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Palladium Catalyzed Insertion Reaction of Isocyanides with 3-Arylisoxazol-5(4*H*)-ones: Synthesis of 4-Aminomethylidene Isoxazolone Derivates

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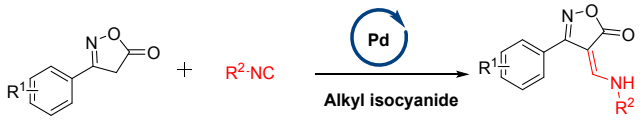


ABSTRACT. A palladium catalyzed insert reaction of isocyanides to 3-arylisoxazol-5(4*H*)-ones for the construction of 4-aminomethylidene isoxazolone derivates is reported. In this transformation, only C-H bond of methylene group was involved, meanwhile the remaining ring structure was retained. In general, this work provided a new protocol for the synthesis of 4-aminomethylidene isoxazolones.

KEYWORDS: isocyanides, 3-phenylisoxazol-5(4*H*)-one, palladium catalyst, enamine compounds

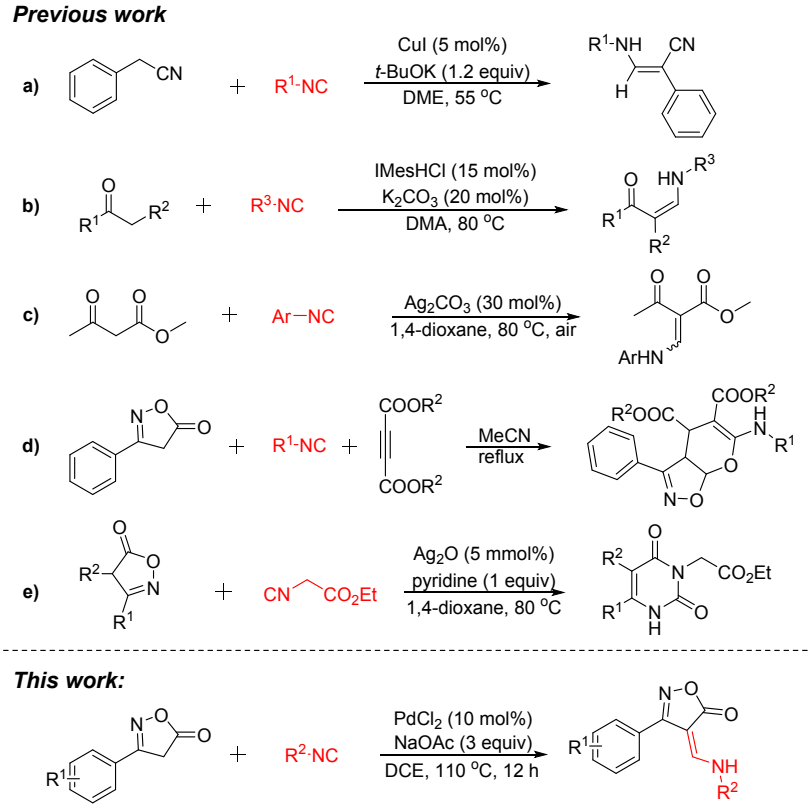
1. INTRODUCTION

Enamines have been far investigated by organic chemists in the past few decades because of its internal biological and pharmacological properties.[1] As a result, their preparations have became one of the research hotspots in organic synthesis field. The classical methods mainly rely on the condensation of amine with carbonly compounds and addition of enolate to unsaturate C-N bonds.[2] While strategies utilizing isocyanide were not explored until recent years. In 2015, Hong's group reported a copper catalyzed transformation of benzonitrile to enamine (scheme 1a) using either alkyl or aryl isocyanide.[3] Two years later, in 2017, they established a NHC promoted insertion reaction of aryl isocyanide to ketones to construct enamines (scheme 1b).[4] Bi's group reported a Ag-catalyzed reaction of aryl isocyanides to synthesize enamines with β-carbonyl ester using Ag_2CO_3. However, when alkyl isocyanides were applied, only hydrolyzed products were obtained (scheme 1c).[5] To the best of our

knowledge, reactions employing alkyl isocyanides such as *tert*-butyl isocyanide for the construction of enamine have not been reported.

In the past few decades, isoxazolone as a compound possessing multiple reaction sites[6], aroused the attention of chemists[7]. In 2010, Esmaeili's group reported a three-component involved reaction utilizing isocyanide, alkyne and isoxazolone constituting compounds with pyran structure (scheme 1d).[8] In 2018, Wei's group successfully realized the silver catalyzed synthesis of pyrimidinedione derivates utilizing isocyanide and isoxazolone (scheme 1e).[9] The highlight is that the C and N atoms of the isocyanide are simultaneously involved in the ring expansion reaction, meanwhile possesses good substrate universality. However, attemption of using *tert*-butyl isocyanide led to the product in less than 10% yield. Upon checking literature, combination of isoxazolone and palladium catalyst was not reported before. Based on our previous research[10] and other palladium catalyzed reaction[11] involving isocyanides, herein we reported a palladium catalyzed insertion reaction of alkyl isocyanides to 3-arylisoxazol-5(4*H*)-ones to construct 4-aminomethylidene isoxazolones (scheme 1). Though reactants are almost the same as Wei's work, the participated palladium catalyst in our reaction activated the C-H bond in methylene group affording the 4-aminomethylidene isoxazolone derivates instead of those ring opening ones.

Scheme 1 Relative Reactions Involving Isocyanides.

