Tetrahedron xxx (2017) 1–8

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A rapid access to substituted oxazoles via PIFA-mediated oxidative cyclization of enamides

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ARTICLE INFO

Article history:
Received 2 December 2016
Received in revised form
7 January 2017
Accepted 10 January 2017
Available online xxx

Keywords:
Oxazole
Hypervalent iodine
Enamide
Oxidative cyclization
PIFA

ABSTRACT

A facile and rapid access to multi-substituted oxazoles has been achieved under mild reaction conditions in a short reaction time. Reaction of enamides **1** with [bis(trifluoroacetoxy)iodo]benzene (PIFA) in trifluoroethanol (TFE) at room temperature for 15 min afforded the desired oxazoles **2** in moderate to excellent yields (58–98%). A wide range of functional group tolerance has been observed for these transformations.

1. Introduction

Oxazoles are one of the valuable scaffolds existing in a wide variety of biologically active compounds, such like pharmaceuticals and agrochemicals (Fig. 1).[1] Therefore, various synthetic methods have been developed for the synthesis of oxazoles with diverse substituents,[2] which include the method based on Van Leusen oxazole synthesis,[3] cyclyzation of enamide by hypervalent iodine reagent $PhI(OTf)_2$ generated in situ,[4] phenyliodine diacetate (PIDA),[5] NBS,[6] and catalytic copper(II) with oxidant,[7] synthesis from amides and amines with ketones through a C–N and C–O bond forming ring closure,[8] annulation of alkynes, nitriles, and *O*-atoms,[9] cyclization of acetylenic amides,[10] ring expansion of keto aziridines,[11] a [2 + 2 + 1] annulation of a terminal alkyne,[12] *t*-BuOOH/I_2-mediated domino oxidative cyclization from alkenes and amines,[13] an iodine-catalyzed tandem oxidative cyclization from aldehydes and β–aminoketones,[14] the cyclization of propargyl alcohols and amides by *p*-toluenesulfonic acid (PTSA) and $Zn(OTf)_2$,[15] I_2-catalyzed C–O bond formation and dehydrogenation with TBHP from β-acylamino ketones.[16] Traditional methods for synthesizing oxazoles have also been composed of the C–C coupling of oxazoles with other reagents[17] and oxidation of oxazolines.[18] However, these methodologies suffer from some disadvantages, such as the requirement of Brønsted acid catalysts, transition-metal catalysts, Lewis acid reagents, or previously prepared substrates, which limit the overall functional group tolerance of the transformation. As indicated above, oxidative cyclyzation of enamide to oxazole under metal-free condition have been reported by employing hypervalent iodine and NBS.[4–6,16] This approach without the use of toxic transition metal would be more environmentally benign process. However these processes require excess Lewis acid, longer reaction time, and higher temperature. In this report, we disclose the successful PIFA-mediated rapid and highly efficient access to substituted oxazoles with broad substrate scope by the use of trifluoroethanol (TFE) as solvent (Fig. 2).

2. Results and discussion

The optimization studies were carried out with enamide **1a** as model substrate (Table 1). Reaction of **1a** derived from benzamide and acetylacetone (see supporting informations) with PIFA (1.1 equiv) in acetonerile at room temperature for 26 h afforded the desired oxazole **2a** in 14% yield (entry 1). Another solvents (CH_2Cl_2, $(ClCH_2)_2$, and EtOH) with the use of PIFA resulted in the unsatisfactory yields (entries 2–4, 11–27%). To our delight, the yield was dramatically grown up to 91% isolated yield by changing the solvent

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http://dx.doi.org/10.1016/j.tet.2017.01.027
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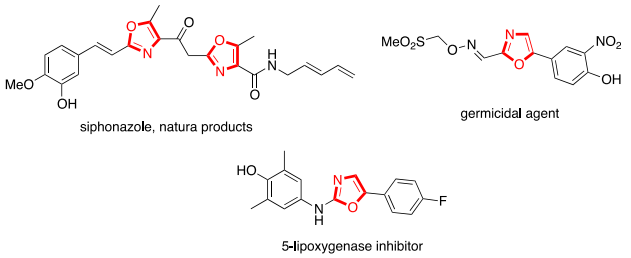


Fig. 1. A natural product and drugs with oxazole structures.

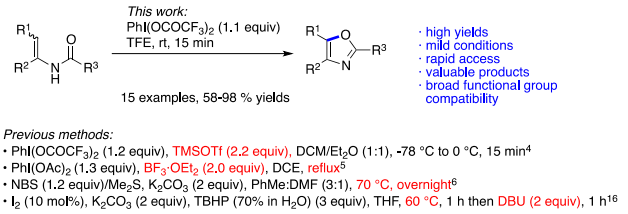
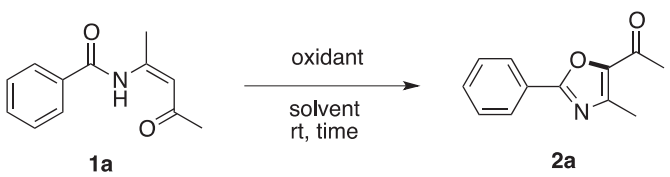


Fig. 2. Transition-metal-free synthesis of oxazoles.

Table 1
Optimization studies for the transformation of enamide **1a** to oxazole **2a**.[a]



Entry	Oxidant (equiv.)	Solvent	Time (h)	Yield (%)
1	PIFA (1.1)	MeCN	26	14[b]
2	PIFA (1.1)	CH_2Cl_2	28	11[c]
3	PIFA (1.1)	$ClCH_2CH_2Cl$	24	27[c]
4	PIFA (1.1)	EtOH	24	22[c]
5	PIFA (1.1)	TFE	0.25	91[b] (93%)[b,d]
6	PIDA (1.1)	TFE	20	81[b]
7	–	TFE	0.25	0

TFE = trifleoroethanol, PIDA = phenyliodine (III) diacetate, PIFA = phenyliodine (III) *bis* (trifluoroacetate).

[a] Reaction conditions: enamide (**1a**; 0.25 mmol, 1 equiv.) and PIFA or PIDA (1.1 equiv.) in TFE at room temperature.

[b] Isolated yield.

[c] GC yield.

[d] Result with 1.0 g of starting material and 1.3 equiv. of PIFA.

to trifluoroethanol (TFE) (entry 5). Iodobenzene diacetate (PIDA) also afforded a good yield of product (entry 6). A reaction without the use of oxidant did not take place (entry 7). A gram-scale transformation also provided oxazole **2a** in a comparable yield (93%, entry 5 in parenthesis).

Next, we carried out the cyclization of several enamides under the optimized conditions to elucidate the scope of the reaction (Table 2). Regarding the R^2 and R^3 substitutions, alkyls (**2b** and **2c**), aromatic (**2d**), and ester (**2l** and **2o**) accept the transformation to provide the corresponding oxazoles in moderate to excellent yields. Substitutions at the aromatic ring did not influence the reactivity in spite of the electronic nature and positions (**2e**, **2f**, **2g**, **2h** and **2i**). Displacement of benzene ring to alkyls (**2j**, **2l**, and **2m**) including a sterically hindered (**2n**) and heteroaromatic ones (**2p**) did not influence the reactivity to afford desired substituted oxazoles in excellent yields except for trifluoromethyl-substituted substrate **1k**, which resulted in complete recovery of starting material. The reason was temporary assumed as follows. Coordination of PIFA to the amide oxygen in **1k** would be inhibited due to the decrease of electron density of amide oxygen by the strong electron-withdrawing nature of trifluoromethyl group (see Fig. 2).

