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EFFICIENT SYNTHESIS OF 4-SUBSTITUTED 4,5-DIHYDROISOXAZOL-3-OLS FROM MORITA-BAYLIS-HILLMAN BROMIDES

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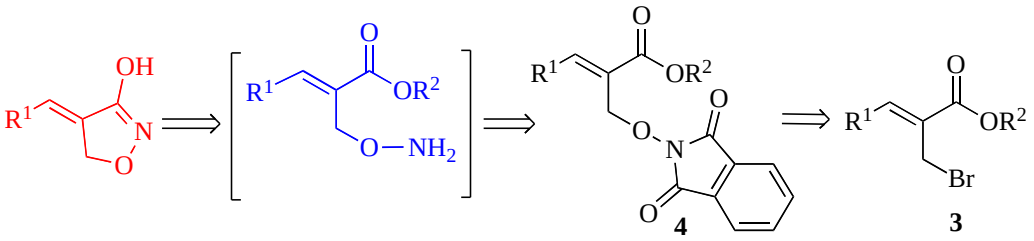
Abstract –An efficient synthesis of 4-substituted 4,5-dihydroisoxazol-3-ols was achieved with high regioselectivities and satisfactory yields *via* addition of *N*-hydroxyphthalimide to Morita-Baylis-Hillman (MBH) bromides with ester moiety, followed by hydrazinolysis and intramolecular cyclization. Surprised, the unexpected isoxazolidine-4-carbonitrile was obtained when using MBH bromide with nitrile moiety as substrate under the similar conditions.

INTRODUCTION

The isoxazol-3-ol framework belongs to an important class of heterocyclic compounds possessing pharmacological properties such as $GABA_A$ receptor antagonists[1-3] and (*S*)-glutamate receptor ligands.[4] Although, a lot of synthetic routes have been achieved for preparation of isoxazol-3-ols,[2,5] none of these methods was involved in the synthesis of 4-substituted 4,5-dihydroisoxazol-3-ols.

In continuation of our interest in the field of Baylis-Hillman chemistry as a source for useful organic transformation methodologies,[6-12] and inspired by Reddy's method[13] for the preparation of the intermediate **4** *via* palladium-catalyzed addition of *N*-hydroxyphthalimide to MBH acetate adducts, we



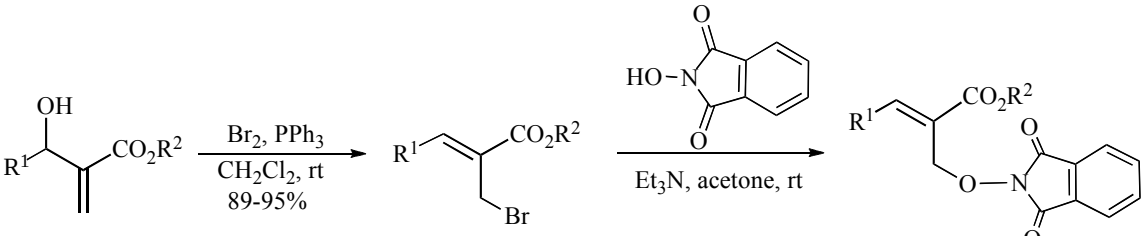
Scheme 1. Retrosynthetic approach for the synthesis of 4,5-dihydroisoxazol-3-ols

proposed that this intermediate might be transformed into 4-substituted 4,5-dihydroisoxazol-3-ols **1** (Scheme 1).

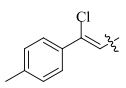
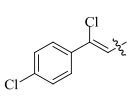
RESULTS AND DISCUSSION

Initially, we tried to prepare the intermediate **4** by treatment of *N*-hydroxyphthalimide with MBH acetate adducts in the presence of K_2CO_3, Et_3N or DBU, however, no reaction occurred even under reflux condition. Fortunately, we had successfully converted the MBH adducts **2** into the corresponding MBH bromides **3** in high to excellent yields using Br_2/PPh_3 system under mild condition, especially for the synthesis of the new type MBH bromides **3h-i**.[12] Then we designed a convenient route to intermediate **4** by addition of *N*-hydroxyphthalimide to MBH bromides. When the MBH bromide **3a** was mixed with *N*-hydroxyphthalimide in the presence of Et_3N in acetone at room temperature, the starting materials were consumed within 30 minutes and the desired product **4a** could be accomplished in excellent yields (97%) with high regioselectivity. Encouraged by this result, various MBH bromides **3** with ester moiety were screened. In all cases, the reaction proceeded smoothly to afford the products **4** in good to excellent yields with high regioselectivity (Table 1).

