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PIFA-Mediated Oxidative Cyclization Reactions of α-Acyl Acrylamides: A Synthetic Route to Substituted Isoxazol-3(2*H*)-ones

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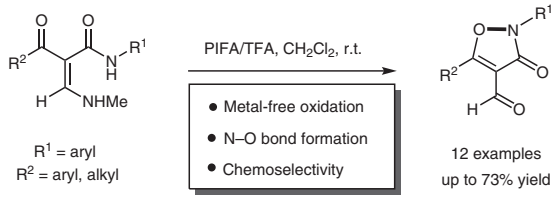

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Abstract An intramolecular cyclization of various α-acyl β-amino acrylamides in the presence of PIFA and TFA is described. This transformation features mild reaction conditions, simple execution, high chemoselectivity, and metal catalyst-free oxidation, and thereby, provides not only an alternative protocol for the construction of N–O bond, but also an efficient and straightforward synthesis of substituted isoxazol-3(2*H*)-ones from readily available α-acyl acrylamides.

Key words acrylamides, cyclization, heterocycles, hypervalent iodine reagents, N–O bond formation, isoxazol-3(2*H*)-ones

Isoxazol-3(2*H*)-ones and their benzo-/hetero-fused analogues constitute the core structural motifs in some naturally occurring and artificial compounds along with diverse bio-, physio-, and pharmacological activities (Figure 1).[1,2] In addition, the functionalized isoxazol-3(2*H*)-ones are widely used in organic chemistry, agrochemistry, and material chemistry.[3] So far, a variety of synthetic approaches to such heterocycles are already available based on either the modification of the pre-constructed heterocyclic skeleton or the direct heterocyclization from appropriate open chain precursors. Among these methods, the most common and notable one involves the cyclocondensation reactions of 1,3-dielectrophiles with hydroxylamine.[4] Recently, Han and coworkers reported a novel synthesis of isoxazol-3(2*H*)-ones from alkynyl aldehydes and nitrosobenzenes via a highly regioselective umpolung strategy.[5] Most recently, we developed an alternative protocol for accessing isoxazol-3(2*H*)-ones via copper-nitrene triggered annulation of α-acyl cinnamides.[6] This intramolecular cyclization represents one of the few examples for a straightforward synthesis of isoxazol-3(2*H*)-one through an N–O bond formation.[7] Nevertheless, the development of novel and efficient approach for the synthesis of isoxazol-3(2*H*)-ones, especially those with wide applicability to achieve more elaborate and flexible substitution patterns, still remains a significant challenge for organic chemists.

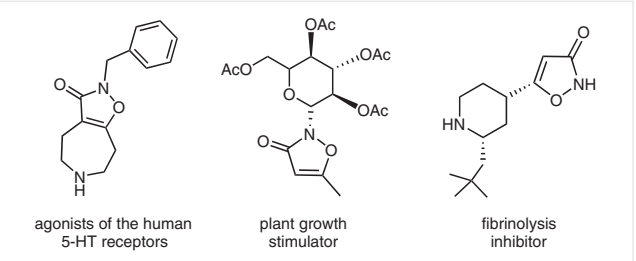
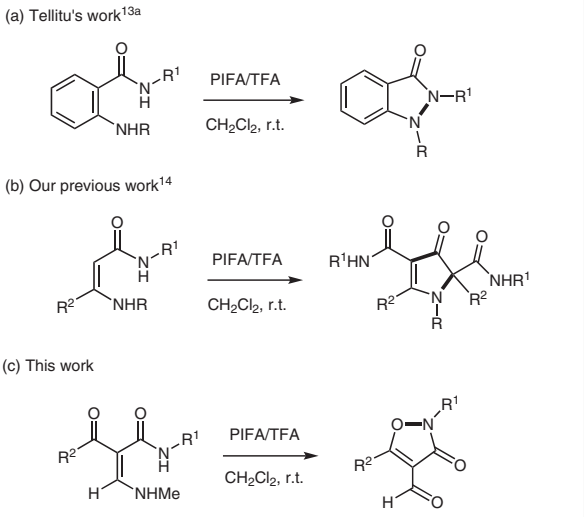


Figure 1 Selected isoxazol-3(2*H*)-ones with bioactivities

Over the past decades, hypervalent iodine reagents have emerged as a very important type of oxidants in organic transformations for their low toxicity, chemoselective oxidizing ability, and the mild reaction conditions required.[8,9] In the early 1990s, Kikugawa and co-workers found that *N*-acyl nitrenium ions could be generated by the oxidation of amides with phenyliodine(III) bis(trifluoroacetate) (PIFA).[10] Later on, it was demonstrated that the nitrenium ions stabilized by the electron-donating effect of a proper neighboring group (alkoxy, aryl, or nitrogen) were useful synthetic intermediates to construct N–C, N–S, or N–N linkage (Scheme 1a).[11–13]