A one-pot process without the isolation of enamide intermediate has been achieved by using 2-methylbenzamide and acetylacetone as the starting materials (Scheme 1). A reaction of both starting materials in the presence of acid catalyst afforded enamide **1e**, after removal of the solvent *in vacuo*, the residue was directly subjected to the optimal conditions to provide target oxazole **2e** in 63% isolated yield.

A plausible mechanism for the formation of oxazoles **2** from enamides **1** mediated by PIFA is shown in Fig. 3. At first, the iodo intermediate **I** was formed from the reaction of the enamide substrate **1** with PIFA by losing one molecule of trifluoroacetic acid and concomitant *E*/*Z*-isomerization. The *E*/*Z*-isomerization would occur easily due to the release of intramolecular hydrogen bond between NH hydrogen and ketone oxygen atom. Then, nucleophilic addition of the carbonyl oxygen atom to the sp^2 carbon occurred, forming five-membered carbocation **II** with the release of PhI and $CF_3CO_2^-$. Subsequent deprotonation provided product **2** by the action of $CF_3CO_2^-$. The effect of fluorous solvent (TFE) in the reaction has not been unclear at present. Presumably, TFE would accelerate the *E*/*Z*-isomerization and deprotonation step (**II** → **2**) by coordination of carbonyl group. The activation of PIFA by coordination, which would enhance the electrophilicity of iodine (III) center, and also enhancing the solubility of reagents would also probable.[19]

Finally, to demonstrate the utility of this reaction, the intermediate for a potential antitumor agent[20] has been synthesized smoothly in 3 steps via the cyclization of enamide **1q** from commercially available starting materials in good yield (Scheme 2). Reaction of ethyl (2-fluorobenzoyl)acetate with ammonium acetate[20] followed by acetyl chloride afforded enamide **1r** in 63% yield (2 steps). The cyclization of enamide **1q** to oxazole **2q** has been accomplished under the standard conditions in 84% yield. Previous synthesis from the same starting materials under the presence of HDNIB ([hydroxy(2,4-dinitrobenzenesulfonyloxy)iodo]benzene) afforded oxazole **2q** in only 20% yield.[19]

3. Conclusion

In conclusions, we have demonstrated a rapid and efficient access to substituted oxazoles from readily available starting materials (typically, amides and 1,3-dicarbonyl compounds). The success rely on the modification of previous method (Fig. 2) by just replacing the solvent to trifluoroethanol, which resulted in higher yields (up to 98% isolated yields), milder reaction conditions (room temperature (standard conditions)), shorter reaction time (15 min (standard conditions)), and broad substrate scope (15 examples) avoiding the use of additives such like Lewis acid and base. Further studies directed toward the application of this method to the synthesis of other biologically active compounds and heterocyclic compounds are now under way and will be reported in due course.

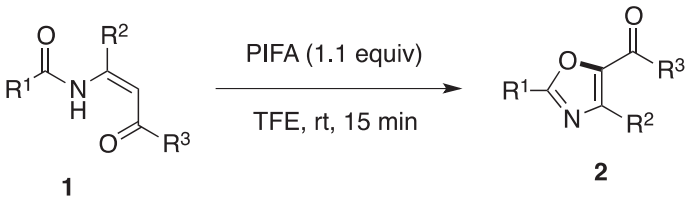
4. Experimental section

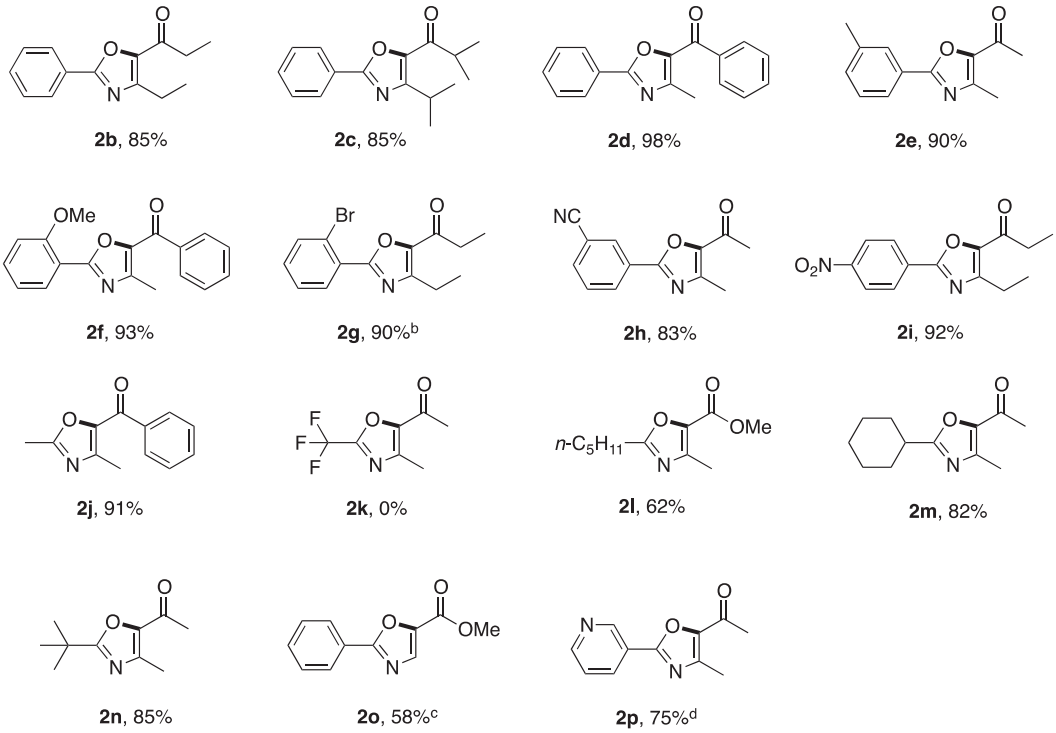
4.1. General

Unless stated otherwise, reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Column chromatography was performed on silica gel (60–120 mesh) using hexane and ethyl acetate. ^1H and ^{13}C NMR spectra were determined in $CDCl_3$ solution using 400 and 100 MHz spectrometers, respectively. Proton

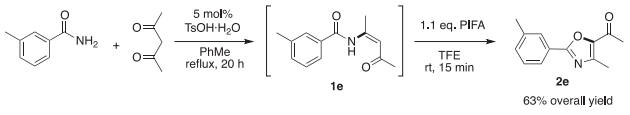
Please cite this article in press as: Kamiya M, et al., A rapid access to substituted oxazoles via PIFA-mediated oxidative cyclization of enamides, Tetrahedron (2017), http://dx.doi.org/10.1016/j.tet.2017.01.027

Table 2
Synthesis of diversely substituted oxazoles.[a]3





[a]Reaction conditions: Enamides **1** (0.18-1.08 mmol, 1 equiv.) and PIFA (1.1-1.3 equiv.) were stirred at room temperature in TFE solvent for 15 min. [b]25 min. [c]7 h. [d]2.3 eq. of PIFA was used at room temperature for 4 h.



