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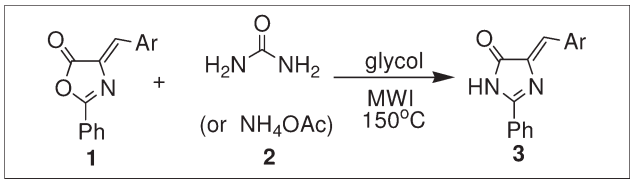

A facile microwave-assisted synthesis of imidazol-5(4*H*)-one derivatives is accomplished *via* reactions of 4-arylmethylene-2-phenyloxazol-5(4*H*)-ones with urea (or ammonium acetate) in ethylene glycol. The cascade reaction is simple to perform and occurs under mild conditions with broad scope of applicability.

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INTRODUCTION

Green fluorescent protein (GFP) including imidazolidinone skeleton (Fig. 1) [1], is an autofluorescent protein of 238 amino acid residues that is derived from the Pacific Northwest jellyfish, *Aequorea victoria* [2]. The GFP chromophore exhibits promising applications in molecular and cell biology due to its intrinsic visible fluorescence, which is easily detectable by fluorescence spectroscopy [3–5]. Therefore, much interest has been geared toward the engineering of novel color variants [6,7] of the GFP in light of its wide applicability in the life sciences.

In addition, the imidazolone core represents an attractive pharmacophore that displays extensively pharmacological and medicinal activities [8,9]. In particular, imidazol-5(4*H*)-one and its derivatives have possessed an unique role in drug discovery and crop protection [10,11], serving as combinatorial chemistry groups. In general routes, the imidazolone ring is formed by condensing glycine ester of acetimidic or phenylacetimidic acid in the solvents, such as benzene, dioxane, and acetone [12–14]. All these methods [12–17] have one or more limitations such as inaccessibility of precursors, narrow substrate scope, and operational complexity. Recently, a microwave-improved synthesis of imidazolones using graphite as support has been reported [15]. In the light of current studies, the development of a practically simple, economical, and high-yielding route to a wide variety of imidazol-5(4*H*)-one derivative (Fig. 2) is strongly desired. Herein, we like to report a cascade reaction of 4-arylmethylene-2-phenyloxazol-5(4*H*)-ones **1** (Compounds **1** were conveniently prepared following a literature procedure: [18]) with urea **2** (or ammonium acetate) for synthesis of imidazol-5(4*H*)-ones under microwave irradiation (MWI) at 150°C in ethylene glycol (Scheme 1).

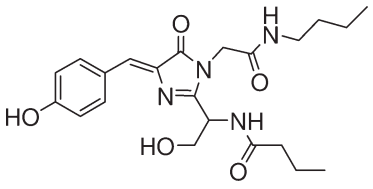


Figure 1. GFP chromophore.

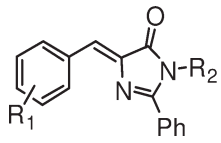
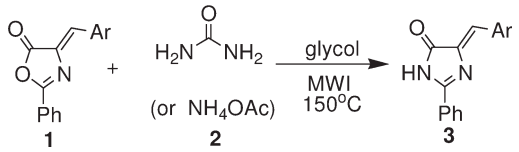


Figure 2. Compounds **3**.

RESULTS AND DISCUSSION

To choose the most appropriate solvents, the MW-assisted reaction (Scheme 2) of 4-(4-chlorobenzylidene)-2-phenyloxazol-5(4*H*)-one (**1c**, 1 mmol) and urea (**2**, 1.5 mmol) was examined using glacial acetic acid (HOAc), ethylene glycol, ethanol (EtOH), *N*,*N*-dimethyl

Scheme 1



formamide (DMF), water as the solvent (2.0 mL) at 150°C, respectively. All the reactions were carried out at the maximum power of 300 W. As shown in Table 1, we could see the reaction in glycol gave the best results (Table 1, entry 2).

To further optimize reaction conditions, the same reaction was performed in ethylene glycol and 300 W at the temperatures ranging from 110 to 180°C in increments of 10°C each time. The yield of product **3c** was improved from 23 to 93%, when the temperature was raised from 110 to 150°C (Table 2, entries 1–5). However, no significant increase in the yield of product **3c** was observed as the reaction temperature was raised from 150 to 180°C (Table 2, entries 5–8). Therefore, 150°C phenyloxazol-5(4*H*)-ones were performed, which leads to the corresponding 4-arylmethylene-2-phenyl-1*H*-imidazol-5(4*H*)-ones with good yields.