In our previous work, we investigated the reaction behaviors of a variety of functionalized amides in the presence of different hypervalent iodine reagents, and achieved efficient synthesis of substituted pyrrolin-4-ones (Scheme 1b),[14] benzo[*d*]thiazoles,[15] isothiazol-3(2*H*)-ones,[16] spiro-fused pyrazolin-5-one *N*-oxides,[17] spiro-fused dihydrofuran-3(2*H*)-ones,[18] and 2,5-dihydrofurans.[19] During these



Scheme 1 PIFA-mediated oxidative cyclization reactions

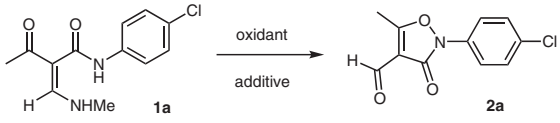
inter- or intramolecular reactions, the construction of C–C, C–N, C–O, N–S, or N–N bond had been established. Obviously, these results reveal that there exists a chemoselective C–O and C–N bond formation during the oxidation of amides. In this context, we prepared a series of functionalized acrylamides from β-oxo amides, and envisaged that under appropriate conditions the oxidation of the newly synthesized acrylamides might generate heteroatom-centered intermediates and lead to cyclization. After a series of detailed investigation, we developed a novel and efficient synthesis of substituted isoxazol-3(2*H*)-ones through a chemoselective intramolecular N–O bond formation (Scheme 1c).

According to our previously reported procedure,[20] a series of α-acyl acrylamides were prepared from commercially available β-oxo amides in good yields, but the preparation of *N*-methoxy-α-acyl acrylamide was not successful. The reaction of α-acyl acrylamide **1a** with PIFA (1.0 equiv) was initially attempted in dichloromethane at room temperature. The reaction proceeded sluggishly, as indicated by TLC, and furnished one main product after workup and purification of the resulting mixture by silica column chromatography (Table 1, entry 1). The product was characterized as 2-(4-chlorophenyl)-5-methyl-3-oxo-2,3-dihydroisoxazole-4-carbaldehyde (**2a**) on the base of its spectral and analytical data.

The optimizations of various reaction parameters, including hypervalent iodines, additives, solvents, and temperatures, were then investigated, and some results are summarized in Table 1. It was observed that the yield of **2a** was significantly improved by increasing the loading amount of PIFA to 1.5 equivalents, though it still required 15.0 hours to complete the reaction (Table 1, entry 2). However, no reaction occurred as indicated by TLC when other hypervalent iodine(III) reagents, such as phenyliodine(III) diacetate (PIDA) and iodosobenzene (PhIO), were employed (entries 3 and 4). Notably, the addition of trifluoroacetic acid (TFA) indeed promoted the reactions of **1a**, as seen by the shortened reaction times (entries 5–8). Further experiments revealed that TFA was the most effective additive among the tested ones (entries 6, 9, and 10). Actually, TFA was frequently used in various PIFA-mediated organic transformations.[13,21] The solvent screening disclosed that the employment of toluene or acetonitrile resulted in lower yields of **2a** (entries 11 and 12), and no desired product was formed in THF as monitored by TLC (entry 13). The higher reaction temperature could shorten the reaction time, but the yield of **2a** was somewhat lowered (entry 14). Therefore, the optimal reaction conditions were obtained when **1a** was treated with PIFA (1.5 equiv) and TFA (1.0 equiv) in dichloromethane at room temperature for 6 hours, whereby the yield of **2a** reached 71% (entry 6).

Next, we examined the influence of different enamine moiety of α-acyl acrylamides on their oxidative reactions under the above optimal reaction conditions (Table 2). As a comparison, the reaction of **3a** was rather sluggish even though the reaction time was increased to 12 hours, which furnished **2a** in moderate yield along with recovery of some starting material (Table 2, entry 2). In stark contrast, the re-

Table 1 Optimization of the Reaction Conditions[a]

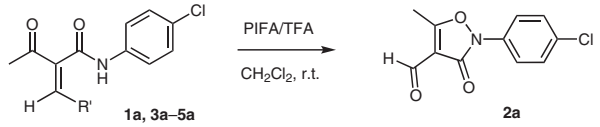


Entry	Oxidant (equiv)	Additive (equiv)	Solvent	Time (h)	Yield (%)[b]
1	PIFA (1.0)	–	CH_2Cl_2	24	32 (53)
2	PIFA (1.5)	–	CH_2Cl_2	15	62
3	PIDA (1.5)	–	CH_2Cl_2	15	NR[c]
4	PhIO (1.5)	–	CH_2Cl_2	15	NR[c]
5	PIFA (1.5)	TFA (3.0)	CH_2Cl_2	3	64
6	**PIFA (1.5)**	**TFA (1.0)**	**CH_2Cl_2**	**6**	**71**
7	PIFA (2.0)	TFA (1.0)	CH_2Cl_2	4	65
8	PIFA (2.0)	TFA (0.5)	CH_2Cl_2	5	63
9	PIFA (1.5)	$BF_3{\cdot}OEt_2$(1.0)	CH_2Cl_2	12	44 (15)
10	PIFA (1.5)	CF_3CH_2OH (1.0)	CH_2Cl_2	6	60
11	PIFA (1.5)	TFA (1.0)	toluene	7	58
12	PIFA (1.5)	TFA (1.0)	MeCN	6	53
13	PIFA (1.5)	TFA (1.0)	THF	12	0 (84)
14	PIFA (1.5)	TFA (1.0)	CH_2Cl_2	1.5	67[d]