Scheme 1. One-pot synthesis of oxazole **2e**.

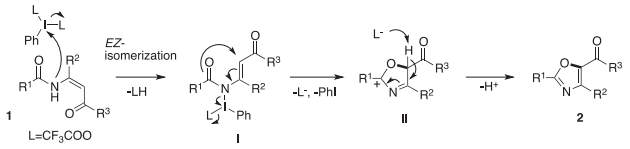
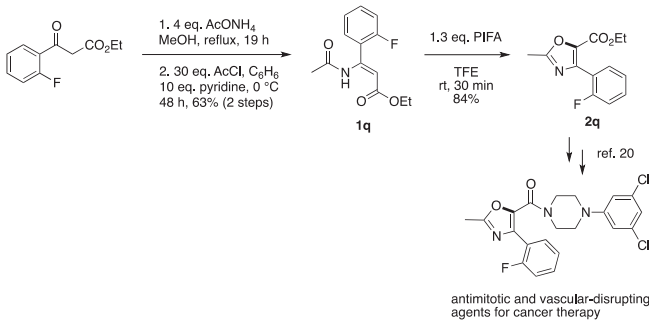


Fig. 3. Plausible mechanism for the formation of oxazole from enamide.



Scheme 2. Formal synthesis of antitumor agent.

chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.0$) as the internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m

(multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on an FT-IR spectrometer. Melting points were determined by using a Büchi melting point B-540 apparatus and are uncorrected. MS spectra were obtained on a mass spectrometer. HRMS was determined using JEOL JNM-AX 500 mass spectrometer.

4.2. General procedures for the synthesis of enamides (**1a-n** and **1p**)[21]

p-Toluenesulfonic acid (4–20 mol%) was added to a stirred solution of amide (1.0 equiv) and diketone (0.8–6.3 equiv) in solvent and the mixture was stirred for a period of time at reflux temperature. After that the mixture was allowed to cool to room temperature. The mixture was washed with saturated aqueous $NaHCO_3$ and water, dried over Na_2SO_4 and solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography or recrystallization to afford pure substituted enamides **1**.

4.2.1. N-((Z)-1-Methyl-3-oxobut-1-enyl)benzamide (**1a**)[22]

Following the general procedure, benzamide (1.5 g, 12.5 mmol), acetylacetone (1.0 g, 10 mmol), and *p*-TsOH (0.12 g, 0.63 mmol) was stirred in toluene (20 ml) for 6 h. Purification by recrystallization with chloroform provided **1a** (1.1 g, 54%) as a pale yellow solid; R*f* 0.47 (hexane:EtOAc = 5:1); mp 81–82 °C (lit.[22] 82–83 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.40 (br. s, 1H), 8.09–7.95 (m, 2H), 7.61–7.45 (m, 3H), 5.47 (s, 1H), 2.54 (s, 3H), 2.21 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.0, 166.0, 156.1, 133.6, 132.6, 128.8 (2C), 127.9 (2C), 106.1, 30.4, 22.0 ppm.

4.2.2. N-((Z)-1-Ethyl-3-oxopent-1-enyl)benzamide (**1b**)

Following the general procedure, benzamide (0.61 g, 5.0 mmol), 3,5-heptanedione (0.51 g, 4.0 mmol), and *p*-TsOH (50.6 mg, 0.27 mmol) was stirred in toluene (9 ml) for 7.5 h. Purification by silica gel column chromatography (hexane:EtOAc = 15:1) provided **1b** (0.63 g, 68%) as a pale yellow solid; R*f* 0.36 (hexane:EtOAc = 15:1); mp 33–35 °C; IR (KBr): 3741, 2971, 1692, 1643, 1601, 1479, 1150, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.34 (br. s, 1H), 8.05 (dd, 2H, *J* = 6.8, 2.0 Hz), 7.59–7.46 (m, 3H), 5.52 (s, 1H), 2.96 (q, *J* = 7.3 Hz, 2H), 2.50 (q, *J* = 7.3 Hz, 2H), 1.24 (t, *J* = 7.3 Hz, 3H), 1.15 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.7, 165.4, 161.0, 133.8, 132.4, 128.8 (2C), 127.9 (2C), 103.7, 36.5, 27.5, 12.7, 8.7 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{14}H_{18}O_2N$: 232.1337, found: 232.1333.

4.2.3. N-((Z)-1-isopropyl-4-methyl-3-oxopent-1-enyl)benzamide (**1c**)

Following the general procedure, benzamide (0.60 g, 5.0 mmol), 2,6-dimethyl-3,5-heptanedione (0.63 g, 4.0 mmol), and *p*-TsOH (49.5 mg, 0.26 mmol) was stirred in toluene (13 ml) for 24 h. Purification by silica gel column chromatography (hexane:EtOAc = 17:1) provided **1c** (0.34 g, 32%) as a yellow oil; R*f* 0.4 (hexane:EtOAc = 17:1); IR (NaCl): 2970, 1599, 1475, 1247, 1139, 1067, 915, 814, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.41 (br. s, 1H), 8.06 (d, *J* = 6.8 Hz, 2H), 7.56–7.49 (m, 3H), 5.65 (s, 1H), 4.12 (sep, *J* = 6.8 Hz, 1H), 2.67 (sep, *J* = 6.8 Hz, 1H), 1.24 (d, *J* = 6.8 Hz, 6H), 1.16 (d, *J* = 7.1 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 207.2, 166.7, 165.5, 134.2, 132.3, 128.8 (2C), 127.9 (2C), 100.0, 41.3, 29.6, 21.5 (2C), 19.0 (2C) ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{16}H_{22}O_2N$: 260.1650, found: 260.1668.

4.2.4. N-((Z)-Methyl-3-oxo-3-phenylpropenyl)benzamide (**1d**)[23]

Following the general procedure, benzamide (0.52 g, 4.3 mmol), 1-phenyl-1,3-butanedione (0.55 g, 3.4 mmol), and *p*-TsOH (60.0 mg, 0.32 mmol) was stirred in toluene (8 ml) for 6.5 h. Purification by silica gel column chromatography (hexane:EtOAc = 8:1) and recrystallization with EtOAc provided **1d** (0.37 g, 41%) as a pale yellow needle crystal; R*f* 0.4 (hexane:EtOAc = 8:1); mp 109 °C (lit.[23] 108–110 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.85 (br. s, 1H), 8.11 (dd, *J* = 7.1, 1.2 Hz, 2H), 7.96 (dd, *J* = 7.1, 1.5 Hz, 2H), 7.66–7.50 (m, 4H), 7.47 (dd, *J* = 7.6, 7.1 Hz, 2H), 6.18 (s, 1H), 2.68 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.8, 166.2, 158.2, 138.7, 133.7, 132.6, 132.4, 128.9 (2C), 128.6 (2C), 128.0 (2C), 127.7 (2C), 102.5, 22.7 ppm.