Table 1. Synthesis of intermediate **4** from Baylis-Hillman adduct **2**



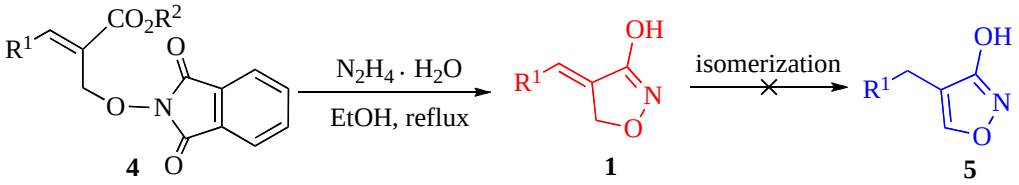
2 **3** **4**

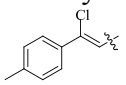
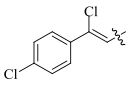
Entry	R^1	R^2	Time	Product	Yield (%)[a]
1	2-Cl-6-FC_6H_3	Me	30 min	**4a**	97
2	2-Cl-6-FC_6H_3	Et	5.0 h	**4b**	91
3	3-$O_2NC_6H_4$	Me	15 min	**4c**	99
4	3-ClC_6H_4	Me	35 min	**4d**	95
5	3,4-$Me_2C_6H_3$	Me	40 min	**4e**	94
6	Et	Et	8.0 h	**4f**	80
7	2-furyl	Me	30 min	**4g**	97
8		Et	45 min	**4h**	97
9		Me	10 min	**4i**	99

[a] Isolated yields based on MBH bromides **3**.

With various intermediates **4** in hand, we then investigated their transformation into the target products 4-substituted 4,5-dihydroisoxazol-3-ols **1** with the aid of hydrazine hydrate. Treatment of compound **4a** with hydrazine hydrate in ethanol under reflux condition for a short time, the hydroxylamine derivatives generated *in situ* could be transformed into **1a** *via* intramolecular cyclization. The side product 2,3-dihydrophthalazine-1,4-dione could be easily removed by filtration and the filtrate was condensed to produce the target compound **1a**, which was identified by comparison of its ^{1}H NMR spectra with that of the similar compounds.[14-15] However, attempt to isomerize further **1a** into isoxazol-3-ol **5a** under various conditions including acidic, basic or solvent-free conditions at high temperature was failed.

Table 2. Synthesis of 4-substituted 4,5-dihydroisoxazol-3-ols **1**

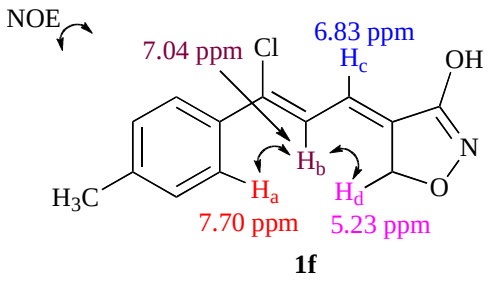


Entry	R^1	R^2	Time (min)	Product	Yield (%)[a]
1	2-Cl-6FC_6H_3	Me	50	**1a**	79
2	2-Cl-6FC_6H_3	Et	120	**1a**	76
3	3-$O_2NC_6H_4$	Me	50	**1b**	73
4	3-ClC_6H_4	Me	50	**1c**	82
5	3,4-$Me_2C_6H_3$	Me	35	**1d**	88
6	Et	Et	120	**-**	-
7	2-furyl	Me	35	**1e**	87
8		Et	80	**1f**	79
9		Me	60	**1g**	76

[a] Isolated yields based on **4**.

Then under similar conditions, various intermediates **4** with ester moieties (-CO_2Me, -CO_2Et) were investigated and the results are summarized in Table 2. It was found that most of compounds **4** could provide the desired cycloadducts **1** with high regioselectivities in moderate to good yields. However, when the intermediate **4f** derived from aliphatic aldehydes was tested under similar conditions, the reaction was very complex and the desired product was not obtained. In addition, the configuration of **1f**

derived from new type MBH bromide was confirmed by the ^{1}H NMR and NOE data. ^{1}H NMR spectra showed four typical chemical shifts of H_a (7.70), H_b (7.04), H_c (6.83), and H_d (5.23). It was found that