[a] Reagents and conditions: **1a** (1.0 mmol), solvent (10.0 mL), r.t.
[b] Isolated yield of **2a** (data in parentheses for the recovery of **1a**).
[c] No reaction.
[d] Under reflux.

action of **4a** resulted in a complex mixture, and no desired product **2a** was observed (entry 3). In the case of **5a**, an inseparable mixture was formed though **2a** could be detected by ^{1}H NMR spectroscopy (entry 4). Thus, it seems that the α-acyl acrylamides with secondary enamine group are more favorable to the oxidative cyclization reaction.

Table 2 Effect of Enamine Group of α-Acyl Acrylamides on Their Cyclization Reactions[a]



Entry	Acrylamide	R′	Time (h)	Yield (%)[b]
1	**1a**	NHMe	6	71
2	**3a**	NHPh	12	52 (24)[c]
3	**4a**	NMe_2	4	0
4	**5a**	NH_2	4	mixture[d]

[a] Reagents and conditions: acrylamide (1.0 mmol), PIFA (1.5 mmol), TFA (1.0 mmol), CH_2Cl_2 (10.0 mL), r.t.
[b] Isolated yield of **2a**.
[c] The data in parentheses for the recovery of **3a**.
[d] Product **2a** could be detected by ^{1}H NMR spectroscopy.

With the optimal reaction conditions in hand, the scope and limitation of the PIFA-mediated oxidative transformation were then investigated. A range of reactions of α-acyl acrylamides **1** were carried out in the presence of PIFA and TFA in dichloromethane at room temperature, and some of the results are summarized in Table 3.

It was observed that the reactions of α-acyl acrylamides **1b–f** bearing varied *N*-arylamide groups (CONHR^1) proceeded smoothly to afford the corresponding isoxazol-3(2*H*)-ones **2b–f** in moderate to good yields (Table 3, entries 2–6). However, no reaction occurred when **1g** with a strong electron-withdrawing nitro group on its phenyl ring was employed (entry 7), whereas the reaction of **1h** with an *N*-alkylamide group failed to give the desired product **2h**, only leading to a complex mixture (entry 8). The versatility of this isoxazol-3(2*H*)-one synthesis was further evaluated by performing α-acyl acrylamides **1i–n** bearing other alkyl- or arylacyl groups (R^{2}CO) under the identical conditions to afford the corresponding isoxazol-3(2*H*)-ones **2i–n** in fairly good yields (entries 9–14). The products **2** were characterized by their spectral and analytical data, and the structure of **2e** was elucidated by X-ray diffraction analysis as shown in Figure 2 (for details, see the Supporting Information).

Thus, we have established a protocol for the operationally simple and efficient construction of N–O bond in a chemoselective manner, which provided a straightforward synthetic route to substituted isoxazol-3(2*H*)-ones from functionalized acrylamides **1**. These obtained results further

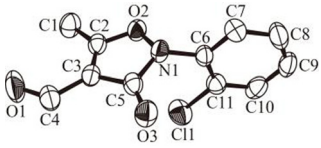
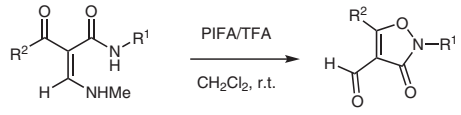


Figure 2 ORTEP drawing of **2e**

demonstrated that amides could be easily oxidized to *N*-acyl nitrenium ions by hypervalent iodine reagent, and only those stabilized by proper neighboring groups (e.g., nonactivated and moderately deactivated or activated *N*-aryl rings) could exhibit sufficiently long life to undergo subsequent organic reactions, as disclosed by other researchers.[10–13,22]

Interestingly, the reaction of **1c** with PIFA (1.5 equiv) and TFA (1.0 equiv) in dichloromethane at room temperature furnished a major product rather than **2c** by prolonging the reaction time from 1 to 4 hours. The product was characterized as *N*-(2-hydroxy-4-methylphenyl)-2-[(methylamino)methylene]-3-oxobutanamide (**6c**) on the basis of its spectral and analytical data (Scheme 2).[23,24] Notably, **6c** was also obtained in 62% yield within 0.5 hour by performing the above reaction under reflux. Clearly, in the case of **1c**, the synthesis of either thermodynamic product **6c** or

