-methoxyphenyl)-4,5-dihydrooxazole (3d).*** Following general experimental procedure, the colorless oil (553 mg, 96%yield) was obtained. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.37–7.32 (m, 1H, Ar-H), 6.94–6.82 (m, 3H, Ar-H), 5.50 (s, 1H, ArCH), 4.44 (q, 2H, $CH_2CH_3$), 3.82 (s, 3H, -$OCH_3$), 2.25 (s, 3H, $CH_3$), 1.41(t, $J$ = 6.9 Hz, 3H, $CH_2CH_3$); $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ 164.9, 164.1, 159.9, 137.1, 130.0, 119.4 (2), 114.6, 113.0, 82.0, 79.5, 64.3, 55.3, 14.0, 13.5; HRMS-ESI (*m/z*): Calcd for $C_{15}H_{16}NaN_2O_4$ $[M+Na]^+$ 311.1002, found: 311.1006.

***5-Cyano-5-ethoxyformacyl-2-methyl-4-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazole (3e).*** Following general experimental procedure, the colorless oil (627 mg, 90% yield) was obtained. $^1$H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 2H, Ar-H), 5.47 (s, 1H, ArCH), 4.45 (q, 2H, $CH_2CH_3$), 3.88 (s, 9H, $OCH_3$), 2.26 (s, 3H, $CH_3$), 1.43 (t, $J$ = 7.1Hz, 3H, $CH_2CH_3$); $^{13}$C NMR(75.5 MHz, $CDCl_3$) δ 164.8, 163.9, 153.4 (2), 138.7, 131.0, 113.1, 104.3 (2), 82.1, 79.6, 64.3, 60.7, 56.1 (2), 13.9, 13.5; HRMS-ESI (*m/z*): Calcd for $C_{17}H_{20}NaN_2O_6$ $[M+Na]^+$ 371.1214, found: 371.1218.

***5-Cyano-5-ethoxyformacyl-4-(3,5-dimethoxyphenyl)-2-methyl-4,5-dihydrooxazole (3f).*** Following general experimental procedure, the white solid (540 mg, 88% yield) was obtained. mp: 60–62°C. $^1$H NMR (300 MHz, $CDCl_3$) δ 6.47(s, 1H, Ar-H), 6.41 (s, 2H, Ar-H), 5.45 (s, 1H, ArCH), 4.44 (q, 2H, $CH_2CH_3$), 3.80 (s, 6H, $OCH_3$), 2.24 (s, 3H, $CH_3$), 1.42 (t, $J$ = 7.1Hz, 3H, $CH_2CH_3$); $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ 164.9, 164.1, 161.1, 137.7, 113.0, 105.3 (2), 100.9 (2), 82.0, 79.5, 64.3, 55.3 (2), 13.9, 13.5; HRMS-ESI (*m/z*): Calcd for $C_{16}H_{18}NaN_2O_5$ $[M+Na]^+$ 341.1108, found: 341.1113.

***5-Cyano-5-ethoxyformacyl-4-(4-fluorophenyl)-2-methyl-4,5-dihydrooxazole (3g).*** Following general experimental procedure, the white solid (469 mg, 85% yield) was obtained. mp:58.6–61°C. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.30–7.09 (m, 4H, Ar-H), 5.51 (s, 1H, ArCH), 4.45 (q, 2H, $CH_2CH_3$), 2.25 (s, 3H, $CH_3$), 1.42 (t, $J$ = 7.1Hz, 3H, $CH_2CH_3$); $^{13}$C NMR(75.5 MHz, $CDCl_3$) δ 164.9, 164.2, 161.6, 131.5, 129.0 (2), 116.5, 116.1, 113.0, 82.0, 79.0, 64.4, 13.9, 13.5; HRMS-ESI (*m/z*): Calcd for $C_{14}H_{13}FNaN_2O_3$ $[M+Na]^+$ 299.0802, found: 299.0804.

***4-(4-Chlorophenyl)-5-cyano-5-ethoxyformacyl-2-methyl-4,5-dihydrooxazole (3h).*** Following general experimental procedure, the white solid (479 mg, 82% yield) was obtained. mp: 78–80°C. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.42–7.22 (m, 4H, Ar-H), 5.51 (s, 1H, ArCH), 4.46(q, 2H, $CH_2CH_3$), 2.26 (s, 3H, $CH_3$), 1.42 (t, $J$ = 7.0 Hz, 3H, $CH_2CH_3$); $^{13}$C NMR(75.5 MHz, $CDCl_3$) δ 164.7, 164.4, 135.3, 134.2, 129.1 (2), 128.5 (2), 112.9, 81.9, 79.0, 64.3, 14.0, 13.5; HRMS-ESI (*m/z*): Calcd for $C_{14}H_{13}ClNaN_2O_3$[M + Na]$^+$ 315.0507, found: 315.0523.