Under the optimal conditions [glycol, 150°C, 300 W (maximum power)], reactions of different 4-arylmethylene-2-phenyloxazol-5(4*H*)-ones were performed, which leads to the corresponding 4-arylmethylene-2-phenyl-1*H*-imidazol-5(4*H*)-ones with good yields. The electronic effect of the aryl group in 4-arylmethylene-2-phenyloxazol-5(4*H*)-ones was investigated. As shown in Table 3, both electron-withdrawing (such as nitro) and electron-donating (such as alkoxy) groups readily provided compounds 3 in good yields. Moreover, the heterocyclic phenyloxazol-5(4*H*)-ones such as 2-phenyl-4-((thiophen-2-yl)methylene) oxazol-5(4*H*)-one (Table 3, entry 9) still displayed a high reactivity under this standard condition.

We envisaged that ammonia, obtained by urea (or ammonium acetate), attacks on carbonyl group in 4-arylmethylene-2-phenyloxazol-5(4*H*)-ones **1** as a nucleophile. Bond formation should lead directly to intermediate **7** *via* ring opening, which then poised to attack adjacent reactive carbonyl group. Finally, an intramolecular condensation occurred and 4-arylmethylene-2-phenyl-1*H*-imidazol-5(4*H*)-ones **3** were obtained (Scheme 3).

Scheme 2

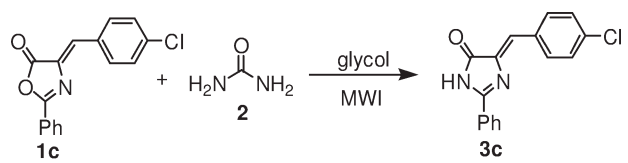


Table 1

Solvent optimization for the synthesis of **3c** under MWI.

Entry	Solvent	Temp (°C)	Time (min)	Yield (%)
1	HOAc	150	5	trace
2	Glycol	150	5	93
3	EtOH	150	5	63
4	DMF	150	5	79
5	Water	150	5	32

In a further study, aromatic amine **4** was employed instead of urea **2** in this case. The reactions proceeded smoothly too. However, the desired products **3** were not detected. Instead, a series of open-chain products **5** were obtained in high yields (Scheme 4). The reason may be attributed to the nucleophilicity of amine. When R is a phenyl group, the resulting *N*-phenylformamide derivative decreases the nucleophilicity of amine, which is difficult to form closed-ring products **3**. The synthesis of these compounds has reported in our previous study (Compounds **5** were conveniently prepared following a literature procedure: [19]).

In summary, we demonstrated a simple method, using readily available starting materials and simple experimental procedures, for the efficient synthesis of imidazol-5(4*H*)-one derivative and related compounds. Particularly, valuable features of this cascade reaction included operational simplicity, high yields, increased safety for small-scale high-speed synthesis, and broader substrate scope.

EXPERIMENTAL

All reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a FTIR-tensor 27 spectrometer in KBr. ^{1}H NMR spectra were measured on a DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analysis was determined by using a Perkin-Elmer 240c elemental analysis instrument.

Table 2

Temperature optimization for the synthesis of **3c** under MWI.

Entry	Temp (°C)	Time (min)	Yield (%)
1	110	5	23
2	120	5	58
3	130	5	75
4	140	5	82
5	150	5	93
6	160	5	71
7	170	5	58
8	180	5	41

Table 3

Physical and analytical data of compounds **3**.

Entry	Compd.	Ar	Time (min)	Yield (%)	Mp (°C)
1	**3a**	C_6H_5	5 (3) [15]	87 (85) [15]	>300 (272–273) [15]
2	**3b**	4-FC_6H_4	5	84	286–287
3	**3c**	4-ClC_6H_4	5 (5) [15]	93 (91) [15]	>300 (289–290) [15]
4	**3d**	2,4-$Cl_2C_6H_3$	6 (4) [15]	83 (97) [15]	268–269 (273–274)[15]
5	**3e**	3,4-$Cl_2C_6H_3$	6	85	277–278
6	**3f**	4-$CH_3C_6H_4$	5 (4) [15]	95 (70) [15]	278–279 (288–289) [15]
7	**3g**	2-$CH_3OC_6H_4$	6	82	278–279 (254–255) [15]
8	**3h**	4-$CH_3OC_6H_4$	5 (3) [15]	87 (84) [15]	>300 (289–290) [15]
9	**3i**	Thien-2-yl	5 (2) [15]	86 (80) [15]	>300 (291–292) [15]