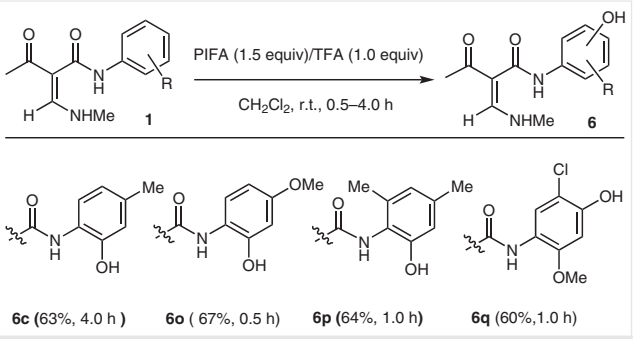
Table 3 Synthesis of Isoxazol-3(2*H*)-ones **2** from α-Acyl Acrylamides **1**[a]



Entry	**1**	R^1	R^2	Time (h)	**2**	Yield (%)[b]
1	**1a**	4-ClC_6H_4	Me	6	**2a**	71
2	**1b**	Ph	Me	3	**2b**	59
3	**1c**	4-MeC_6H_4	Me	1	**2c**	51
4	**1d**	4-BrC_6H_4	Me	6	**2d**	73
5	**1e**	2-ClC_6H_4	Me	12	**2e**	56
6	**1f**	3-ClC_6H_4	Me	12	**2f**	54
7	**1g**	4-$NO_2C_6H_4$	Me	12	**2g**	NR[c]
8	**1h**	Me	Me	12	**2h**	mixture
9	**1i**	4-ClC_6H_4	*n*-Pr	5	**2i**	70
10	**1j**	4-ClC_6H_4	Ph	6	**2j**	68
11	**1k**	Ph	Ph	2	**2k**	62
12	**1l**	Ph	4-MeC_6H_4	2	**2l**	63
13	**1m**	Ph	4-ClC_6H_4	2	**2m**	62
14	**1n**	Ph	4-$MeOC_6H_4$	2	**2n**	67

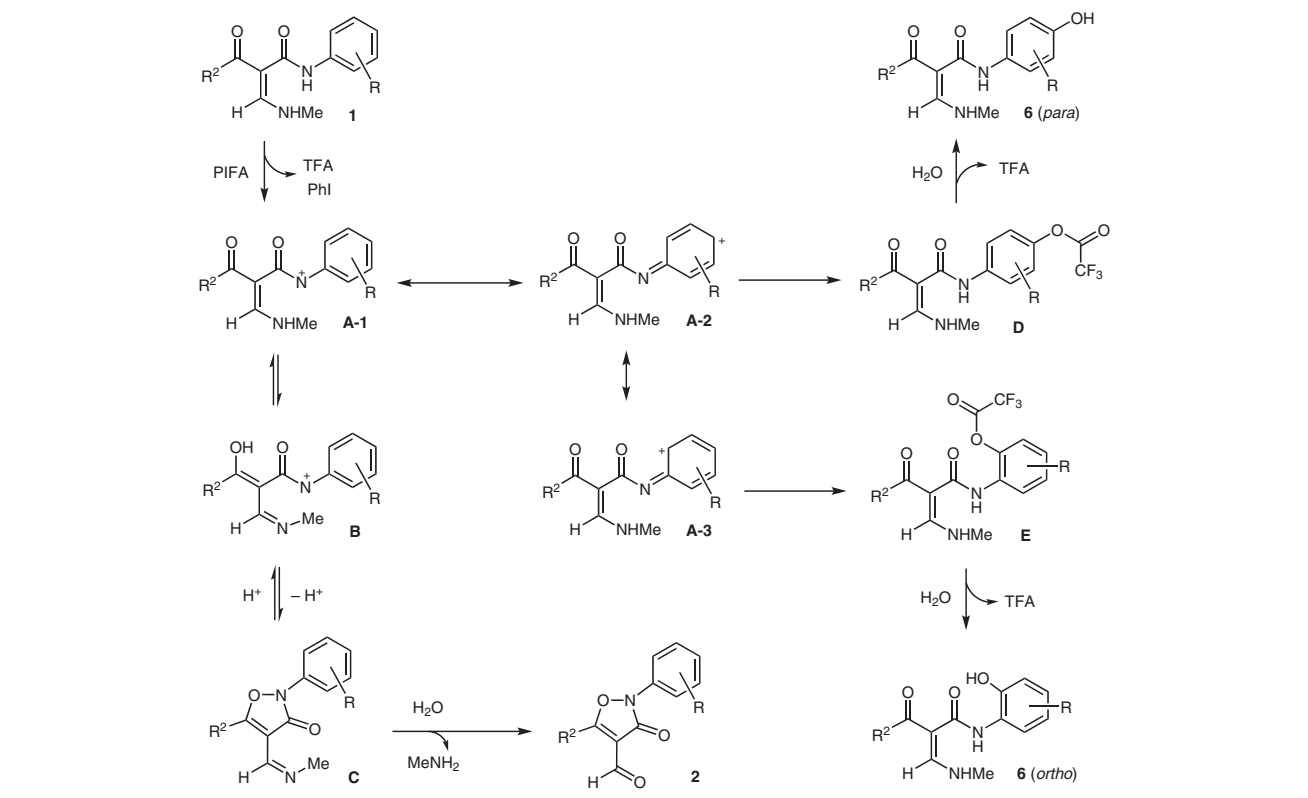
[a] Reagents and conditions: **1** (1.0 mmol), PIFA (1.5 mmol), TFA (1.0 mmol), CH_2Cl_2 (10.0 mL), r.t.
[b] Isolated yields.
[c] No reaction.