***4-(4-Bromophenyl)-5-cyano-5-ethoxyformacyl-2-methyl-4,5-dihydrooxazole (3i).*** Following general experimental procedure, the white solid (551 mg, 82% yield) was obtained. mp: 86–88°C. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, $J$ = 8.2 Hz, 2H, Ar-H), 7.17 (d, $J$ = 8.1 Hz, 2H, Ar-H), 5.49 (s, 1H, ArCH), 4.45 (q, 2H, $CH_2CH_3$), 2.25 (s, 3H, $CH_3$), 1.42 (t, $J$ = 7.1Hz,3H, $CH_2CH_3$); $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ 164.7, 164.5, 134.6, 132.1 (2), 128.8 (2), 123.6, 112.9, 81.9, 79.0, 64.5, 14.0, 13.6; HRMS-ESI (*m/z*): Calcd for $C_{14}H_{13}BrNaN_2O_3$ $[M+Na]^+$ 359.0001, found:359.0000.

***5-Cyano-5-ethoxyformacyl-2-methyl-4-(4-nitrophenyl)-4,5-dihydrooxazole (3j).*** Following general experimental procedure, the white solid (481 mg, 79% yield) was obtained. mp: 99–101°C. $^1$H NMR(300 MHz, $CDCl_3$) δ 8.31 (d, $J$ = 8.5 Hz, 2H, Ar-H), 7.52 (d, $J$ = 8.4Hz, 2H, Ar-H), 5.65 (s, 1H, ArCH), 4.49 (q, 2H, $CH_2CH_3$), 2.29 (s, 3H, $CH_3$), 1.45 (t, $J$ = 7.1 Hz, 3H, $CH_2CH_3$); $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ 165.1, 164.3, 148.5, 142.5, 129.5, 128.3 (2), 124.1, 112.7, 81.7, 78.6, 64.8, 14.0, 13.6; HRMS-ESI (*m/z*): Calcd for $C_{14}H_{13}NaN_3O_5$ $[M+Na]^+$ 326.0747, found: 326.0751.

***5-Cyano-5-ethoxyformacyl-4-(furan-2-yl)-2-methyl-4,5-dihydrooxazole(3k).*** Following general experimental procedure, the white solid (461 mg, 93% yield) was obtained. mp: 65–67°C. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.50 (s, 1H, furyl-H), 6.44 (d, $J$ = 6.30 Hz, 2H, furyl-H), 5.57 (s, 1H, furylCH), 4.42 (q, 2H, $CH_2CH_3$), 2.22 (s, 3H, $CH_3$), 1.40 (t, $J$ = 7.0 Hz, 3H, $CH_2CH_3$); $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ 164.8, 164.4, 148.0, 144.0, 112.8, 110.8, 109.9, 80.0, 74.1, 64.4, 13.9, 13.5; HRMS-ESI (*m/z*): Calcd for $C_{12}H_{12}NaN_2O_4$ $[M+Na]^+$ 271.0689, found: 271.0692.

***5-Cyano-5-ethoxyformacyl-2-methyl-4-(naphthalen-1-yl)-4,5-dihydrooxazole (3l).*** Following general experimental procedure, the white crystal (552 mg, 90% yield) was obtained. mp: 112–114°C. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.92–7.52 (m, 7H, Naphthyl-H), 6.43 (s, 1H, NaphthylCH), 4.47 (q, 2H, $CH_2CH_3$), 2.32 (s, 3H, $CH_3$), 1.42 (t, $J$ = 7.1 Hz,3H, $CH_2CH_3$); $^{13}$C NMR(75.5 MHz, $CDCl_3$) δ 165.3, 164.2, 133.9, 130.8, 130.0, 129.4, 126.7, 126.0 (2), 125.6, 125.5, 122.1, 112.9, 82.3, 75.6, 64.5, 13.9, 13.6; HRMS-ESI (*m/z*): Calcd for $C_{18}H_{16}NaN_2O_3$ $[M+Na]^+$ 331.1053, found: 331.1056.

***(±)-5-Cyano-5-ethoxyformacyl-2-methyl-4-styryl-4, 5-dihydrooxazole (3m).*** Following general experimental procedure, the yellow oil (408 mg, 72% yield) was obtained. $^1$H NMR (300 MHz, $CDCl_3$) δ7.46–7.31 (m, 5H, Ar-H), 6.77 (d, $J$ =15.69 Hz, 1H, ArCH), 6.30–6.22 (m, 1H, CH), 5.04 (d, $J$ =7.2 Hz, 1H, CHCH), 4.41 (q, 2H, $CH_2CH_3$), 2.17 (s, 3H, $CH_3$), 1.38 (t, $J$ = 7.1 Hz, 3H, $CH_2CH_3$); $^{13}$C NMR(75.5 MHz, $CDCl_3$) δ 164.6, 163.6, 135.6, 128.6 (3), 126.8 (2), 123.3, 121.3, 113.3, 80.8, 77.6, 64.3, 13.9, 13.5; HRMS-ESI (*m/z*): Calcd for $C_{16}H_{16}NaN_2O_3$ $[M+Na]^+$ 307.1053, found 307.1053.

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