4.2.5. 3-Methyl-N-((Z)-1-methyl-3-oxobut-1-enyl)benzamide (**1e**)

Following the general procedure, *m*-toluamide (0.65 g, 4.8 mmol), acetylacetone (0.39 g, 3.9 mmol), and *p*-TsOH (40.0 mg, 0.2 mmol) was stirred in toluene (12 ml) for 6 h. Purification by silica gel column chromatography (hexane:EtOAc = 7:1) provided **1e** (0.64 g, 77%) as a pale yellow solid; R*f* 0.31 (hexane:EtOAc = 7:1); mp 67–68 °C; IR (KBr): 3054, 1962, 1689, 1638, 1592, 1481, 1261, 1169, 811, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.33 (br. s, 1H), 7.88–7.78 (m, 2H), 7.43–7.34 (m, 2H), 5.46 (s, 1H), 2.53 (s, 3H), 2.44 (s, 3H) 2.20 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.9, 166.2, 156.0, 138.7, 133.6, 133.3, 128.7, 128.6, 124.8, 106.0, 30.4, 22.0, 21.4 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{13}H_{16}O_2N$: 218.1181, found: 218.1160.

4.2.6. 2-Methoxy-N-((Z)-1-methyl-3-oxo-3-phenylpropenyl) benzamide (**1f**)

Following the general procedure, *o*-methoxybenzamide (0.20 g, 1.3 mmol), 1-phenyl-1,3-butanedione (0.21 g, 1.32 mmol), and *p*-TsOH (18.0 mg, 0.07 mmol) was stirred in toluene (2.5 ml) for 6 h. Purification by silica gel column chromatography (hexane:EtOAc = 5:1) provided **1f** (0.16 g, 40%) as a pale yellow oil; R*f* 0.4 (hexane:EtOAc = 5:1); IR (NaCl): 3457, 3069, 1925, 1677, 1628, 1590, 1475, 1023, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.50 (br. s, 1H), 8.08 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.99–7.92 (m, 2H), 7.55–7.42 (m, 4H), 7.09–7.01 (m, 2H), 6.12 (s, 1H), 4.17 (s, 3H), 2.67 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.2, 165.4, 157.9, 156.3, 139.2, 133.8, 132.4, 132.0, 128.4 (2C), 127.6 (2C), 122.0, 120.8, 111.4, 103.2, 55.6, 24.0 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{18}H_{18}O_3N$: 296.1287, found: 296.1289.

4.2.7. 2-Bromo-N-((Z)-1-ethyl-3-oxopent-1-enyl)benzamide (**1g**)

Following the general procedure, *o*-Bromobenzamide (0.52 g, 2.6 mmol), 3,5-heptanedione (0.27 g, 2.1 mmol), and *p*-TsOH (30.0 mg, 0.16 mmol) was stirred in toluene (2.5 ml) for 6 h. Purification by silica gel column chromatography (hexane:EtOAc = 8:1) provided **1g** (0.36 g, 56%) as a pale yellow oil; R*f* 0.34 (hexane:EtOAc = 8:1); IR (NaCl): 2976, 1819, 1706, 1593, 1483, 1244, 1119, 1032, 823, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.64 (br. s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.54 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.39 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.31 (dt, *J* = 8.0, 1.7 Hz, 1H), 5.51 (s, 1H), 2.95 (q, *J* = 7.3 Hz, 2H), 2.47 (q, *J* = 7.3 Hz, 2H), 1.26 (t, *J* = 7.3 Hz, 3H), 1.08 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.4, 166.2, 159.7, 137.6, 133.8, 131.6, 128.8, 127.6, 119.8, 104.2, 36.5, 27.4, 12.6, 8.3 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{14}H_{17}O_2N^{79}Br$: 310.0443, $C_{14}H_{17}O_2N^{81}Br$: 312.0422, found: 310.0459, 312.0422.

4.2.8. 3-Cyano-N-((Z)-1-methyl-3-oxobut-1-enyl)benzamide (**1h**)

Following the general procedure, 3-cyanobenzamide (0.22 g, 1.50 mmol), acetylacetone (0.44 g, 4.41 mmol), and *p*-TsOH (15.0 mg, 0.08 mmol) was stirred in toluene (5 ml) for 5.5 h. Purification by recrystallization with EtOH provided **1h** (0.25 g, 72%) as a pale brown needle crystal; R*f* 0.3 (hexane:EtOAc = 3:1); mp 178–180 °C; IR (KBr): 3067, 2231, 1688, 1635, 1594, 1477, 1260, 1166, 793, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.50 (br. s, 1H), 8.31 (s, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 5.54 (s, 1H), 2.53 (s, 3H), 2.23 (s, 3H) ppm; ^{13}C NMR

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(100 MHz, $CDCl_3$) δ = 200.5, 163.7, 155.4, 135.5, 135.0, 132.0, 131.5, 129.8, 117.8, 113.4, 106.9, 30.5, 21.8 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{13}H_{13}O_2N_2$: 229.0977, found: 229.0947.

4.2.9. N-((Z)-1-Ethyl-3-oxopent-1-enyl)-4-nitrobenzamide (**1i**)

Following the general procedure, 4-nitrobenzamide (1.66 g, 10.0 mmol), 3,5-heptanedione (1.0 g, 8.0 mmol), and *p*-TsOH (151.2 mg, 0.8 mmol) was stirred in xylene (12 ml) for 18.5 h. Purification by silica gel column chromatography (hexane:EtOAc = 7:1) and recrystallization with EtOH provided **1i** (0.85 g, 39%) as a pale yellow needle crystal; R*f* 0.42 (hexane:EtOAc = 7:1); mp 107–110 °C; IR (KBr): 3442, 2977, 1695, 1643, 1614, 1478, 1344, 1241, 1148, 1102, 846, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 13.53 (br. s, 1H), 8.36 (d, *J* = 8.8 Hz, 2H), 8.21 (d, *J* = 8.8 Hz, 2H), 5.59 (s, 1H), 2.96 (q, *J* = 7.4 Hz, 2H), 2.54 (q, *J* = 7.4 Hz, 2H), 1.25 (t, *J* = 7.4 Hz, 3H), 1.16 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 204.2, 163.3, 160.3, 150.0, 139.4, 129.0 (2C), 124.0 (2C), 104.6, 36.6, 27.3, 12.5, 8.5 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{14}H_{17}O_4N_2$: 277.1188, found: 277.1145.

4.2.10. N-((Z)-1-Methyl-3-oxo-3-phenylpropenyl)acetamide (**1j**)[24]

Following the general procedure, acetamide (0.29 g, 4.9 mmol), 1-phenyl-1,3-butanedione (0.77 g, 4.7 mmol), and *p*-TsOH (50.0 mg, 0.3 mmol) was stirred in toluene (9 ml) for 24 h. Purification by silica gel column chromatography (hexane:EtOAc = 4:1) provided **1j** (0.60 g, 73%) as a pale orange solid; R*f* 0.38 (hexane:EtOAc = 4:1); mp 96–98 °C (lit.[24] 98–99 °C); ^1H NMR (400 MHz, $CDCl_3$) δ = 12.82 (br. s, 1H), 7.90 (d, *J* = 7.3 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 2H), 6.05 (s, 1H), 2.52 (s, 3H), 2.23 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.4, 169.9, 157.5, 138.6, 132.4, 128.5 (2C), 127.6 (2C), 101.5, 25.5, 22.5 ppm.