kinetic product **2c** could be controlled by simply changing the reaction conditions. On the contrary, the reaction of **1a** under reflux still delivered **2a** as the predominant product and only trace amount of the corresponding phenol **6a** was detected even though the reaction time was prolonged to 24 hours. For the α-acyl acrylamides **1o–q** decorated with strongly electron-donating *o*-methoxy, *p*-methoxy or dimethyl groups R on their *N*-aryl rings, the reactions proceeded smoothly to afford exclusively the corresponding *N*-aryl hydroxylated products **6o–q** in moderate yields (Scheme 2). When the reaction of **1p** was performed in the presence of PIFA without TFA at room temperature, it furnished the hydroxylated product **6p** in 57% yield after 6.0 hours. Attempts to synthesize the corresponding isoxazol-3(2*H*)-ones **2o**,**p** from **1o**,**p** by varying the reaction conditions were fruitless. These results reveal that the electronic effect of amide motifs of α-acyl acrylamides **1** is of crucial importance for their transformation mediated by PIFA.



Scheme 2 *N*-Aryl hydroxylation of α-acyl acrylamides **1**

On the basis of all the obtained results, a mechanism for the metal-free oxidative reaction of α-acyl acrylamides **1** is proposed as depicted in Scheme 3. In the presence of TFA, α-acyl acrylamide **1** reacts with PIFA to generate an electrophilic species **A**,[10–13] which might be represented by several resonance structures including *N*-acyl nitrenium ion **A-1** and phenonium ions **A-2** and **A-3**.[11b,22a,25] The stability of these resonance forms depends on the electronic effect of the amide motifs. Under acidic conditions, an intramolecular cyclization of *N*-acyl nitrenium ion **B**, keto-enol tautomer of **A-1**, bearing non-activated and moderately activated or deactivated *N*-aryl rings (**1a–f** and **1i–n**) takes place in a chemoseletive manner to afford the intermediate **C**,[13] which undergoes hydrolysis during workup to give isoxazol-3(2*H*)-one **2**. Considering of the formation of intermediate **B**, it is not hard to understand that no desired product **2a** was formed from **4a**. On the other hand, the positive charge of intermediate **A** bearing strong activated *N*-aryl rings (**1o–q**) can be delocalized preferentially on the *para* (**A-2**) and



Scheme 3 Proposed mechanism for the oxidative reaction of α-acyl acrylamides **1** with PIFA/TFA

ortho (**A-3**) positions of the aromatic rings and trapped by a trifluoroacetate anion to form intermediate **D** or **E**,[11b,23] followed by hydrolysis to give the hydroxylated product **6**.

In summary, we have described herein an intramolecular cyclization of α-acyl acrylamides **1** in the presence of PIFA and TFA. This transformation features mild reaction conditions, simple execution, high chemoselectivity, and metal catalyst-free oxidation, and thereby, provides an alternative protocol not only for the construction of N–O bond, but also for the efficient and straightforward synthesis of substituted isoxazol-3(2*H*)-ones. Further studies on the mechanism involved in the reactions and the utilization and extension of the scope of the protocol are currently underway in our laboratory.

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C at 300 MHz (or 400 MHz) and 100 MHz (or 75 MHz), respectively, with TMS as internal standard. IR spectra (KBr) were recorded on FTIR-spectrophotometer in the range of 400–4000 cm^{-1}. High-resolution mass spectra (ESI-TOF-Q/HRMS) were recorded on a Bruker micrOTOF-Q II mass spectrometer. Melting points were determined on a TECH X-4 micro-melting point apparatus. All reactions were monitored by TLC with GF254 silica gel-coated plates. Chromatography was carried out on flash silica gel (300–400 mesh).

The preparation of α-acyl acrylamides **1a–q** and **3a** are described in the Supporting Information.

Isoxazol-3(2*H*)-ones 2; General Procedure

To a well-stirred solution of PIFA (645 mg, 1.5 mmol) and TFA (0.076 mL, 1.0 mmol) in CH_2Cl_2 (10 mL) was added α-acyl acrylamide **1** (1.0 mmol) at r.t. The reaction mixture was kept at r.t. under stirring until the completion of the reaction as indicated by TLC. The resulting mixture was poured into brine (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with H_2O, dried (anhyd $MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel with PE/EtOAc as the eluent to give the desired product **2** (Table 3).