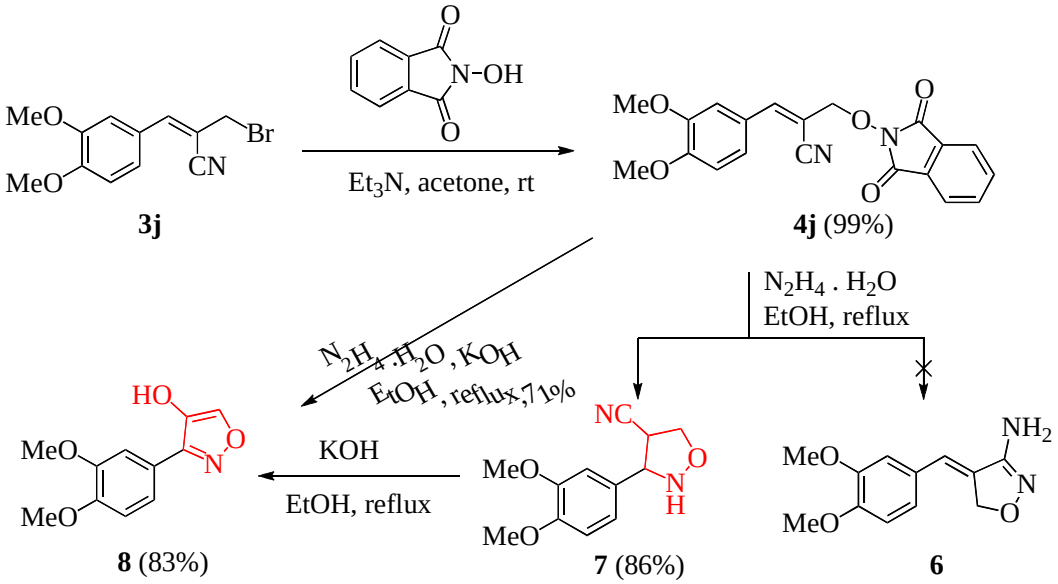


1f

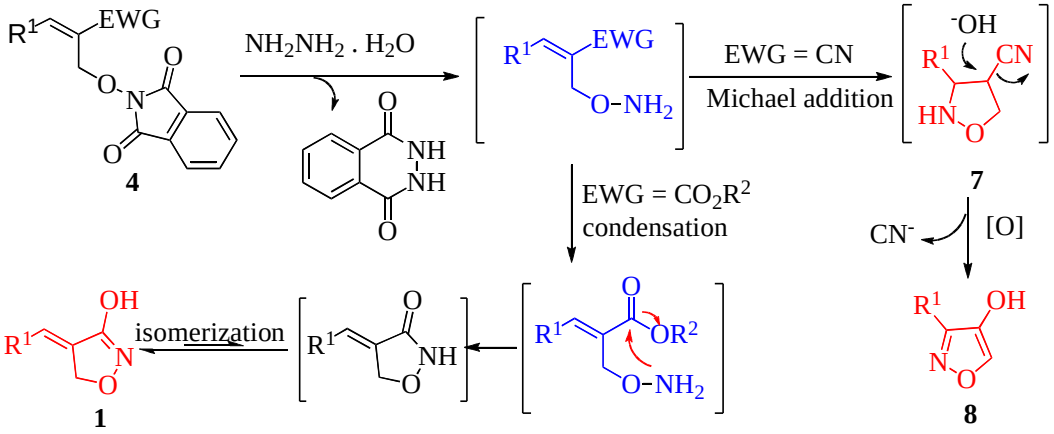
Figure 1

large NOE existed between H_a and H_b, H_b and H_d, respectively, while no evident NOE was observed between H_b and H_c or H_c and H_d. So the compound **1f** should be (*Z,Z*)-isomer (Figure 1).

To examine further the generality of the reaction and its applicability to the allyloxy phthalimides with nitrile moiety (Scheme 2), the compound **4j** derived from bromide **3j** was tried to mix with hydrazine hydrate under the standard condition, the unexpected product **7** instead of the desired product **6** was obtained in 86 % yield, which was identified by ^{1}H NMR, ^{13}C NMR, MS and HRMS. Interestingly, when compound **7** was treated with KOH solution, or when **4j** reacted with hydrazine hydrate in a KOH solution, 3-(3,4-dimethoxyphenyl)isoxazol-4-ol **8** was obtained with 83% and 71% yields, respectively. According to the above results, a possible mechanism for the formation of 4,5-dihydroisoxazol-3-ols **1** and the unexpected product **8** was outlined in Scheme 3.



Scheme 2. Synthesis of the unexpected products **7** and **8** from MBH bromide **3j**



Scheme 3. Proposed mechanism for the formation of **1**, **7** and **8**.