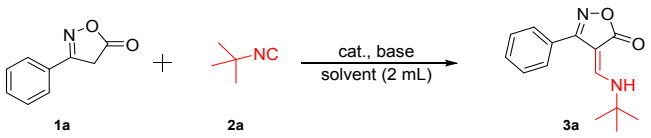


2. RESULTS AND DISCUSSION

Initially, we investigated the reaction of 3-phenylisoxazol-5(*4H*)-one (**1a**) and *tert*-butyl isocyanide (**2a**) in the presence of $PdCl_2$ (10 mol%) and NaOAc (3 equiv) in toluene (2 mL), 110 ℃ for 12 h. To our delight, the reaction furnished 3-phenylisoxazol-5(4*H*)-one **3a** in 18% yield. The structure of **3a** was confirmed by NMR, IR and single crystal diffraction (see Supporting Information). For example, shown as the ^{1}H NMR data of **3a** in Experiment Section, peaks at δ 9.39 (d, J = 14.4 Hz, 1H), δ 7.62 (d, J = 14.6 Hz, 1H), δ 1.37 (s, 9H) stand for N-H, alkenyl-H and methyl-H, respectively. For ^{13}C NMR data, peaks at δ 175.1, 161.4 and 149.3 represent for carbonyl-C, imino-C and enamine-C respectively

With this promising result in hand, we further opitimized reaction conditons. When $PdCl_2$ was replaced by Ag_2CO_3 and $Co(OAc)_2$ respectively, only trace amount of **3a** was detected. Other palladium catalysts like $Pd(PPh_3)_4$ and $Pd(OAc)_2$ gave **3a** in low yields (Table 1, entries 2-3). However, copper catalyst like CuI could only led to a messy system. After determining $PdCl_2$ as the best catalyst, base was also screened. Pyridine, triethylamine and Cs_2CO_3 were introduced respectively, unfortunately only lower yields were observed (Table 1, entries 7-9). Base amount was also investigated, when 2 equivalent amounts of NaOAc was applied, the yield of **3a** decreased to 3% (Table 1, entry 10), meanwhile expanded dosage made no difference (Table 1, entry 11). Various kinds of solvent were used later, and it was worth noting that DCE gave the best result (Table 1, entry 14). Reaction of lower catalyst load was also carried out, and only lower yield observed. Besides, reaction time and temperature were screened respectively as shown in table 1 entries 17-20. Finally, **1a** (0.2 mmol), **2a** (0.4 mmol), $PdCl_2$ (10 mol%), NaOAc (3 equiv) in DCE (2 mL) at 110 ℃ for 12 h was determined as optimized condition.

Table 1 Optimization of the Reaction Conditions[a]



1a 2a 3a

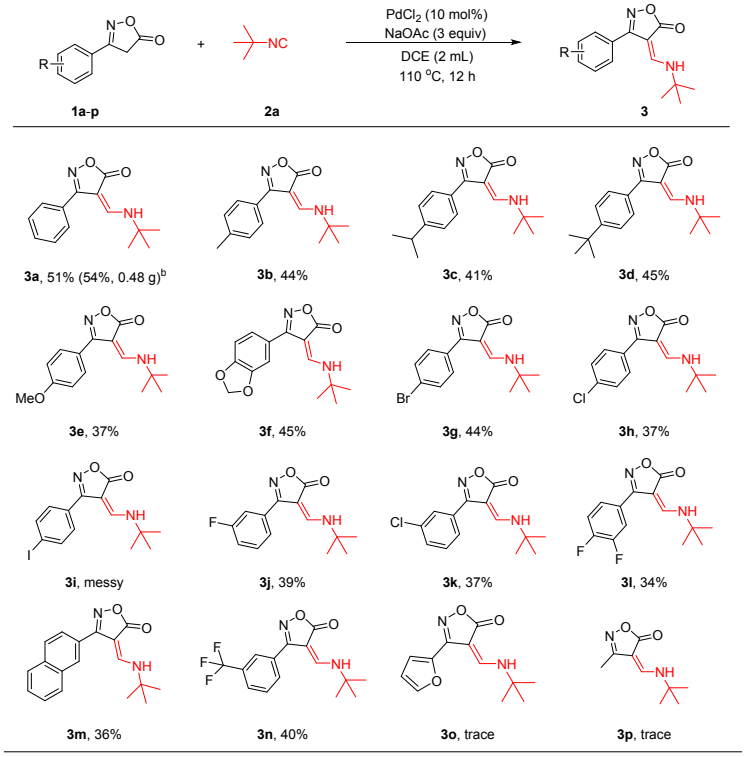
entry	catalyst (10 mol%)	base (equiv)	solvent (2 mL)	yield[b] (%)
1	Ag_2CO_3	NaOAc (3)	toluene	trace
2	$Pd(PPh_3)_4$	NaOAc (3)	toluene	6
3	$Pd(OAc)_2$	NaOAc (3)	toluene	17
4	$PdCl_2$	NaOAc (3)	toluene	18
5	$Co(OAc)_2$	NaOAc (3)	toluene	trace
6	CuI	NaOAc (3)	toluene	messy
7	$PdCl_2$	Et_3N (3)	toluene	12
8	$PdCl_2$	Pyridine (3)	toluene	7
9	$PdCl_2$	Cs_2CO_3 (3)	toluene	trace
10	$PdCl_2$	NaOAc (2)	toluene	3
11	$PdCl_2$	NaOAc (4)	toluene	18
12	$PdCl_2$	NaOAc (3)	DMF	NR
13	$PdCl_2$	NaOAc (3)	MeCN	8
14	**$PdCl_2$**	**NaOAc (3)**	**DCE**	**51**
15	$PdCl_2$	NaOAc (3)	1,4-Dioxane	NR
16[c]	$PdCl_2$	NaOAc (3)	DCE	41

17[d]	$PdCl_2$	NaOAc (3)	DCE	41
18[e]	$PdCl_2$	NaOAc (3)	DCE	49
19[f]	$PdCl_2$	NaOAc (3)	DCE	40
20[g]	$PdCl_2$	NaOAc (3)	DCE	40

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), palladium catalyst(10 mol%), solvent (2 mL), base(3 equiv), 110 ℃, 12 h. [b] Yields were isolated yields. [c] Catalyst load is 5 mol%. [d] The reaction temperature is 95 ℃. [e] The reaction temperature is 125 ℃. [f] The reaction time is 6 h. [g] The reaction time is 24 h.