2-(4-Chlorophenyl)-5-methyl-3-oxo-2,3-dihydroisoxazole-4-carbaldehyde (2a)

Pale yellow solid (169 mg, 71%); mp 78–79 °C. The reaction of substrate **3a** (315 mg, 1.0 mmol) under identical conditions gave **2a** in 52% yield.

IR (KBr): 3115, 3094, 3044, 2925, 2865, 2763, 1713, 1656, 1628, 1591, 1493, 1424, 1406, 1369, 816, 760 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.69 (s, 3 H), 7.43 (d, *J* = 8.7 Hz, 2 H), 7.66 (d, *J* = 8.7 Hz, 2 H), 9.93 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.9, 174.2, 161.6, 134.3, 131.9, 129.4, 118.4, 110.6, 13.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_8ClNO_3Na$: 260.0085; found: 260.0118.

5-Methyl-3-oxo-2-phenyl-2,3-dihydroisoxazole-4-carbaldehyde (2b)

Light red solid (120 mg, 59%); mp 66–68 °C.

IR (KBr): 3101, 3069, 2862, 2792, 1689, 1682, 1616, 1590, 1495, 1486, 1422, 1384, 1359, 771, 689 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.70 (s, 3 H), 7.29 (t, *J* = 7.5 Hz, 1 H), 7.47 (t, *J* = 7.8 Hz, 2 H), 7.70 (d, *J* = 7.8 Hz, 2 H), 9.95 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.1, 174.0, 161.6, 135.7, 129.3, 126.6, 117.4, 110.6, 13.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_9NO_3Na$: 226.0475; found: 226.0501.

5-Methyl-3-oxo-2-(*p*-tolyl)-2,3-dihydroisoxazole-4-carbaldehyde (2c)

White solid (111 mg, 51%); mp 62–63 °C.

IR (KBr): 3088, 3034, 2924, 2862, 2788, 1692, 1614, 1581, 1512, 1422, 1383, 1363, 808 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3 H), 2.67 (s, 3 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 9.78 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.2, 173.8, 161.7, 136.9, 133.2, 129.8, 118.3, 110.5, 21.0, 13.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{11}NO_3Na$: 240.0631; found: 240.0659.

2-(4-Bromophenyl)-5-methyl-3-oxo-2,3-dihydroisoxazole-4-carbaldehyde (2d)

Pale yellow solid (206 mg, 73%); mp 71–72 °C.

IR (KBr): 3098, 3069, 3040, 2858, 2752, 1719, 1665, 1631, 1580, 1493, 1425, 1403, 1365, 827, 763 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69 (s, 3 H), 7.58 (d, *J* = 9.2 Hz, 2 H), 7.61 (d, *J* = 9.2 Hz, 2 H), 9.93 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.9, 174.2, 161.5, 134.8, 132.4, 119.6, 118.5, 110.6, 13.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_8BrNO_3Na$: 303.9580; found: 303.9597.

2-(2-Chlorophenyl)-5-methyl-3-oxo-2,3-dihydroisoxazole-4-carbaldehyde (2e)

White solid (133 mg, 56%); mp 76–77 °C.

IR (KBr): 3076, 2931, 2858, 2754, 1706, 1692, 1611, 1593, 1474, 1416, 1381, 771, 747 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.67 (s, 3 H), 7.39–7.59 (m, 4 H), 9.94 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.2, 176.8, 164.9, 133.8, 132.4, 132.1, 131.0, 130.8, 127.8, 109.5, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_8ClNO_3Na$: 260.0085; found: 260.0105.

X-ray Crystal Data[26]

$C_{11}H_8ClNO_3$, white crystal, *M* = 237.64, triclinic, P-1, *a* =6.8948(8) Å, *b* = 7.2403(9) Å, *c* = 10.7983(13) Å, *α* = 90.885(2)°, *β* = 102.147(2)°, *γ* = 94.426(2)°, *V* = 525.14(11) Å^3, Z = 7, T = 273 K, F000 = 244.0, F000' = 244.41, *R* = 0.0509 (1706), *wR2* = 0.1598 (2088).

2-(3-Chlorophenyl)-5-methyl-3-oxo-2,3-dihydroisoxazole-4-carbaldehyde (2f)

Pale yellow solid (128 mg, 54%); mp 63–64 °C.

IR (KBr): 3105, 3081, 2925, 2864, 2737, 1694, 1614, 1593, 1482, 1433, 1381, 786, 736, 711 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.71 (s, 3 H), 7.25 (d, *J* = 7.8 Hz, 1 H), 7.39 (t, *J* = 8.1 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.72 (t, *J* = 1.8 Hz, 1 H), 9.93 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.8, 174.4, 161.6, 136.7, 135.1, 130.4, 126.3, 116.8, 114.7, 110.6, 13.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_8ClNO_3Na$: 260.0085; found: 260.0108.

2-(4-Chlorophenyl)-3-oxo-5-propyl-2,3-dihydroisoxazole-4-carbaldehyde (2i)

White solid (186 mg, 70%); mp 62–63 °C.