In conclusion, we have developed a simple and novel protocol for the transformation of MBH bromides into 4-substituted 4,5-dihydroisoxazol-3-ols with satisfactory yields *via* addition of *N*-hydroxyphthalimide to MBH bromides with ester moiety, followed by hydrazinolysis and intramolecular cyclization. Merits of the present process are easy available starting materials, simple experimental procedure, environmental friendliness and high yields.

EXPERIMENTAL

Melting points were determined by Büchi B-540 melting point apparatus and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian 400-MHz spectrometer. Mass spectra were obtained on a Thermo Finnigan LCQ-Advantage spectrometer (ESI, APCI) or a Finnigan Trace DSQ spectrometer (EI, CI). HRMS was carried out on an APEX (Bruker) mass III spectrometer.

General Procedure for Synthesis of Morita-Baylis-Hillman Bromides 3:[12]

To a stirring solution of Ph_3P (4.0 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added Br_2 (4.0 mmol) dropwise, followed by dropwise addition a solution of MBH adducts **2** (4.0 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at rt for 30 min. Then the reaction was quenched with 20% aqueous $Na_2S_2O_3$ solution (5 mL) and extracted with a mixture of petroleum ether-EtOAc (v/v = 4/1) (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford **3**, which can be used without further purification. An analytically pure sample can be obtained by flash column chromatography on silica gel (petroleum ether : EtOAc = 8:1).

(*E*)-2-(Bromomethyl)-3-(3,4-dimethoxyphenyl)acrylonitrile (3j)

Pale yellow solid; mp 107.1-108.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 2.0 Hz, 1H), 7.25 (dd,

J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 7.13 (s, 1H), 6.89 (d, J = 8.4 Hz, 1H), 4.23 (s, 2H), 3.94 (s, 6H). MS (CI): *m/z* (%) = 282 (100) [M^++1]. HRMS calculated for $C_{12}H_{12}BrNO_2$ [M^+]: 281.0051. Found: 281.0053.

General Procedure for Synthesis of compounds 4:

To a suspension of *N*-hydroxyphthalimide (3.0 mmol) in acetone (15 mL) was added triethylamine (3.0 mmol) in one portion, after stirred at rt for 10 min, Morita-Baylis-Hillman bromide **3** (3.0 mmol) was added and the reaction was stirred at rt. After complete conversion (monitored by TLC), the mixture was poured into 50 mL of ice water. The precipitate was filtered and washed with water (3 × 10 mL). The solid was compressed and washed with petroleum ether (3 × 15 mL) and dried under vacuum to afford **4**, which was used without further purification.

(*E*)-Methyl 3-(2-chloro-6-fluorophenyl)-2-((1,3-dioxoisoindolin-2-yloxy)methyl)acrylate (4a)

Off white power; mp 119.9-120.5 ^oC. IR (KBr): 1716, 1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (s, 4H), 7.67 (s, 1H), 7.27-7.21 (m, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.94 (t, J = 8.4 Hz, 1H), 4.94 (s, 2H), 3.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 163.5 (2×CO), 159.0 (d, J = 248.7 Hz), 136.9, 134.6 (2×CH, CH), 131.6, 130.1 (d, J = 9.1 Hz), 129.1 (2×C), 125.5, 123.6 (2×CH), 121.6 (d, J = 18.9 Hz), 114.7 (d, J = 21.9 Hz), 71.7, 53.0. MS (ESI): *m/z* (%) = 412 (100) $[M+Na]^+$. HRMS calculated for $C_{19}H_{13}ClFNO_5Na$ $[M+Na]^+$: 412.0364. Found: 412.0371.

(*E*)-Ethyl 3-(2-chloro-6-fluorophenyl)-2-((1,3-dioxoisoindolin-2-yloxy)methyl)acrylate (4b)

White power; mp 83.5-84.7 ^oC. IR (KBr): 1728, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (s, 4H), 7.67 (s, 1H), 7.24-7.22 (m,1H), 7.02 (d, J = 8.0 Hz, 1H), 6.94 (t, J = 8.0 Hz, 1H), 4.94 (s, 2H), 4.44 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 163.1 (2×CO), 158.8 (d, J = 248.7 Hz), 136.2, 134.3, 134.2 (2×CH), 131.7, 130.7 (d, J = 9.8 Hz), 128.9 (2×C), 125.1 (d, J = 3.1 Hz), 123.3 (d, J = 22.0 Hz, 2×CH), 121.5 (d, J = 18.9 Hz), 114.3 (d, J = 22.7 Hz), 71.4 (d, J = 4.5 Hz), 61.6, 14.1. MS (ESI): *m/z* (%) = 426 (100) $[M+Na]^+$. HRMS calculated for $C_{20}H_{15}ClFNO_5Na$ $[M+Na]^+$: 426.0520. Found: 426.0520.