With the optimized reaction condition in hand, we examined the scope of isoxazolones, as shown in table 2. Template reaction can give the target product (**3a**) in the yield of 51%. If the reaction amount is amplified to 3.6 mmol, product can be obtained in the yield of 54% (0.48 g). When the phenyl ring of the isoxazolone has an electron-donating group such as alkyl group (**3b-3d**), methoxy group (**3e**) and dioxymethylene group (**3f**), the yields are similar to that of the template. Next, we examined some halogen-substituted substrates (**3g-3l**), and we can see that the reaction system of para-iodine-substituted isoxazolone is messy, which may be caused by the excessive activity of iodine. When a strong electron withdrawing group such as trifluoromethyl (**3n**) is present on the benzene ring, the yield is not much different from that containing the electron donating group, so it is speculated that electron effect of the reaction is not very important. Reaction can also occur when the benzene ring is changed to a naphthalene ring (**3m**). However, only trace amount of product can be detected accompanied by residual reactant and a slightly messy system when the heterocyclic skeleton (**3o**) isoxazole is involved. By changing the benzene ring to methyl (**3p**), as a result of the instability of **1p,** only traces of the product and 27% residual reactant could be observed.

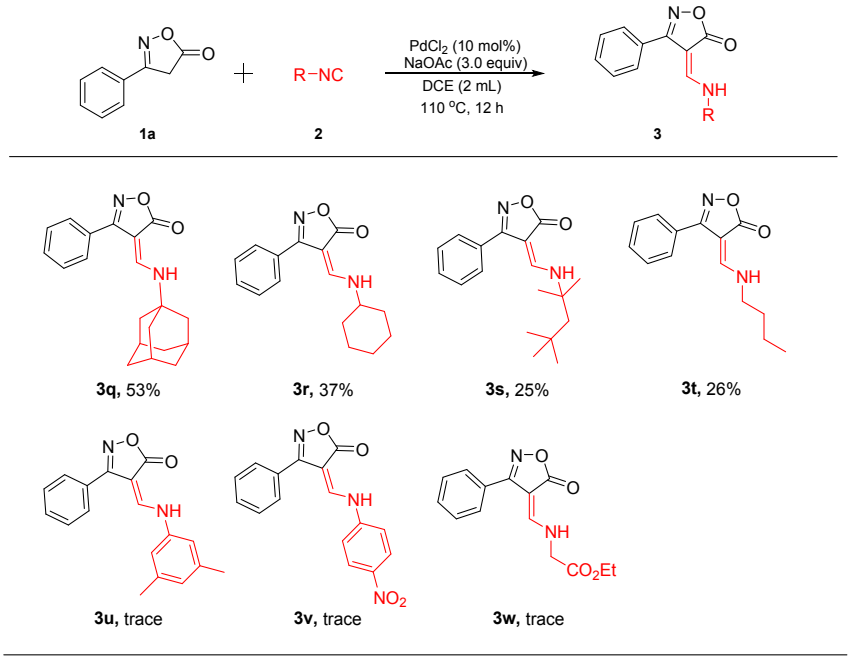
Table 2 Reactions of Substituted Isoxazolones with *tert*-butyl Isocyanide[a]



[a] Reaction conditions: **1a-p** (0.2 mmol), **2a** (0.4 mmol), $PdCl_2$ (10 mol%), DCE (2 mL), NaOAc (3 equiv), 110 ℃, 12 h.
[b] Reaction conditions: **1a** (3.6 mmol), **2a** (7.2 mmol), $PdCl_2$ (10 mol%), DCE (36 mL), NaOAc (3 equiv), 110 ℃, 12 h. Yields were isolated yields.

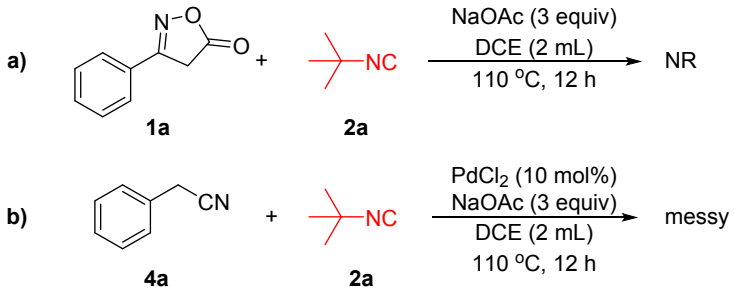
Subsequently, we used various isocyanides to react with 3-phenylisoxazol-5(4*H*)-one to investigate the universality of the reaction for the isocyanide substrate, as shown in table 3. It was found that target products (**3a, 3q-3t**) could be obtained when alkyl isocyanides are used. Unfortunately, when aryl isocyanides (**3u**, **3v**) were introduced, products and reactants are all of trace amount accompanied by several trace by-products. For trial of ethyl isocyanate (**3p**), beside traces of product, 20% remaining **1a** and other traces of by-products were found.