IR (KBr): 3106, 3084, 2961, 2863, 2813, 2770, 1697, 1683, 1610, 1590, 1489, 1439, 1367, 825, 749 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.6 Hz, 3 H), 1.77–1.87 (m, 2 H), 3.04 (t, *J* = 7.6 Hz, 2 H), 7.43 (d, *J* = 9.2 Hz, 2 H), 7.66 (d, *J* = 9.2 Hz, 2 H), 9.92 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.8, 177.8, 161.7, 134.3, 131.8, 129.4, 118.3, 110.0, 29.3, 20.0, 13.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{12}ClNO_3Na$: 288.0398; found: 288.0424.

2-(4-Chlorophenyl)-3-oxo-5-phenyl-2,3-dihydroisoxazole-4-carbaldehyde (2j)

Yellow solid (204 mg, 68%); mp 111–113 °C.

IR (KBr): 3105, 3065, 2862, 2770, 1700, 1687, 1598, 1582, 1562, 1492, 1451, 822, 760, 739, 684 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 9.0 Hz, 2 H), 7.60 (t, *J* = 7.2 Hz, 2 H), 7.70 (t, *J* = 7.5 Hz, 1 H), 7.78 (d, *J* = 9.0 Hz, 2 H), 8.25–8.28 (m, 2 H), 10.05 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.2, 169.6, 162.3, 134.2, 132.0, 129.5, 129.3, 129.1, 128.8, 124.8, 118.4, 108.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{10}ClNO_3Na$: 322.0241; found: 322.0256.

3-Oxo-2,5-diphenyl-2,3-dihydroisoxazole-4-carbaldehyde (2k)

Yellow solid (164 mg, 62%); mp 93–94 °C.

IR (KBr): 3059, 2862, 2775, 1696, 1684, 1592, 1583, 1564, 1496, 755, 738, 683 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.38 (t, *J* = 7.6 Hz, 1 H), 7.57 (t, *J* = 7.6 Hz, 2 H), 7.67 (t, *J* = 7.2 Hz, 2 H), 7.77 (d, *J* = 7.2 Hz, 1 H), 7.82–7.84 (m, 2 H), 8.22–8.24 (m, 2 H), 9.87 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.4, 169.3, 162.4, 135.7, 134.0, 129.3, 129.0, 128.8, 126.7, 124.9, 117.4, 108.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{11}NO_3Na$: 288.0631; found: 288.0646.

3-Oxo-2-phenyl-5-(*p*-tolyl)-2,3-dihydroisoxazole-4-carbaldehyde (2l)

Pale yellow solid (176 mg, 63%); mp 92–93 °C.

IR (KBr): 3076, 3037, 2914, 2861, 2772, 1695, 1681, 1609, 1587, 1555, 1508, 1496, 1461, 1372, 830, 745, 686 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.48 (s, 3 H), 7.31 (t, *J* = 7.5 Hz, 1 H), 7.39 (d, *J* = 8.1 Hz, 2 H), 7.50 (t, *J* = 7.8 Hz, 2 H), 7.81 (d, *J* = 7.8 Hz, 2 H), 8.20 (d, *J* = 8.4 Hz, 2 H), 10.05 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.5, 169.5, 162.7, 145.3, 135.8, 129.7, 129.3, 128.8, 126.5, 122.2, 117.4, 108.2, 21.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{13}NO_3Na$: 302.0788; found: 302.0802.

5-(4-Chlorophenyl)-3-oxo-2-phenyl-2,3-dihydroisoxazole-4-carbaldehyde (2m)

Yellow solid (186 mg, 62%); mp 136–138 °C.

IR (KBr): 3092, 3069, 2860, 1699, 1683, 1582, 1552, 1495, 1371, 832, 746, 707 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 7.5 Hz, 1 H), 7.51 (t, *J* = 7.5 Hz, 2 H), 7.57 (d, *J* = 8.7 Hz, 2 H), 7.80 (d, *J* = 7.8 Hz, 2 H), 8.30 (d, *J* = 8.7 Hz, 2 H), 10.05 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.6, 167.8, 162.5, 140.6, 135.6, 130.1, 129.4, 126.9, 123.4, 117.6, 108.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{10}ClNO_3Na$: 322.0241; found: 322.0239.

5-(4-Methoxyphenyl)-3-oxo-2-phenyl-2,3-dihydroisoxazole-4-carbaldehyde (2n)

Pale yellow solid (197 mg, 67%); mp 147–149 °C.

IR (KBr): 3068, 3017, 2980, 2951, 2924, 2853, 1712, 1698, 1687, 1608, 1595, 1584, 1575, 1548, 1507, 1495, 1368, 841, 747, 687 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.93 (s, 3 H), 7.07 (d, *J* = 8.7 Hz, 2 H), 7.30 (t, *J* = 7.5 Hz, 1 H), 7.50 (t, *J* = 7.8 Hz, 2 H), 7.80 (d, *J* = 8.1 Hz, 2 H), 8.37 (d, *J* = 8.7 Hz, 2 H), 10.03 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.6, 169.0, 164.3, 163.1, 135.8, 131.0, 129.3, 126.4, 117.3, 114.4, 107.2, 55.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{13}NO_4Na$: 318.0737; found: 318.0742.