(*E*)-Methyl 2-((1,3-dioxoisoindolin-2-yloxy)methyl)-3-(3-nitrophenyl)acrylate (4c)

White power; mp 173.7-174.7 ^oC. IR (KBr): 1724, 1519 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 2.0 Hz, 1H), 8.28-8.26 (m, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.15 (s, 1H), 7.83 (dd, J_1 = 3.2 Hz, J_2 = 5.6 Hz, 2H), 7.77 (dt, J_1 = 3.2 Hz, J_2 = 5.6 Hz, 2H), 7.70 (t, J = 8.0 Hz, 1H), 5.06 (s, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 163.2 (2×CO), 148.4, 145.3, 135.5, 135.4, 134.5 (2×CH), 130.0, 128.8 (2×C),

128.1, 124.6, 124.3, 123.5 (2×CH), 70.9, 52.7. MS (ESI): *m/z* (%) = 421 (100) $[M+K]^+$. HRMS calculated for $C_{19}H_{14}N_2O_7K$ $[M+K]^+$: 421.0438. Found: 421.0427.

(*E*)-Methyl 3-(3-chlorophenyl)-2-((1,3-dioxoisoindolin-2-yloxy)methyl)acrylate (4d)

White power; mp 137.1-137.9 °C. IR (KBr): 1739, 1625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.84-7.81 (m, 2H), 7.78-7.74 (m, 2H), 7.62-7.60 (m, 1H), 7.56 (s, 1H), 7.42-7.39 (m, 2H), 5.08 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 163.2 (2×CO), 146.5, 135.6, 134.7, 134.4 (2×CH), 130.1, 129.9, 129.6, 128.8 (2×C), 128.0, 126.7, 123.5 (2×CH), 71.2, 52.5. MS (ESI): *m/z* (%) = 394 (100) $[M+Na]^+$. HRMS calculated for $C_{19}H_{14}ClNO_5Na$ $[M+Na]^+$: 394.0458. Found: 394.0463.

(*E*)-Ethyl 3-(3,4-dimethylphenyl)-2-((1,3-dioxoisoindolin-2-yloxy)methyl)acrylate (4e)

White power; mp 145.5-147.2 °C. IR (KBr): 1731, 1624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.83-7.81 (m, 2H), 7.75-7.73 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 5.14 (s, 2H), 3.83 (s, 3H), 2.30 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 163.3 (2×CO), 148.6, 139.2, 137.2, 134.3 (2×CH), 131.5, 131.1, 130.0, 128.9 (2×C), 127.8, 123.9, 123.4 (2×CH), 71.8, 52.3, 19.8, 19.6. MS (ESI): *m/z* (%) = 388 (100) $[M+Na]^+$. HRMS calculated for $C_{22}H_{21}NO_5Na$ $[M+Na]^+$: 388.1161. Found: 388.1155.

(*E*)-Ethyl 2-((1,3-dioxoisoindolin-2-yloxy)methyl)pent-2-enoate (4f)

White power; mp 62.9-63.8 °C. IR (KBr): 1723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.84-7.81 (m, 2H), 7.77-7.74 (m, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 5.02 (s, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 2.41 (q, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 163.4 (2×CO), 153.7, 134.4 (2×CH), 128.8 (2×C), 125.6, 123.4 (2×CH), 70.4, 61.0, 22.3, 14.1, 13.1. MS (ESI): m/z (%) = 326 (100) $[M+Na]^+$. HRMS calculated for $C_{16}H_{17}NO_5Na$ $[M+Na]^+$: 326.1004. Found: 326.1013.

(*E*)-Methyl 2-((1,3-dioxoisoindolin-2-yloxy)methyl)-3-(furan-2-yl)acrylate (4g)

Off white power; mp 124.8-125.4 °C. IR (KBr): 1739, 1621 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.79-7.75 (m, 2H), 7.72-7.68 (m, 2H), 7.67 (s, 1H), 7.51 (d, *J* = 1.6 Hz, 1H), 6.87 (d, *J* = 3.2 Hz, 1H), 6.43 (q, *J* = 1.6 Hz, 1H), 5.41 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 163.5 (2×CO), 150.0, 145.9, 134.2 (2×CH), 132.0, 128.7 (2×C), 123.3 (2×CH), 121.0, 118.9, 112.5, 71.7, 52.4. MS (ESI): *m/z* (%) = 350 (100) $[M+Na]^+$. HRMS calculated for $C_{17}H_{13}NO_6Na$ $[M+Na]^+$: 350.0641. Found: 350.0633.