Table 3 Reactions of 3-Phenylisoxazol-5(*4H*)-one with Isocyanides[a]



[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $PdCl_2$ (10 mol%), DCE (2 mL), NaOAc (3 equiv), 110 ℃, 12 h. Yields were isolated yields.

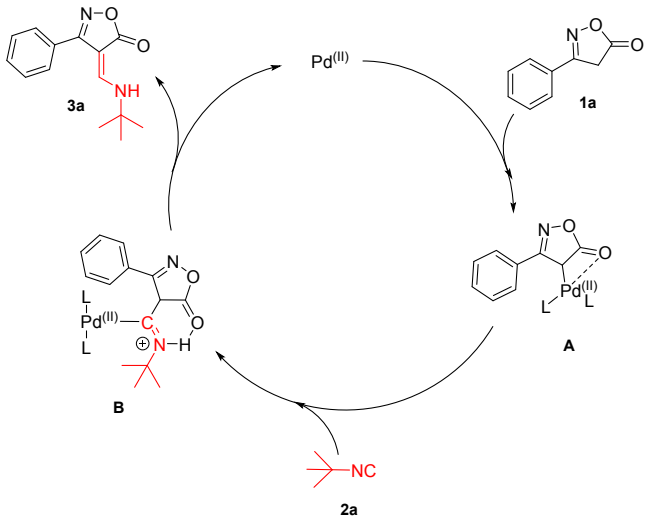
Scheme 2 Control Experiments



Reaction conditions: a) **1a** (0.2 mmol), **2a** (0.4 mmol), DCE (2 mL), NaOAc (3 equiv), 110 ℃, 12 h. b) **4a** (0.2 mmol), **2a** (0.4 mmol), $PdCl_2$ (10 mol%), DCE (2 mL), NaOAc (3 equiv), 110 ℃, 12 h.

To investigate the possible mechanism, a series of reactions were designed. As shown in scheme 2a, when $PdCl_2$ was removed, no reaction occurred which means palladium catalyst is indispensable when activating the C-H bond of methylene. Further, phenylacetonitrile **4a** was employed instead of 3-Phenylisoxazol-5(*4H*)-one **1a** (scheme 2b). As a result, the system was messy, indicating that not only the active methylene group but the oxygen atom was also important in this transformation. Besides, as reported that in DCE solvent a C-H form of **1a** was favoured[12], making our hypothetical more reasonable.

Scheme 3 Plausible Reaction Mechanism.



Based on our experiment results and documents related, a plausible mechanism was shown in scheme 3. First, palladium catalyst reacts with **1a** affords intermediate **A**. Next, the insertion of isocyandie **2a** to **A** furnishes intermediate **B**. The protonation of **B** gives the target product **3a** and releases palladium catalyst.

3. CONCLUSION

In summary, we developed a new method for the synthesis of 4-aminomethylidene isoxazolone derivates. This work provided a new strategy for the preparation of the enamines from the alkyl isocyanides with high atom economy. As supplement of former researchs, reaction of alkyl isocyanide was successfully achieved. Though yields are not high enough now, this work still has a promising future.

4. EXPERIMENTAL SECTION

1. General Information. All commerically available compounds were used without further purification, unless noted otherwise. Solvents for chromatography were analytical grade and used without further purification. Analytical thin-layer chromatography (TLC) was performed on silica gel, visualized by irradiation with UV light. 200-300 mesh silica gel was used for column chromatography. ^{1}H-NMR

and ^{13}C-NMR were recorded on a BRUKER 400 MHz spectrometer in $CDCl_3$. Chemical shifts (δ) were reported referenced to an internal tetramethylsilane standard or the $CDCl_3$ residual peak (δ 7.26)for ^{1}H NMR. Chemical shifts of ^{13}C NMR are reported relative to $CDCl_3$ (δ 77.16). Data are reported in the following order: chemical shift (δ) in ppm; multiplicities are indicated s (singlet), bs (broad singlet), d (doublet), t (triplet), m (multiplet); coupling constants (J) are in Hertz (Hz). IR spectra were recorded on a BRUKER VERTEX 70 spectrophotometer and are reported in terms of frequency of absorption (cm^{-1}). HRMS spectra were obtained by using BRUKER micrOTOF-Q III instrument with ESI source.

2.1 General procedure for the preparation of 1a-1p

Take **1a** as example, 3-phenylisoxazol-5(4*H*)-one(**1a**) were synthesized according to the methods of previous lectures without modifications.[13]

Procedure 1: To a suspension of NaH (0.5600 g, 23.3 mmol) in toluene (20 mL) was added acetophenone (0.58 mL, 5.00 mmol) , the resulting mixture was stirred at room temperature for 30 minutes. After that, $(MeO)_2CO$ (0.85 mL, 10 mmol) was added when the mixture was heated at 110℃ oil bath. After 12 hours, the reaction was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (3x20 mL). The combined organic layers were dried over Na_2SO_4 and solvent was removed under reduced pressure.

Procedure 2: A suspension of $NH_2OH{\cdot}HCl$ (0.5291 g, 7.51 mmol) and NaOAc (0.6214 g, 7.57 mmol) in ethanol (20 mL) was stirred at room temperature for 5 minutes, and then the product of last step dissolved in ethanol was added drop wisely. The mixture was heated at 78℃ oil bath over night. After cooling to room temperature, the suspension was concentrated in vacuo, and purified by flash column chromatography over a short plug of silica gel.