Phenols 6; General Procedure

To a well-stirred solution of PIFA (645 mg, 1.5 mmol) and TFA (0.076 mL, 1.0 mmol) in CH_2Cl_2 (10 mL) was added the required α-acyl acrylamide **1c**,**o**–**q** (1.0 mmol) at r.t. The reaction mixture was kept at r.t. under stirring until the completion of the reaction as indicated by TLC. The resulting mixture was poured into brine (50 mL), neutralized with sat. aq $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with H_2O, dried (anhyd $MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel with PE/EtOAc as the eluent to give the desired product **6**.

***N*-(2-Hydroxy-4-methylphenyl)-2-[(methylamino)methylene]-3-oxobutanamide (6c)**

Pale yellow solid (156 mg, 63%); mp 173–174 °C.

IR (KBr): 3277, 3192, 3060, 3037, 2943, 2920, 1654, 1626, 1610, 1600, 1561, 1525, 1399, 1382, 1290, 885, 830, 811 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 2.34 (s, 3 H), 3.22 (d, *J* = 5.1 Hz, 3 H), 6.66 (d, *J* = 7.8 Hz, 1 H), 6.83 (s, 1 H), 6.87 (d, *J* = 7.8 Hz, 1 H), 7.80 (d, *J* = 13.5 Hz, 1 H), 9.65 (s, 1 H), 10.24 (br s, 1 H), 12.12 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 194.8, 167.3, 163.3, 146.9, 132.3, 125.5, 120.5, 119.8, 115.8, 101.3, 36.5, 26.6, 21.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{16}N_2O_3Na$: 271.1053; found: 271.1072.

***N*-(2-Hydroxy-4-methoxyphenyl)-2-[(methylamino)methylene]-3-oxobutanamide (6o)**

Pale yellow solid (177 mg, 67%); mp 163–164 °C.

IR (KBr): 3300, 3191, 3140, 3060, 3001, 2935, 2835, 1657, 1613, 1598, 1521, 1464, 1421, 1381, 1287, 889, 830, 798 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 3.22 (d, *J* = 5.1 Hz, 3 H), 3.77 (s, 3 H), 6.43 (dd, *J* = 8.7, 2.7 Hz, 1 H), 6.57 (d, *J* = 2.7 Hz, 1 H), 6.89 (d, *J* = 8.7 Hz, 1 H), 7.80 (d, *J* = 13.5 Hz, 1 H), 9.88 (s, 1 H), 10.23 (br s, 1 H), 12.09 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 194.8, 167.1, 163.3, 155.7, 148.3, 121.5, 121.4, 103.8, 101.9, 101.3, 55.4, 36.5, 26.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{16}N_2O_4Na$: 287.1002; found: 287.1021.

***N*-(2-Hydroxy-4,6-dimethylphenyl)-2-[(methylamino)methylene]-3-oxobutanamide (6p)**

Pale yellow solid (168 mg, 64%); mp 182–183 °C.

IR (KBr): 3229, 3007, 2968, 2940, 2920, 2855, 1659, 1614, 1556, 1538, 1468, 1380, 1293, 886, 797, 727 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3 H), 2.32 (s, 3 H), 2.35 (s, 3 H), 3.23 (d, *J* = 5.1 Hz, 3 H), 6.59 (s, 1 H), 6.71 (s, 1 H), 7.82 (d, *J* = 13.5 Hz, 1 H), 9.15 (s, 1 H), 10.29 (br s, 1 H), 12.00 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.6, 168.0, 163.6, 151.0, 135.5, 132.9, 122.7, 122.3, 116.2, 100.5, 36.7, 26.5, 21.0, 19.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}N_2O_3Na$: 285.1210; found: 285.1228.

***N*-(5-Chloro-4-hydroxy-2-methoxyphenyl)-2-[(methylamino)methylene]-3-oxobutanamide (6q)**

Pale yellow solid (179 mg, 60%); mp 191–193 °C.

IR (KBr): 3245, 3187, 3154, 3062, 2941, 2918, 1650, 1615, 1598, 1572, 1535, 1465, 1447, 1409, 1378, 1290, 887, 810 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 3.18 (d, *J* = 5.1 Hz, 3 H), 3.89 (s, 3 H), 5.48 (br s, 1 H), 6.59 (s, 1 H), 7.79 (d, *J* = 13.2 Hz, 1 H), 8.40 (s, 1 H), 10.67 (br s, 1 H), 11.97 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.0, 167.1, 163.4, 148.7, 148.5, 121.7, 120.8, 110.0, 101.1, 100.7, 56.4, 35.6, 26.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{15}ClN_2O_4Na$: 321.0613; found: 321.0629.

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Supporting Information

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