4.2.11. (Z)-3-Hexanoylaminobut-2-enoic acid methyl ester (**1l**)

Following the general procedure, hexanamide (0.1 g, 0.87 mmol), methyl acetoacetate (0.1 g, 0.87 mmol), and *p*-TsOH (16.5 mg, 0.09 mmol) was stirred in toluene (2 ml) for 20 h. Purification by silica gel column chromatography (hexane:EtOAc = 17:1) provided **1l** (0.13 g, 67%) as a pale yellow oil; R*f* 0.6 (hexane:EtOAc = 5:1); IR (NaCl): 3236, 2954, 1719, 1676, 1632, 1259, 1151, 808, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 11.11 (br. s, 1H), 4.90 (s, 1H), 3.70 (s, 3H), 2.39 (s, 3H), 2.35 (t, *J* = 7.6 Hz, 2H), 1.75–1.61 (m, 2H), 1.40–1.28 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.2, 169.6, 155.4, 95.8, 51.0, 38.3, 31.2, 24.8, 22.3, 22.0, 13.9 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{11}H_{20}O_3N$: 214.1443, found: 214.1436.

4.2.12. Cyclohexanecarboxylic acid ((Z)-1-methyl-3-oxobut-1-enyl) amide (**1m**)

Following the general procedure, cyclohexanecarboxamide (0.40 g, 3.1 mmol), acetylacetone (1.95 g, 19.5 mmol), and *p*-TsOH (74.2 mg, 0.39 mmol) was stirred in toluene (15 ml) for 24 h. Purification by silica gel column chromatography (hexane:EtOAc = 12:1) provided **1m** (0.54 g, 83%) as a pale yellow solid; R*f* 0.41 (hexane:EtOAc = 12:1); mp 34–36 °C; IR (KBr): 2933, 2855, 1701, 1596, 1478, 1441, 1262, 1159, 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 12.41 (br. s, 1H), 5.33 (s, 1H), 2.38 (d, *J* = 0.7 Hz, 3H), 2.26 (tt, *J* = 11.6, 3.4 Hz, 1H), 2.14 (s, 3H), 1.96 (d, *J* = 13.2 Hz, 2H), 1.85–1.76 (m, 2H), 1.69 (d, *J* = 11.0 Hz, 1H), 1.47 (dq, *J* = 12.0, 2.9 Hz, 2H), 1.38–1.16 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.6, 175.1, 155.9, 105.3, 46.9, 30.3, 29.3 (2C), 25.6, 25.5 (2C), 21.9 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{12}H_{20}O_2N$: 210.1494, found: 210.1469.

4.2.13. 2,2-Dimethyl-N-((Z)-1-methyl-3-oxobut-1-enyl) propionamide (**1n**)

Following the general procedure, pivalamide (1.0 g, 9.9 mmol), acetylacetone (4.95 g, 49.4 mmol), and *p*-TsOH (211.0 mg, 1.1 mmol) was stirred in toluene (25 ml) for 16.5 h. Purification by silica gel column chromatography (hexane:EtOAc = 15:1) provided **1n** (1.38 g, 76%) as a pale yellow oil; R*f* 0.32 (hexane:EtOAc = 15:1); IR (NaCl): 3700, 2968, 1709, 1644, 1595, 1482, 1260, 1134 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 12.64 (br. s, 1H), 5.36 (s, 1H), 2.39 (s, 3H), 2.15 (s, 3H), 1.29 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.6, 178.7, 156.1, 105.5, 40.4, 30.3, 27.3 (3C), 22.0 ppm.

4.2.14. N-((Z)-1-Methyl-3-oxobut-1-enyl)nicotinamide (**1p**)

Following the general procedure, nicotinamide (0.5 g, 4.1 mmol), acetylacetone (2.1 g, 20.5 mmol), and *p*-TsOH (160.0 mg, 0.82 mmol) was stirred in xylene (20 ml) for 23 h. Purification by silica gel column chromatography (hexane:EtOAc = 1:2) provided **1p** (0.54 g, 64%) as a yellow solid; R*f* 0.4 (hexane:EtOAc = 1:2); mp 93–94 °C; IR (KBr): 3050, 1691, 1639, 1603, 1483, 1267, 1195, 1101, 1018, 973, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 13.48 (br. s, 1H), 9.27 (s, 1H), 8.81 (d, *J* = 4.8 Hz, 1H), 8.30 (ddd, *J* = 8.2, 2.0, 1.7 Hz, 1H), 7.46 (dd, *J* = 8.2, 4.8 Hz, 1H), 5.53 (s, 1H), 2.54 (s, 3H), 2.22 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.4, 164.2, 155.4, 152.9, 149.5, 135.2, 129.3, 123.5, 106.7, 30.5, 21.8 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{11}H_{13}O_2N_2$: 205.0977, found: 205.0972.

4.3. Synthesis of (Z)-methyl 3-(benzamido)acrylate (**1o**).[25]

Benzoquinone (1.8 g, 16.6 mmol, 1.6 equiv) *p*-toluenesulfonic acid (1.0 g, 5.3 mmol, 0.5 equiv), palladium (II) acetate (0.2 g, 0.9 mmol, 10 mol%), molecular sieves (1.5 g, 4 Å) was added to a stirred solution of benzamide (1.2 g, 10.0 mmol, 1.0 equiv) in toluene (50 ml) and the mixture was stirred for 1 min at room temperature under open air; then to this mixture were added methyl acrylate (9.9 g, 115 mmol, 11.5 equiv), and the mixture was stirred for 25 h at room temperature under open air. The reaction mixture was then filtered (Celite). The mixture was washed with water (×2), dried over Na_2SO_4, and solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:EtOAc = 8:1) to afford pure substituted **1o** (1.1 g, 52%) as a white solid; R*f* 0.37 (hexane:EtOAc = 8:1); mp 70 °C (lit.[25] 73–74 °C); ^1H NMR (400 MHz, $CDCl_3$) δ = 11.49 (br. d, *J* = 7.6 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 2H), 7.76 (dd, *J* = 10.8, 8.8 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 5.28 (d, *J* = 8.8 Hz, 1H), 3.78 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.0, 164.5, 138.9, 132.9, 132.1, 128.9 (2C), 127.7 (2C), 96.7, 51.4 ppm.

4.4. General procedures for the synthesis of oxazoles **2a-q**

PIFA (1.1–1.3 equiv) was added to a stirred solution of enamides **1** (1.0 equiv) in TFE and the mixture was stirred for 15 min at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture diluted with EtOAc and extracted with EtOAc. The organic layers were washed with water and brine and dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography to afford pure substituted oxazoles **2**.