^{1}H, ^{13}C spectra data of **1a**,**1b**, **1e-i**, **1o** can refer to published document [9].

^{1}H, ^{13}C spectra data of **1m** can refer to published document [14].

^{1}H, ^{13}C spectra data of **1p** can refer to published document [15].

Substrates **1c**, **1d**, **1j**, **1k**, **1n** are newly synthesized, and the ^{1}H and ^{13}C spectra data is shown below.

2.2 General procedure for the preparation of isocyanides

Isocyanides were prepared according to the literatures methods with minor modifications.[16]

2.3 Experiment procedure

Take **3a** as example, 3-phenylisoxazol-5(4*H*)-one (**1a**) (0.2 mmol), $PdCl_2$ (10 mol%), NaOAc (3 equiv) was added in a schlenk tube. After protected with Ar atmosphere, DCE (2 mL) was added followed by the injection of *tert*-butyl isocyanide (**2a**) (2 equiv). At last, the schlenk tube was placed in oil bath at 110 ℃ for 12 h. When the reaction finished and cooled to room temperature, solvent was removed in vacuo, and purified by flash column chromatography over a short plug of silica gel to give the product **3a**.

3-(4-isopropylphenyl)isoxazol-5(4H)-one **(1c) Yield:** 74% (747.3 mg). Orange solid. M.p. 77.2 - 78.5 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.52 (m, 2H), 7.39 – 7.29 (m, 2H), 3.78 (s, 2H), 2.96 (hept, J = 6.9 Hz, 1H), 1.27 (d, J = 7.0 Hz, 6H) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 175.0, 163.1, 153.8, 127.4, 126.8, 125.3, 34.3, 34.2, 23.8 ppm. HRMS (ESI) *m/z*: calcd for $C_{12}H_{13}NO_2$ $[M+Na]^+$ 226.0838, found: 226.0838. IR (neat, v, cm^{-1}) = 2962, 2928, 2869, 1801 cm^{-1}.

3-(4-(tert-butyl)phenyl)isoxazol-5(4H)-one **(1d) Yield:** 57% (619.0 mg). Pale yellow solid. M.p. 101.5 - 102.3 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.55 (m, 2H), 7.52 – 7.44 (m, 2H), 3.77 (s, 2H), 1.34 (s, 9H) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 175.1, 163.1, 156.0, 126.5, 126.2, 124.8, 35.2, 34.1, 31.1 ppm. HRMS (ESI) *m/z*: calcd for $C_{13}H_{15}NO_2$ $[M+Na]^+$ 240.0995, found: 240.0995. IR (neat, v, cm^{-1}) = 2955, 1805, 1475 cm^{-1}.

3-(3-fluorophenyl)isoxazol-5(4H)-one **(1j) Yield:** 15% (135.5 mg). Red solid. M.p. 83.2 - 84.7 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.36 (m, 3H), 7.28 – 7.21 (m, 1H), 3.81 (s, 2H) ppm. ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 174.5, 162.9 (d, $J_{C\text{-}F}$ = 246.9 Hz), 162.4 (d, $J_{C\text{-}F}$ = 2.9 Hz), 131.1 (d, $J_{C\text{-}F}$ = 8.2 Hz), 129.7 (d, $J_{C\text{-}F}$ = 8.0 Hz), 122.7 (d, $J_{C\text{-}F}$ = 3.2 Hz), 119.3 (d, $J_{C\text{-}F}$ =21.2 Hz), 113.5 (d, $J_{C\text{-}F}$ = 23.3 Hz), 34.0 +ppm. HRMS (ESI) *m/z*: calcd for $C_9H_6FNO_2$ $[M+Na]^+$ 202.0275, found: 202.0276. IR (neat, v, cm^{-1}) = 2936, 1793, 1568 cm^{-1}.

3-(3-chlorophenyl)isoxazol-5(4H)-one **(1k) Yield:** 15% (148.0 mg). Red solid. M.p. 87.5 – 89.1 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.61 (m, 1H), 7.56 – 7.47 (m, 2H), 7.44 – 7.38 (m, 1H), 3.79 (s, 2H) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 174.5, 162.3, 135.4, 132.2, 130.6, 129.3, 126.6, 124.9, 33.9 ppm. HRMS (ESI) *m/z*: calcd for $C_9H_6ClNO_2$ $[M+Na]^+$ 217.9979, found: 217.9982. IR (neat, v, cm^{-1}) = 3073, 2959, 2926, 2849, 1792 cm^{-1}.

3-(3-(trifluoromethyl)phenyl)isoxazol-5(4H)-one **(1n) Yield:** 10% (107.9 mg). Red solid. M.p. 84.2 - 85.3 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.90 (m, 1H), 7.90 – 7.86 (m, 1H), 7.81 – 7.76 (m, 1H), 7.66 – 7.61 (m, 1H), 3.85 (s, 2H) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 174.3, 162.2, 131.9 (q, $J_{C\text{-}F}$ = 33.0 Hz), 130.0, 129.9 (d, $J_{C\text{-}F}$ = 0.9 Hz), 128.7 (q, $J_{C\text{-}F}$ = 3.6 Hz), 128.6, 123.5 (q, $J_{C\text{-}F}$ = 271.0 Hz), 123.5 (q, $J_{C\text{-}F}$ = 3.8 Hz), 33.8 ppm. HRMS (ESI) *m/z*: calcd for $C_{10}H_6F_3NO_2$ $[M+Na]^+$ 252.0243, found: 252.0245. IR (neat, v, cm^{-1}) = 3078, 2982, 2948, 2350, 1796 cm^{-1}.