(2*E*,4*Z*)-Ethyl 5-chloro-2-((1,3-dioxoisoindolin-2-yloxy)methyl)-5-*p*-tolylpenta-2,4-dienoate (4h)

Yellow power; mp 158.0-158.6 °C. IR (KBr): 1736, 1599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 11.2 Hz, 1H), 7.82-7.78 (m, 2H), 7.74-7.70 (m, 4H), 7.50 (d, *J* = 11.2 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 5.18 (s, 2H), 4.33 (q, *J* = 6.8 Hz, 2H), 2.41 (s, 3H), 1.37 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 163.7 (2×CO), 144.0, 142.0, 141.1, 134.7 (2×CH), 134.2, 129.6 (2×CH), 129.1 (2×C), 127.3 (2×CH), 125.7, 123.8 (2×CH), 119.2, 71.2, 61.6, 21.6, 14.5. MS (ESI): *m/z* (%) = 426 (100) $[M^+ + 1]$. HRMS calculated for $C_{23}H_{20}ClNO_5$ $[M^+]$: 425.1030. Found: 425.1041.

(2*E*,4*Z*)-Methyl 5-chloro-5-(4-chlorophenyl)-2-((1,3-dioxoisoindolin-2-yloxy)methyl)penta-2,4-dienoate (4i)

Yellow power; mp 207.9-208.3 °C. IR (KBr): 1733, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 11.2 Hz, 1H), 7.83-7.72 (m, 6H), 7.61 (d, *J* = 11.2 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 5.17 (s, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 163.4 (2×CO), 142.1 141.5, 136.4, 135.1, 134.5 (2×CH), 128.8 (2×C, 2×CH), 128.3 (2×CH), 126.0, 123.6 (2×CH), 120.3, 70.9, 52.5. MS (ESI): *m/z* (%) = 454 (100) $[M+Na]^+$. HRMS calculated for $C_{21}H_{15}C_{l2}NO_5Na$ $[M+Na]^+$: 454.0225. Found: 454.0218.

(*E*)-3-(3,4-Dimethoxyphenyl)-2-((1,3-dioxoisoindolin-2-yloxy)methyl)acrylonitrile (4j)

Pale yellow power; mp 163.7-164.5 °C. IR (KBr): 2215, 1732, 1518 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, J_1 = 3.2 Hz, J_2 = 5.6 Hz, 2H), 7.76 (dd, J_1 = 3.2 Hz, J_2 = 5.6 Hz, 2H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.27 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H), 7.25 (s, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 4.91 (s, 2H), 3.94 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3 (2×CO), 151.9, 149.9, 149.0, 134.6 (2×CH), 128.6 (2×C), 125.3, 124.9, 123.7 (2×CH), 118.0, 110.73, 110.66, 101.1, 78.8, 55.9 (2×OCH_3). MS (ESI): *m/z* (%) = 387 (100) $[M+Na]^+$. HRMS calculated for $C_{20}H_{16}N_2O_5Na$ $[M+Na]^+$: 387.0957. Found: 387.0946.

General Procedure for Synthesis of 4,5-dihydroisoxazol-3-ols 1:

To a stirred solution of intermediates **4** (1.0 mmol) in EtOH (10 mL) was added 50% hydrazine hydrate (4.0 mmol) at rt, the solution rapidly became bright yellow, and a precipitate was formed. The reaction mixture was refluxed for a given time, cooled to rt and adjusted to 3-4 using HCl (2 M)/AcOH and then filtered. The filtrate was evaporated under vacuum. The crude product was purified by silica gel column chromatography using (petroleum ether: EtOAc = 4 : 1, containing 1% AcOH) as eluent to afford **1**.

(*E*)-4-(2-Chloro-6-fluorobenzylidene)-4,5-dihydroisoxazol-3-ol (1a)

Off white power; mp 173.4-174.4 °C. IR (KBr): 3445, 1698 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ

12.04 (br s, 1H, OH), 7.51-7.43 (m, 2H, ArH), 7.36-7.31 (m, 1H, ArH), 6.91 (s, 1H, CH), 4.96 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2, 159.4 (d, J = 248.8 Hz), 136.7, 133.9 (d, J = 5.3 Hz), 131.2 (d, J = 9.9 Hz), 125.8 (2×C), 121.4 (d, J = 18.9 Hz), 115.1 (d, J = 22.7 Hz), 71.5 (d, J = 16.0 Hz). MS (ESI): *m/z* (%) = 226 (100) [M^+-1]. HRMS calculated for $C_{10}H_7ClFNO_2$ [M^+]: 227.0149. Found: 227.0153.