4.4.1. 1-(4-Methyl-2-phenyloxazol-5-yl)ethanone (**2a**)[6]

Following the general procedure, enamide **1a** (1.0 g, 4.9 mmol) and PIFA (2.8 g, 6.4 mmol) in TFE (37.0 ml) was stirred for 15 min. Purification by silica gel column chromatography (hexane:EtOAc = 5:1) provided **2a** (0.92 g, 93%) as a white solid; R*f* 0.32 (hexane:EtOAc = 5:1); mp 66–67 °C (lit.[6] 61–63 °C); ^1H NMR (400 MHz, $CDCl_3$) δ = 8.12 (d, *J* = 7.6 Hz, 2H), 7.60–7.46 (m, 3H), 2.58

Please cite this article in press as: Kamiya M, et al., A rapid access to substituted oxazoles via PIFA-mediated oxidative cyclization of enamides, Tetrahedron (2017), http://dx.doi.org/10.1016/j.tet.2017.01.027

(s, 3H), 2.57 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.6, 161.4, 146.3, 145.1, 131.6, 128.9 (2C), 127.1 (2C), 126.3, 27.5, 13.8 ppm.

4.4.2. 1-(4-Ethyl-2-phenyl-oxazol-5-yl)propan-1-one (**2b**)

Following the general procedure, enamide **1b** (54.9 mg, 0.24 mmol) and PIFA (112.3 mg, 0.26 mmol) in TFE (3.0 ml) was sterred for 15 min. Purification by silica gel column chromatography (hexane:EtOAc = 17:1) provided **2b** (46.1 mg, 85%) as a white solid; R*f* 0.35 (hexane:EtOAc = 15:1); mp 33 °C; IR (KBr): 2975, 1677, 1583, 1539, 1455, 1373, 1269, 1134, 1092, 1008, 931, 786, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (dd, *J* = 2.0, 7.8 Hz, 2H), 7.55–7.46 (m, 3H), 2.99 (q, *J* = 7.6 Hz, 2H), 2.95 (q, *J* = 7.3 Hz, 2H), 1.31 (t, *J* = 7.6 Hz, 3H), 1.24 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.9, 161.2, 151.5, 144.1, 131.4, 128.9 (2C), 127.1 (2C), 126.6, 33.0, 20.9, 12.7, 7.5 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{14}H_{16}O_2N$: 230.1181, found: 230.1167.

4.4.3. 1-(4-Isopropyl-2-phenyl-oxazol-5-yl)-2-methyl-propan-1-one (**2c**)

Following the general procedure, enamide **1c** (0.26 g, 1.0 mmol) and PIFA (0.49 g, 1.1 mmol) in TFE (3.7 ml) was sterred for 15 min. Purification by silica gel column chromatography (hexane:EtOAc = 18:1) provided **2c** as a white solid (0.22 g, 85%); R*f* 0.30 (hexane:EtOAc = 18:1); mp 55 °C; IR (KBr): 2971, 1669, 1568, 1458, 1365, 1278, 1085, 966, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 7.8, 2.0 Hz, 2H), 7.54–7.46 (m, 3H), 3.70 (sep, *J* = 6.8 Hz, 1H), 3.42 (sep, *J* = 6.8 Hz, 1H), 1.31 (d, *J* = 6.8 Hz, 6H), 1.26 (d, *J* = 6.8 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.5, 161.2, 156.5, 142.6, 131.3, 128.8 (2C), 127.1 (2C), 126.8, 37.5, 26.3, 21.2 (2C), 18.3 (2C) ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{16}H_{20}O_2N$: 258.1494, found: 258.1555.

4.4.4. (4-Methyl-2-phenyl-oxazol-5-yl)phenyl-methanone (**2d**)

Following the general procedure, enamide **1d** (51.6 mg, 0.19 mmol) and PIFA (92.0 mg, 0.21 mmol) in TFE (3.0 ml) was sterred for 15 min. Purification by silica gel column chromatography (hexane:EtOAc = 8:1) provided **2d** as a white solid (50.1 mg, 98%); R*f* 0.40 (hexane:EtOAc = 8:1); mp 87–89 °C (lit.[6] 62–64 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.16–8.00 (m, 4H), 7.70–7.45 (m, 6H), 2.63 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 182.7, 161.8, 149.2, 144.8, 137.3, 132.8, 131.7, 129.3 (2C), 129.0 (2C), 128.5 (2C), 127.2 (2C), 126.3, 14.3 ppm.

4.4.5. 1-(4-Methyl-2-(m-tolyl)oxazol-5-yl)ethanone (**2e**)

Following the general procedure, enamide **1e** (0.18 g, 0.85 mmol) and PIFA (0.40 g, 0.94 mmol) in TFE (3.5 ml) was stirred for 15 min. Purification by silica gel column chromatography (hexane:EtOAc = 8:1) provided **2e** as a white solid (0.17 g, 93%); R*f* 0.35 (hexane:EtOAc = 8:1); mp 73–76 °C; IR (KBr): 2925, 1673, 1585, 1468, 1382, 1266, 1100, 945, 730, 635 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 (s, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.42–7.31 (m, 2H), 2.57 (2s, 6H), 2.44 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.6, 161.6, 146.2, 145.0, 138.8, 132.5, 128.9, 127.7, 126.1, 124.3, 27.5, 21.3, 13.7 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{13}H_{14}O_2N$: 216.1024, found: 216.1003.

4.4.6. [2-(2-Methoxyphenyl)-4-methyloxazol-5-yl] phenylmethanone (**2f**)

Following the general procedure, enamide **1f** (51.7 mg, 0.18 mmol) and PIFA (80.1 mg, 0.19 mmol) in TFE (1.4 ml) was stirred for 15 min. Purification by silica gel column chromatography (hexane:EtOAc = 3:1) provided **2f** as a white solid (47.8 mg, 93%); R*f* 0.36 (hexane:EtOAc = 3:1); mp 86–88 °C; IR (KBr): 1632, 1560, 1520, 1465, 1383, 1182, 1015, 911, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.29–8.19 (m, 2H), 8.16–8.06 (m, 1H), 7.68–7.46 (m, 4H), 7.14–7.03 (m, 2H), 4.00 (s, 3H), 2.68 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 182.2, 160.7, 158.1, 148.9, 144.5, 137.2, 133.0, 132.7, 131.0, 129.6 (2C), 128.2 (2C), 120.8, 115.3, 111.9, 55.9, 14.3 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{18}H_{16}O_3N$: 294.1130, found: 294.1129.

4.4.7. 1-[2-(2-Bromophenyl)-4-ethyloxazol-5-yl]propan-1-one (**2g**)

Following the general procedure, enamide **1g** (0.25 g, 0.80 mmol) and PIFA (0.41 g, 0.96 mmol) in TFE (3.7 ml) was stirred for 25 min. Purification by silica gel column chromatography (hexane:EtOAc = 10:1) provided **2g** as a pale brown solid (0.22 g, 90%); R*f* 0.36 (hexane:EtOAc = 10:1); mp 44–46 °C; IR (KBr): 2975, 1675, 1573, 1441, 1375, 933, 735, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.40–7.31 (m, 1H), 3.00 (q, *J* = 7.6 Hz, 2H), 2.97 (q, *J* = 7.3 Hz, 2H), 1.32 (t, *J* = 7.6 Hz, 3H), 1.23 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.3, 159.8, 150.8, 144.3, 134.7, 132.0 (2C), 127.5 (2C), 121.2, 33.2, 20.8, 12.7, 7.5 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{14}H_{15}O_2N^{79}Br$: 308.0286, $C_{14}H_{15}O_2N^{81}Br$: 310.0266, found: 308.0290, 310.0290.