Sample experimental

4-Arylmethylene-2-phenyl-1H-imidazol-5(4H)-one (3). In a 10 mL Emrys™ reaction vial, 4-arylmethylene-2-phenyloxazol-5(4*H*)-ones (1 mmol) with urea (1.5 mmol), ammonium acetate (1.5 mmol), in ethylene glycol (2.0 mL) were mixed and then capped. The mixture was irradiated by microwave at 300 W and 150°C for a given time. The automatic mode stirring helped the mixing and uniform heating of the reactants. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and then poured into cold water, filtered to give the crude products, which were further purified by recrystallization from 95% EtOH. The reaction time and the yields are listed in Table 3. The analytical data of new products are as following:

4-Benzylidene-2-phenyl-1H-imidazol-5(4H)-one (3a). IR (KBr): 3124, 3067, 2989, 1698, 1639, 1539, 1496, 1452, 1419, 1322, 1266, 1187, 1031, 922, 775, 687 cm^{-1}.

^{1}H NMR (400 MHz, DMSO) (δ, ppm): 12.12 (s, 1H, NH), 8.32 (d, J = 7.2 Hz, 2H, ArH), 8.18 (d, J = 7.6 Hz, 2H, ArH), 7.67–7.69 (m, 3H, ArH), 7.52–7.44 (m, 3H, ArH), 7.04 (s, 1H, CH).

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{12}N_2O$: 249.1023; found: 249.1023.

Anal calcd. For $C_{16}H_{12}N_2O$, C, 77.40; H, 4.87; N, 11.28; found C, 77.50; H, 4.79; N, 11.32%.

4-(4-Fluorobenzylidene)-2-phenyl-1H-imidazol-5(4H)-one (3b). IR (KBr): 3159, 3128, 3071, 2991, 1707, 1645, 1595, 1500, 1457, 1235, 1157, 921, 842, 784, 691 cm^{-1}.

^{1}H NMR (400 MHz, DMSO) (δ, ppm): 12.14 (s, 1H, NH), 8.41 (t, J = 8.0 Hz, 2H, ArH), 8.18 (d, J = 8.0 Hz, 2H, ArH), 7.68–7.59 (m, 3H, ArH), 7.35 (t, J = 8.8 Hz, 2H, ArH), 7.06 (s, 1H, CH).

Anal calcd. For $C_{16}H_{11}FN_2O$, C, 72.17; H, 4.16; N, 10.52; found C, 72.24; H, 4.14; N, 10.59%.

4-(4-Chlorobenzylidene)-2-phenyl-1H-imidazol-5(4H)-one (3c). IR (KBr): 3153, 3124, 3066, 2987, 1703, 1641, 1541, 1456, 1261, 1180, 1092, 923, 788, 691 cm^{-1}.

^{1}H NMR (400 MHz, DMSO) (δ, ppm): 12.18 (s, 1H, NH), 8.36 (d, J = 8.4 Hz, 2H, ArH), 8.19 (d, J = 8.4 Hz, 2H, ArH), 7.67–7.56 (m, 5H, ArH), 7.05 (s, 1H, CH).

Anal calcd. For $C_{16}H_{11}ClN_2O$, C, 67.97; H, 3.92; N, 9.91; found C, 67.88; H, 3.89; N, 9.99%.

4-(2,4-Dichlorobenzylidene)-2-phenyl-1H-imidazol-5(4H)-one (3d). IR (KBr): 3159, 3129, 3062, 2986, 1708, 1638, 1536, 1455, 1413, 1361, 1249, 1181, 1098, 915, 694 cm^{-1}.