(*E*)-4-(3-Nitrobenzylidene)-4,5-dihydroisoxazol-3-ol (1b)

Off white power; mp 245.0-245.6 °C. IR (KBr): 3431, 1659 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.97 (br s, 1H, OH), 8.22 (s, 1H, ArH), 8.19 (s, 1H, ArH), 7.81 (d, J = 8.0 Hz, 1H, ArH), 7.74 (t, J = 8.0 Hz, 1H, ArH), 7.06 (s, 1H, CH), 5.41 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.8, 148.2, 136.6, 134.8, 134.0, 130.4, 123.5, 122.8, 121.5, 71.6. MS (ESI): *m/z* (%) = 219 (100) [M^+-1]. HRMS calculated for $C_{10}H_8N_2O_4$ [M^+]: 220.0484. Found: 220.0471.

(*E*)-4-(3-Chlorobenzylidene)-4,5-dihydroisoxazol-3-ol (1c)

White power; mp 167.3-168.5 °C. IR (KBr): 3446, 1654 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.87 (br s, 1H, OH), 7.50-7.42 (m, 3H, ArH), 7.33 (d, J = 7.6 Hz, 1H, ArH), 6.91 (s, 1H, CH), 5.34 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.0, 137.0, 133.7, 132.5, 130.7, 128.7, 128.3, 127.4, 122.6, 71.5. MS (ESI): *m/z* (%) = 208 (100) [M^+-1]. HRMS calculated for $C_{10}H_8ClNO_2$ [M^+]: 209.0244. Found: 209.0249.

(*E*)-4-(3,4-Dimethylbenzylidene)-4,5-dihydroisoxazol-3-ol (1d)

Off white power; mp 170.9-172.0 °C. IR (KBr): 3444, 1642 m^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.71 (br s, 1H, OH), 7.22 (d, J = 7.6 Hz, 1H, ArH), 7.15 (s, 1H, ArH), 7.09 (d, J = 7.6 Hz, 1H, ArH), 6.87 (s, 1H, CH), 5.28 (s, 2H, CH_2), 2.25 (s, 6H, 2×CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.7, 137.4, 136.9, 132.3, 130.3, 130.0, 129.1, 126.7, 124.8, 71.3, 19.4, 19.3. MS (CI): *m/z* (%) = 203 (100) [M^+]. HRMS calculated for $C_{12}H_{13}NO_2$ [M^+]: 203.0946. Found: 203.0951.

(*E*)-4-(Furan-2-ylmethylene)-4,5-dihydroisoxazol-3-ol (1e)

Off white power; mp 164.7-165.5 °C. IR (KBr): 3441, 1644 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.77 (br s, 1H, OH), 7.86 (s 1H, ArH), 6.79 (t, J = 3.2 Hz, 1H, ArH), 6.74 (d, J = 3.2 Hz, 1H, ArH), 6.65 (s, 1H, CH), 5.24 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.3, 151.0, 145.3, 128.0, 113.9, 112.8, 111.8, 72.1. MS (ESI): *m/z* (%) = 164 (100) [M^+-1]. HRMS calculated for $C_8H_7NO_3$ [M^+]: 165.0426. Found: 165.0429.

(*E*)-4-((*Z*)-3-Chloro-3-*p*-tolylallylidene)-4,5-dihydroisoxazol-3-ol (1f)

Yellow power; mp 216.5-217.4 °C. IR (KBr): 3441, 1639 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.71 (br s, 1H, OH), 7.70 (d, *J* = 8.0 Hz, 2H, ArH), 7.28 (d, *J* = 8.0 Hz, 2H, ArH), 7.04 (d, *J* = 11.2 Hz, 1H, ClC=C*H*CH=C), 7.83 (d, *J* = 11.2 Hz, 1H, ClC=CHC*H*=C), 5.23 (s, 2H, CH_2), 2.35 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.7, 139.6, 136.7, 135.4, 133.4, 129.3 (2×CH), 126.3 (2×CH), 121.2, 118.2, 71.6, 20.8. MS (ESI): *m/z* (%) = 248 (100) [M^+-1]. HRMS calculated for $C_{13}H_{12}ClNO_2$ [M^+]: 249.0557. Found: 249.0561.