4.4.8. 3-(5-Acetyl-4-methyloxazol-2-yl)benzonitrile (**2h**)

Following the general procedure, enamide **1h** (45.1 mg, 0.20 mmol) and PIFA (93.3 mg, 0.22 mmol) in TFE (1.4 ml) was stirred for 15 min. Purification by silica gel column chromatography (hexane:EtOAc = 2:1) provided **2h** as a white solid (37.3 mg, 83%); R*f* 0.35 (hexane:EtOAc = 2:1); mp 164–165 °C; IR (KBr): 3071, 2228, 1680, 1579, 1384, 1296, 1133, 945, 634 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.40 (s, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 2.59 (s, 3H), 2.58 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.4, 158.9, 146.3, 145.5, 134.5, 130.9, 130.5, 130.0, 127.7, 117.7, 113.5, 27.6, 13.7 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{13}H_{11}O_2N_2$: 227.0821, found: 227.0797.

4.4.9. 1-[4-Ethyl-2-(4-nitrophenyl)oxazol-5-yl]propan-1-one (**2i**)

Following the general procedure, enamide **1i** (0.30 g, 1.08 mmol) and PIFA (0.51 g, 1.19 mmol) in TFE (3.5 ml) was sterred for 15 min. Purification by silica gel column chromatography (hexane:EtOAc = 7:1) provided **2i** as a pale yellow solid (0.27 g, 92%); R*f* 0.39 (hexane:EtOAc = 7:1); mp 108–109 °C; IR (KBr): 2983, 1677, 1577, 1518, 1339, 1092, 932, 858, 714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.36 (d, *J* = 8.7 Hz, 2H), 8.30 (d, *J* = 8.7 Hz, 2H), 3.01 (q, *J* = 7.6 Hz, 2H), 2.98 (q, *J* = 7.3 Hz, 2H), 1.32 (t, *J* = 7.6 Hz, 3H), 1.25 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.8, 158.8, 151.7, 149.3, 144.9, 132.0, 127.9 (2C), 124.2 (2C), 33.2, 20.8, 12.6, 7.4 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{14}H_{15}O_4N_2$: 275.1032, found: 275.1002.

4.4.10. (2,4-Dimethyloxazol-5-yl)phenylmethanone (**2j**)

Following the general procedure, enamide **1j** (54.2 mg, 0.27 mmol) and PIFA (150.8 mg, 0.35 mmol) in TFE (1.8 ml) was stirred for 15 min. Purification by silica gel column chromatography (hexane:EtOAc = 3:2) provided **2j** as a yellow oil (49.1 mg, 91%); R*f* 0.39 (hexane:EtOAc = 3:2); IR (NaCl): 2927, 1646, 1591, 1553, 1349, 1177, 913, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.43 (dd, *J* = 8.0, 7.6 Hz, 2H), 2.48 (s, 3H), 2.41 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 182.7, 162.7, 147.9, 145.1, 137.2, 132.7, 129.2 (2C), 128.4 (2C), 14.3, 14.1 ppm.

4.4.11. 4-Methyl-2-pentyloxazole-5-carboxylic acid methyl ester (**2l**)

Following the general procedure, enamide **1l** (48.8 mg, 0.23 mmol) and PIFA (130.7 mg, 0.30 mmol) in TFE (2.0 ml) was stirred for 15 min. Purification by silica gel column chromatography (hexane:EtOAc = 8:1) provided **2l** as a pale blue oil (30.2 mg, 62%);

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Rf 0.35 (hexane:EtOAc = 8:1); IR (NaCl): 2956, 1725, 1616, 1553, 1442, 1389, 1344, 1279, 1194, 1148, 1106, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 3.91 (s, 3H), 2.77 (t, J = 7.6 Hz, 2H), 2.45 (s, 3H), 1.79 (quin, J = 7.6 Hz, 2H), 1.40–1.30 (m, 4H), 0.90 (t, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.8, 159.2, 146.2, 137.1, 51.9, 31.3, 28.3, 26.6, 22.2, 13.9, 13.3 ppm; HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{11}H_{18}O_3N$: 212.1287, found: 212.1263.

4.4.12. 1-(2-Cyclohexyl-4-methyloxazol-5-yl)ethanone (**2m**)

Following the general procedure, enamide **1m** (49.5 mg, 0.24 mmol) and PIFA (139.3 mg, 0.32 mmol) in TFE (2.0 ml) was sterred for 15 min. Purification by silica gel column chromatography (hexane:EtOAc = 8:1) provided **2m** as a yellow solid (40.2 mg, 82%); Rf 0.34 (hexane:EtOAc = 8:1); mp 38–39 °C; IR (NaCl): 2932, 2857, 1681, 1592, 1540, 1386, 1362, 1132, 1081, 951, 635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 2.81 (tt, J = 11.6, 3.6 Hz, 1H), 2.47 (s, 3H), 2.45 (s, 3H), 2.07 (d, J = 12.8 Hz, 2H), 1.89–1.79 (m, 2H), 1.73 (d, J = 12.0 Hz, 1H), 1.67–1.53 (m, 2H), 1.45–1.23 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.6, 169.0, 144.9 (2C), 37.6, 30.4 (2C), 27.4, 25.6, 25.5 (2C), 13.6 ppm; HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{12}H_{18}O_2N$: 208.1338, found: 208.1356.

4.4.13. 1-(2-tert-Butyl-4-methyloxazol-5-yl)ethanone (**2n**)

Following the general procedure, enamide **1n** (53.5 mg, 0.29 mmol) and PIFA (163.2 mg, 0.38 mmol) in TFE (2.0 ml) was stirred for 15 min. Purification by silica gel column chromatography (hexane:EtOAc = 6:1) provided **2n** as a yellow solid (44.9 mg, 85%); Rf 0.35 (hexane:EtOAc = 6:1); mp 44 °C; IR (KBr): 2977, 1678, 1591, 1536, 1381, 1364, 1290, 1266, 1124, 951, 636 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 2.48 (s, 3H), 2.46 (s, 3H), 1.42 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.7, 172.0, 145.0, 144.8, 33.9, 28.4 (3C), 27.4, 13.6 ppm; HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{10}H_{16}O_2N$: 182.1181, found: 182.1167.