(Z)-4-((tert-butylamino)methylene)-3-phenylisoxazol-5(4H)-one (3a) **Yield:** 51% (24.9 mg). Orange Solid. M.p. 120.2 - 123.1 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (d, J = 14.4 Hz, 1H, N-H), 7.62 (d, J = 14.6 Hz, 1H, alkenyl-H), 7.53 – 7.51 (m, 2H, Ar-H), 7.47 – 7.44 (m, 3H, Ar-H), 1.37 (s, 9H, ^{t}Bu-H) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 175.1 (carbonyl-C), 161.4 (imino-C), 149.3 (enamine-C), 130.4 (Ar-C), 129.3 (Ar-C), 129.0 (Ar-C), 127.8 (Ar-C), 89.1 (alkenyl-C), 55.0 (^{t}Bu-C), 29.7 (methyl-C) ppm. HRMS (ESI) *m/z*: calcd for $C_{14}H_{16}N_2O_2$ $[M+H]^+$ 245.1290, found: 245.1291. IR (neat, v, cm^{-1}) = 3320 (N-H), 2180, 2035, 1694, 1633 cm^{-1}.

(Z)-4-((tert-butylamino)methylene)-3-(p-tolyl)isoxazol-5(4H)-one (3b) **Yield:** 44% (22.7 mg). Orange Solid. M.p. 199.2 - 201.5 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (d, J = 13.8 Hz, 1H), 7.65 (d, J = 14.5 Hz, 1H), 7.46 – 7.44 (m, 2H), 7.31 – 7.29 (m, 2H), 2.41 (s, 3H), 1.41 (s, 9H) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 175.2, 161.4, 149.2, 140.6, 129.9, 127.7, 126.1, 89.3, 54.9, 29.7, 21.5 ppm. HRMS (ESI) *m/z*: calcd for $C_{15}H_{18}N_2O_2$ $[M+H]^+$ 259.1447, found: 259.1447. IR (neat, v, cm^{-1}) = 3206, 2970, 1693, 1626 cm^{-1}.

(Z)-4-((tert-butylamino)methylene)-3-(4-isopropylphenyl)isoxazol-5(4H)-one (3c) **Yield:** 41% (23.5 mg). White Solid. M.p. 183.7 - 185.5 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, J = 14.6 Hz, 1H), 7.67 (d, J = 14.6 Hz, 1H), 7.57 – 7.42 (m, 2H), 7.39 – 7.28 (m, 2H), 2.97 (hept, J = 6.9 Hz, 1H), 1.42 (s, 9H), 1.29 (d, J = 6.9 Hz, 6H) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 175.3, 161.4, 151.5, 149.3, 127.8, 127.4, 126.5, 89.3, 54.9, 34.2, 29.8, 24.0 ppm. HRMS (ESI) *m/z*: calcd for $C_{17}H_{22}N_2O_2$ $[M+H]^+$ 287.1760, found: 287.1760. IR (neat, v, cm^{-1}) = 3270, 2075, 1702,1633 cm^{-1}.

(Z)-3-(4-(tert-butyl)phenyl)-4-((tert-butylamino)methylene)isoxazol-5(4H)-one (3d) **Yield:** 45% (27.0 mg). Orange Solid. M.p. 166.4 - 168.5 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (d, J = 14.6 Hz, 1H), 7.69 (d, J = 14.6 Hz, 1H), 7.54 – 7.48 (m, 4H), 1.42 (s, 9H), 1.36 (s, 9H) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 175.3, 161.3, 153.8, 149.4, 127.5, 126.3, 126.2, 89.3, 55.0, 35.0, 31.3, 29.8 ppm. HRMS

(ESI) *m/z*: calcd for $C_{18}H_{24}N_2O_2$ $[M+Na]^+$ 323.1735, found: 323.1735. IR (neat, *v*, cm^{-1}) = 3360, 2958, 1702, 1637 cm^{-1}.

(Z)-4-((tert-butylamino)methylene)-3-(4-methoxyphenyl)isoxazol-5(4H)-one (3e) **Yield:** 37% (20.3 mg). Pale yellow Solid. M.p. 157.3 - 160.7 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (d, J = 13.2 Hz, 1H), 7.64 (d, J = 14.5 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.03 – 6.99 (m, 2H), 3.85 (s, 3H), 1.41 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 175.2, 161.3, 161.1, 149.3, 129.1, 121.3, 114.7, 89.4, 55.5, 54.9, 29.8 ppm. HRMS (ESI) *m/z*: calcd for $C_{15}H_{18}N_2O_3$ $[M+H]^+$ 275.1396, found: 275.1396. IR (neat, *v*, cm^{-1}) = 3204, 2979, 2968, 1699, 1634 cm^{-1}.

(Z)-3-(benzo[d][1,3]dioxol-5-yl)-4-((tert-butylamino)methylene)isoxazol-5(4H)-one (3f) **Yield:** 45% (25.9 mg). Orange Solid. M.p. 164.0 - 166.1 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ 9.41 (d, J = 14.7 Hz, 1H), 7.64 (d, J = 14.6 Hz, 1H), 7.06 – 6.99 (m, 2H), 6.92 – 6.90 (m, 1H), 6.03 (s, 2H), 1.41 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 175.1, 161.0, 149.5, 149.2, 148.5, 122.7, 122.0, 109.0, 108.1, 101.7, 89.3, 55.0, 29.8 ppm. HRMS (ESI) *m/z*: calcd for $C_{15}H_{16}N_2O_4$ $[M+Na]^+$ 311.1008, found: 311.1007. IR (neat, *v*, cm^{-1}) = 3225, 2975, 1979, 1717, 1633 cm^{-1}.