(*E*)-4-((*Z*)-3-Chloro-3-(4-chlorophenyl)allylidene)-4,5-dihydroisoxazol-3-ol (1g)

Yellow power; mp 208.3-209.5 °C. IR (KBr): 3448, 1633 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.77 (br s, 1H, OH), 7.85-7.81 (m, 2H, ArH), 7.55-7.52 (m, 2H, ArH), 7.13 (d, *J* = 11.2 Hz, 1H, ClC=C*H*CH=C), 6.80 (d, *J* = 11.2 Hz, 1H, ClC=CHC*H*=C), 5.25 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.5, 136.6, 135.0, 134.3, 128.5 (2×CH), 128.1 (2×CH), 127.9, 122.9, 117.7, 71.7. MS (APCI): *m/z* (%) = 268 (100) [M^+-1]. HRMS calculated for $C_{12}H_9Cl_2NO_2$ [M^+]: 269.0010. Found: 269.0001.

Procedure for 3-(3,4-dimethylphenyl)isoxazolidine-4-carbonitrile (7)

To a stirred solution of compound **4j** (364 mg, 1.0 mmol) in EtOH (10 mL) was added 50% hydrazine hydrate (400 mg, 4.0 mmol) at rt, the solution rapidly became bright yellow, and a precipitate was formed. The reaction mixture was refluxed for 40 min, cooled to rt, and filtered. The filtrate was evaporated under vacuum. The crude product was purified by silica gel column chromatography using (petroleum ether: EtOAc = 4: 1) as eluent to obtain **7** (201 mg, 86% yield).

Off white power; mp 142.6-143.3 °C. IR (KBr): 2239, 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.96-6.89 (m, 3H, ArH), 5.22 (br s,1H, NH), 4.67 (d, *J* = 8.0 Hz, 1H, HNC*H*CH), 4.39 (t, *J* = 8.0 Hz, 1H, C*H*H), 4.24 (dd, J_1 = 6.4 Hz, J_2 = 8.0 Hz, 1H, CH*H*), 3.91 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.78 (q, *J* = 8.0 Hz, 1H, C*H*CN). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3, 149.0, 119.8, 117.8, 111.1, 110.7, 110.4, 73.7, 65.4, 55.9, 55.8, 40.1. MS (ESI): *m/z* (%) = 235 (100) [M^++1]. HRMS calculated for $C_{12}H_{14}N_2O$ [M^+]: 234.1004. Found: 234.0991.

Procedure for 3-(3,4-dimethoxyphenyl)isoxazol-4-ol (8)

Method A: To a stirred solution of compound **4j** (364 mg, 1.0 mmol) in EtOH (10 mL) were added 50% hydrazine hydrate (400 mg, 4.0 mmol) and KOH (11.2 mg, 0.2 mmol) at rt, the solution rapidly became bright yellow, and a precipitate was formed. The reaction mixture was refluxed for 60 min, cooled to rt

and adjusted pH to 3-4 with HCl (2 M)/AcOH and then filtered. The filtrate was evaporated under vacuum. The crude product was purified by silica gel column chromatography using (petroleum ether: EtOAc = 4 : 1, containing 1% AcOH) as eluent to obtain **8** (157 mg, 71 % yield).

Method B: To a stirred solution of compound **7** (117 mg, 0.5 mmol) in EtOH (10 mL), and KOH (5.6 mg, 0.1 mmol) was added and the reaction mixture was refluxed for 40 min, cooled to rt and adjusted pH to 3-4 with HCl (2 M)/AcOH and then evaporated under vacuum. The crude product was purified by silica gel column chromatography using (petroleum ether: EtOAc = 4 : 1, containing 1% AcOH) as eluent to obtain **8** (87.5 mg, 83 % yield).

Pale yellow power; mp 90.4-91.1 ^{o}C. IR (KBr): 3451, 1516 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (br s, 1H, OH), 8.10 (s, 1H, NOC*H*=C), 7.23 (d, J = 1.6 Hz, 1H, ArH), 7.04 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H, ArH), 6.86 (d, J = 8.0 Hz, 1H, ArH), 3.90 (s, 6H, 2×CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7, 150.1, 149.2, 124.7, 121.6, 110.7, 110.4, 107.9, 55.83, 55.79, 29.6. MS (EI): *m/z* (%) = 221 (5) [M^+], 163 (100), 148 (35), 120 (10), 92 (15), 77 (7). HRMS calculated for $C_{11}H_{11}NO_4$ [M^+]: 221.0688. Found: 221.0679.

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