4.4.14. Methyl 2-phenyloxazole-5-carboxylate (**2o**)

Following the general procedure, enamide **1o** (50.8 mg, 0.25 mmol) and PIFA (118.2 mg, 0.27 mmol) in TFE (3.0 ml) was stirred for 7 h. Purification by silica gel column chromatography (hexane:EtOAc = 10:1) provided **2o** as a white needle crystal (29.0 mg, 58%); Rf 0.27 (hexane:EtOAc = 10:1); mp 88–90 °C (lit.[6] 85–87 °C); ^1H NMR (400 MHz, $CDCl_3$) δ = 8.15 (dd, J = 7.3, 1.5 Hz, 2H), 7.86 (s, 1H), 7.58–7.47 (m, 3H), 3.95 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.3, 158.2, 142.0, 135.5, 131.6, 128.9 (2C), 127.2 (2C), 126.3, 52.2 ppm.

4.4.15. 1-(4-Methyl-2-pyridin-3-yl-oxazol-5-yl)-ethanone (**2p**)

PIFA (245.7 mg, 0.57 mmol) was added to a stirred solution of enamide **1p** (50.5 mg, 0.25 mmol) in TFE (4.0 ml) and the mixture was stirred for 4 h at room temperature. The reaction mixture was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:EtOAc = 1:3) to afford substituted oxazole **2p** as a pale yellow solid (37.7 mg, 75%); Rf 0.41 (hexane:EtOAc = 1:3); mp 93–95 °C; IR (KBr): 3527, 3475, 1669, 1595, 1416, 1595, 1071, 914, 781, 641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.34 (d, J = 1.2 Hz, 1H), 8.76 (dd, J = 4.9, 1.5 Hz, 1H), 8.38 (dt, J = 8.0, 2.0 Hz, 1H), 7.46 (dd, J = 8.0, 4.9 Hz, 1H), 2.58 (2s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.4, 159.0, 152.1, 148.2, 146.2, 145.4, 134.2, 123.7, 122.7, 27.5, 13.7 ppm; HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{11}H_{11}O_2N_2$: 203.0820, found: 203.0791.

4.5. One-pot method for the synthesis of oxazole **2e** (Scheme 1)

p-Toluenesulfonic acid (5.5 mg, 0.03 mmol, 5.0 mol%) was added to a stirred solution of *m*-toluamide (63.6 mg, 0.47 mmol, 1.0 equiv.) and acetylacetone (47.2 mg, 0.47 mmol, 1.0 equiv) in toluene (2 mL) and the mixture was stirred for 6 h at reflux temperature. After that the mixture was allowed to cool to room temperature, and solvent was evaporated *in vacuo*. The residue was dissolved in TFE (3 ml) and added to a solution of PIFA (266.0 mg, 0.61 mmol, 1.3 equiv.), and the mixture was stirred for 15 min at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture diluted with EtOAc and extracted with EtOAc. The organic layers were washed with water and brine and dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:EtOAc = 5:1) to afford pure substituted oxazole **2e** (63.9 mg, 63%).

4.6. Formal synthesis of antitumor agent (Scheme 2)

4.6.1. (Z)-3-Acetylamino-3-(2-fluorophenyl)acrylic acid ethyl ester (**1q**)

Ammonium acetate (1.73 g, 2.24 mmol, 4.0 equiv.) was added to a stirred solution of ethyl (2-fluorobenzoyl)acetate (1.18 g, 5.60 mmol, 1.0 equiv.) in MeOH (10 ml) and the mixture was stirred for 19 h at reflux temperature. After that the solvent was evaporated *in vacuo* and the redidure was dissolved with EtOAc. The solution was washed with water (x 2) and brine and dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:EtOAc = 8:1) to afford pure substituted enamine as a yellow oil (1.16 g, quant.) Rf 0.28 (hexane:EtOAc = 8:1), which was used directly in the next step.

Pyridine (0.38 g, 4.8 mmol, 10.0 equiv.) was added to a stirred solution of enamine (0.10 g, 0.48 mmol, 1.0 equiv.) in benzene (3 ml) and the solution was cooled to 0 °C. Acetyl chloride (0.28 g, 3.58 mmol, 7.5 equiv.) was added dropwise, and the mixture was stirred for 48 h at 0 °C under an atmosphere of nitrogen. Then, acetyl chloride (0.84 g, 10.7 mmol, 22.5 equiv) was dropwise to complete reaction. The reaction was quenched with brine, extracted with $CHCl_3$ (x 3) and dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:EtOAc = 5:1) to afford pure substituted enamide **1q** as a pale yellow oil (76.8 mg, 63%); Rf 0.28 (hexane:EtOAc = 5:1); IR (NaCl): 3280, 2983, 1724, 1676, 1630, 1488, 1294, 1079, 1033, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 10.92 (br. s, 1H) 7.42–7.32 (m, 1H), 7.28 (ddd, J = 7.6, 7.4, 1.7 Hz, 1H), 7.15 (dt, J = 7.6, 1.2 Hz, 1H), 7.03 (ddd, J = 10.6, 8.5, 1.2 Hz, 1H), 5.15 (s, 1H), 4.23 (q, J = 7.1 Hz, 2H), 2.15 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.6, 167.8, 159.4 (d, J_{CF} = 247.8 Hz), 149.2, 130.9 (d, J_{CF} = 8.2 Hz), 129.0 (d, J_{CF} = 2.5 Hz), 124.3 (d, J_{CF} = 14.0 Hz), 123.9 (d, J_{CF} = 3.3 Hz), 115.1 (d, J_{CF} = 21.4 Hz), 100.7, 60.4, 24.6, 14.2 ppm; HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{13}H_{15}O_3NF$: 252.1036, found: 252.1092.

4.6.2. 4-(2-Fluorophenyl)-2-methyloxazole-5-carboxylic acid ethyl ester (**2q**)

PIFA (109.5 mg, 0.26 mmol, 1.3 equiv) was added to a stirred solution of enamide **1q** (49.2 mg, 0.20 mmol, 1.0 equiv) in TFE (2 ml) and the mixture was stirred for 30 min at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture diluted with EtOAc and extracted with EtOAc. The organic layers were washed with water and brine and dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:EtOAc = 4:1) to afford pure substituted oxazole **2q** as a pale brown oil (41.1 mg, 84%); Rf 0.33 (hexane:EtOAc = 4:1); IR (NaCl): 2979, 1726, 1567, 1491, 1378, 1256, 1130, 1020, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.49 (ddd, J = 7.6, 7.3, 1.9 Hz, 1H), 7.40–7.30 (m, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.07 (dd, J = 9.1, 7.6 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 2.53 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$)

Please cite this article in press as: Kamiya M, et al., A rapid access to substituted oxazoles via PIFA-mediated oxidative cyclization of enamides, Tetrahedron (2017), http://dx.doi.org/10.1016/j.tet.2017.01.027

δ = 163.5, 160.0 (d, J_{CF} = 250.2 Hz), 157.9, 140.8, 138.4, 131.2 (d, J_{CF} = 3.3 Hz), 131.1 (d, J_{CF} = 3.3 Hz), 123.8 (d, J_{CF} = 4.2 Hz), 119.2 (d, J_{CF} = 14.0 Hz), 115.6 (d, J_{CF} = 21.4 Hz), 61.3, 14.2, 13.9 ppm; HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{13}H_{13}O_3NF$: 250.0879, found: 250.0878.

Acknowledgments

This work was financially supported by JSPS KAKENHI Grant Number 25410051.

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