(Z)-3-(4-bromophenyl)-4-((tert-butylamino)methylene)isoxazol-5(4H)-one (3g) **Yield:** 44% (28.3 mg). Pale pink Solid. M.p. 188.5 - 191.1 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ 9.45 (d, J = 14.6 Hz, 1H), 7.66 – 7.59 (m, 3H), 7.48 – 7.40 (m, 2H), 1.42 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 175.0, 160.5, 149.1, 132.6, 129.3, 128.0, 124.9, 89.0, 55.1, 29.7 ppm. HRMS m/z: calcd for $C_{14}H_{15}BrN_2O_2$ $[M+H]^+$ 323.0395, found: 323.0398. IR (neat, *v*, cm^{-1}) = 3213, 1702, 1651, 1517 cm^{-1}.

(Z)-4-((tert-butylamino)methylene)-3-(4-chlorophenyl)isoxazol-5(4H)-one (3h) **Yield:** 37% (20.6 mg). Pink Solid. M.p. 183.0 - 185.1 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ 9.45 (d, J = 14.5 Hz, 1H), 7.62 (d, J = 14.6 Hz, 1H), 7.52 – 7.45 (m, 4H), 1.42 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 175.0, 160.5, 149.1, 136.6, 129.6, 129.1, 127.5, 89.0, 55.1, 29.7 ppm. HRMS (ESI) *m/z*: calcd for $C_{14}H_{15}ClN_2O_2$ $[M+H]^+$ 279.0900, found: 279.0897. IR (neat, *v*, cm^{-1}) = 3219, 2915, 1704, 1652 cm^{-1}.

(Z)-4-((tert-butylamino)methylene)-3-(3-fluorophenyl)isoxazol-5(4H)-one (3j) **Yield:** 39% (20.4 mg). Pale yellow Solid. M.p. 162.3 - 165.9 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ 9.47 (d, J = 12.3 Hz, 1H), 7.65 (d, J = 14.5 Hz, 1H), 7.53 – 7.43 (m, 1H), 7.39 – 7.32 (m, 1H), 7.32 – 7.27 (m, 1H), 7.24 – 7.17 (m, 1H), 1.43 (s, 10H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 175.0, 164.3, 161.8, 160.3 (d, $J_{C\text{-}F}$ = 2.3 Hz), 149.2, 131.0 (d, $J_{C\text{-}F}$ = 8.3 Hz), 123.5 (d, $J_{C\text{-}F}$ = 3.2 Hz), 117.4 (d, $J_{C\text{-}F}$ = 21.0 Hz), 114.9 (d, $J_{C\text{-}F}$ = 22.8 Hz), 88.8, 55.2, 29.7 ppm. HRMS (ESI) *m/z*: calcd for $C_{14}H_{15}FN_2O_2$ $[M+Na]^+$ 285.1015, found: 285.1011. IR (neat, *v*, cm^{-1}) = 3255, 3222, 2982, 1698, 1643 cm^{-1}.

(Z)-4-((tert-butylamino)methylene)-3-(3-chlorophenyl)isoxazol-5(4H)-one (3k) **Yield:** 37% (20.6 mg). Pale pink Solid. M.p. 164.3 - 166.2 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ 9.46 (d, J = 13.3 Hz, 1H), 7.63 (d, J = 14.6 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.50 – 7.45 (m, 1H), 7.45 – 7.38 (m, 2H), 1.42 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 175.0, 160.2, 149.1, 135.3, 130.8, 130.6, 130.5, 127.9, 125.9, 88.9, 55.2, 29.7 ppm. HRMS (ESI) *m/z*: calcd for $C_{14}H_{15}ClN_2O_2$ $[M+H]^+$ 279.0900, found: 279.0892. IR (neat, *v*, cm^{-1}) = 3233, 2059, 2013, 1695,1639 cm^{-1}.

(Z)-4-((tert-butylamino)methylene)-3-(3,4-difluorophenyl)isoxazol-5(4H)-one (3l) **Yield:** 34% (19.0 mg). Orange Solid. M.p. 168.0-170.1 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ 9.49 (d, J = 14.9 Hz, 1H), 7.65 (d, J = 14.6 Hz, 1H), 7.49 – 7.37 (m, 1H), 7.35 – 7.23 (m, 2H), 1.45 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 174.9, 159.6, 151.2, 149.1, 129.7, 126.0, 124.2, 117.7, 116.5, 88.8, 55.3, 29.7 ppm. HRMS (ESI) *m/z*: calcd for $C_{14}H_{14}F_2N_2O_2$ $[M+H]^+$ 281.1102, found: 281.1102. IR (neat, *v*, cm^{-1}) = 3217, 2972, 1695, 1634 cm^{-1}.

(Z)-4-((tert-butylamino)methylene)-3-(naphthalen-2-yl)isoxazol-5(4H)-one (3m) **Yield:** 36% (21.2 mg). Pink Solid. M.p. 154.9 - 156.2 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ 9.46 (d, J = 14.6 Hz, 1H), 8.05 – 8.04 (m, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.94 – 7.87 (m, 2H), 7.75 – 7.72 (m, 1H), 7.67 – 7.65 (m, 1H), 7.61 – 7.53 (m, 2H), 1.42 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 175.2, 161.5, 149.4, 134.1, 133.3, 129.2, 128.6, 128.0, 127.7, 127.5, 127.0, 126.4, 124.8, 89.5, 55.0, 29.8 ppm. HRMS (ESI) *m/z*: calcd for $C_{18}H_{18}N_2O_2$ $[M+Na]^+$ 317.1266, found: 317.1266. IR (neat, *v*, cm^{-1}) = 3256, 3212, 2964, 2920, 1691, 1639 cm^{-1}.

(Z)-4-((tert-butylamino)methylene)-3-(3-(trifluoromethyl)phenyl)isoxazol-5(4H)-one (3n) **Yield:** 40% (25.0 mg). Pale yellow Solid. M.p. 167.2 - 169.1 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ 9.47 (d, J = 14.4 Hz, 1H), 7.82 (s, 1H), 7.76 – 7.74 (m, 2H), 7.68 – 7.59 (m, 2H), 1.42 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 174.9, 160.2, 149.0, 131.9, 131.6, 131.0, 129.9, 127.1 (q, $J_{C\text{-}F}$ = 3.6 Hz), 124.7 (q, $J_{C\text{-}F}$ = 3.8 Hz), 123.8 (d, $J_{C\text{-}F}$ = 270.1 Hz), 88.8, 55.3, 29.7 ppm. HRMS (ESI) *m/z*: calcd for $C_{15}H_{15}F_3N_2O_2$ $[M+Na]^+$ 335.0983, found: 335.0988. IR (neat, *v*, cm^{-1}) = 3277, 2962, 2358, 2190, 1699, 1634 cm^{-1}.

(E)-4-((((3s,5s,7s)-adamantan-1-yl)amino)methylene)-3-phenylisoxazol-5(4H)-one (3q) **Yield:** 53% (34.2 mg). White Solid. M.p. 207.4 - 209.6 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ 9.37 (d, J = 14.7 Hz, 1H), 7.66 (d, J = 14.6 Hz, 1H), 7.58 – 7.55 (m, 2H), 7.53 – 7.48 (m, 3H), 2.24 – 2.19 (m, 3H), 1.87 (d, J = 2.9 Hz, 6H), 1.75 (d, J = 12.8 Hz, 3H), 1.66 (d, J = 11.8 Hz, 3H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 175.2, 161.5, 148.5, 130.4, 129.3, 129.1, 127.9, 89.1, 55.1, 42.9, 35.7, 29.3 ppm. HRMS (ESI) *m/z*: calcd for $C_{20}H_{22}N_2O_2$ $[M+H]^+$ 323.1760, found: 323.1760. IR (neat, *v*, cm^{-1}) = 3206, 2908, 2175, 1699, 1634 cm^{-1}.

(Z)-4-((cyclohexylamino)methylene)-3-phenylisoxazol-5(4H)-one (3r) **Yield:** 37% (20.0 mg). Yellow Solid. M.p. 167.9 - 169.2 ℃.^1H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.62 (d, J = 14.3 Hz, 1H), 7.58 – 7.56 (m, 2H), 7.50 – 7.47 (m, 3H), 3.43 – 3.26 (m, 1H), 2.00 (d, J = 9.7 Hz, 2H), 1.84 (dd, J = 9.3, 3.6 Hz, 2H), 1.68 – 1.24 (m, 6H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 175.2, 161.4, 151.5, 130.4, 129.2, 129.0, 127.9, 89.4, 59.1, 33.7, 24.9, 24.5 ppm. HRMS (ESI) *m/z*: calcd for $C_{16}H_{18}N_2O_2$ $[M+Na]^+$ 293.1266, found: 293.1251. IR (neat, *v*, cm^{-1}) = 3328, 2362, 1692, 1633 cm^{-1}.

(Z)-3-phenyl-4-(((2,4,4-trimethylpentan-2-yl)amino)methylene)isoxazol-5(4H)-one (3s) **Yield:** 25% (15.0 mg). Orange Solid. M.p. 105.3 - 107.3 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, J = 14.6 Hz, 1H), 7.62 (d, J = 14.6 Hz, 1H), 7.58 – 7.56 (m, 2H), 7.54 – 7.49 (m, 3H), 1.66 (s, 2H), 1.45 (s, 6H), 1.01 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 161.4, 149.1, 130.4, 129.3, 129.1, 127.8, 89.1, 58.4, 55.4, 31.9, 31.5, 29.6 ppm. HRMS (ESI) *m/z*: calcd for $C_{18}H_{24}N_2O_2$ $[M+H]^+$ 301.1916, found: 301.1915. IR (neat, *v*, cm^{-1}) = 2959, 2904, 1687, 1633 cm^{-1}.

(Z)-4-((butylamino)methylene)-3-phenylisoxazol-5(4H)-one (3t) **Yield:** 26% (12.7 mg). Gray Solid. M.p. 186.2 - 188.1 ℃. ^1H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 7.71 – 7.67 (m, 2H), 7.55 – 7.47 (m, 3H), 6.03 (d, J = 2.2 Hz, 1H), 3.94 (t, 2H), 1.64 (p, J = 7.7 Hz, 2H), 1.39 (h, J = 7.4 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 163.5, 153.4, 150.2, 131.66, 131.5, 129.3, 126.5, 99.0, 40.6, 29.9, 20.4, 13.9 ppm. HRMS (ESI) *m/z*: calcd for $C_{14}H_{16}N_2O_2$ $[M+H]^+$ 245.1290, found: 245.1291. IR (neat, *v*, cm^{-1}) = 3229, 2035, 1787, 1687 cm^{-1}.

ASSOCIATED CONTENT

Supporting Information Available.

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

Copies o ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of the synthetic products (PDF)

Crystallographic data for **3a** (CIF)

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