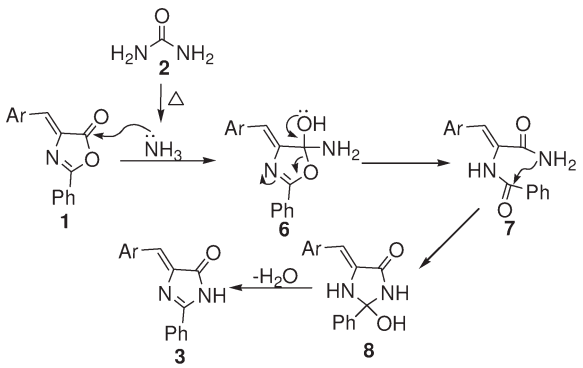
^{1}H NMR (400 MHz, DMSO) (δ, ppm): 12.36 (s, 1H, NH), 9.06 (s, 1H, ArH), 8.15 (d, J = 7.2 Hz, 2H, ArH), 7.70–7.61(m, 4H, ArH), 7.51 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, ArH), 7.18 (s, 1H, CH).

Anal calcd. For $C_{16}H_{10}Cl_2N_2O$, C, 60.59; H, 3.18; N, 8.83; found C, 60.65; H, 3.14; N, 8.89%.

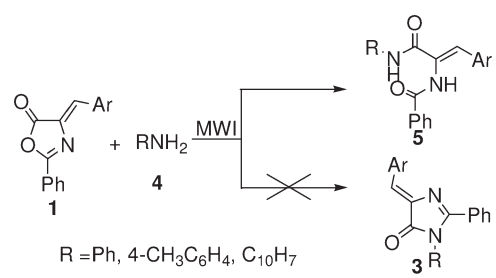
4-(3,4-Dichlorobenzylidene)-2-phenyl-1H-imidazol-5(4H)-one (3e). IR (KBr): 3127, 3068, 2986, 1711, 1646, 1547, 1455, 1416, 1355, 1249, 1125, 908, 784, 685 cm^{-1}.

^{1}H NMR (400 MHz, DMSO) (δ, ppm): 12.23 (s, 1H, NH), 8.60 (s, 1H, ArH), 8.33 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H, ArH), 8.18 (d, J = 7.2 Hz, 2H, ArH), 7.76 (d, J = 8.4 Hz, 1H, ArH), 7.68–7.61 (m, 3H, ArH), 7.04 (s, 1H, CH).

Scheme 3



Scheme 4



Anal calcd. For $C_{16}H_{10}Cl_2N_2O$, C, 60.59; H, 3.18; N, 8.83; found C, 60.51; H, 3.25; N, 8.78%.

4-(4-Methylbenzylidene)-2-phenyl-1H-imidazol-5(4H)-one (3f). IR (KBr): 3152, 3122, 3062, 2984, 1701, 1638, 1598, 1496, 1456, 1256, 1180, 1028, 922, 816, 789, 690 cm^{-1}.

^1H NMR (400 MHz, DMSO) (δ, ppm): 12.09 (s, 1H, NH), 8.22 (d, J = 7.8 Hz, 2H, ArH), 8.17 (d, J = 8.0 Hz, 2H, ArH), 7.67–7.59 (m, 3H, ArH), 7.32 (d, J = 8.0 Hz, 2H, ArH), 7.01 (s, 1H, CH), 2.38 (s, 3H, CH_3).

Anal calcd. For $C_{17}H_{14}N_2O$, C, 77.84; H, 5.38; N, 10.68; found C, 77.89; H, 5.31; N, 10.79%.

4-(2-Methoxybenzylidene)-2-phenyl-1H-imidazol-5(4H)-one (3g). IR (KBr): 3147, 3071, 2985, 2839, 1691, 1633, 1455, 1249, 1168, 1026, 923, 755 cm^{-1}.

^1H NMR (400 MHz, DMSO) (δ, ppm): 12.11 (s, 1H, NH), 8.92 (d, J = 8.0 Hz, 1H, ArH), 8.17 (d, J = 8.0 Hz, 2H, ArH), 7.65–7.58 (m, 3H, ArH), 7.46–7.41 (m, 2H, ArH), 7.13–7.10 (d, J = 7.6 Hz, 1H, ArH), 7.09 (s, 1H, CH), 3.92 (s, 3H, OCH_3).

Anal calcd. For $C_{17}H_{14}N_2O_2$, C, 73.37; H, 5.07; N, 10.07; found C, 73.42; H, 5.11; N, 10.00%.

4-(4-Methoxybenzylidene)-2-phenyl-1H-imidazol-5(4H)-one (3h). IR (KBr): 3121, 3065, 2969, 1699, 1596, 1456, 1304, 1264, 1172, 1028, 922, 827, 690 cm^{-1}.

^1H NMR (400 MHz, DMSO) (δ, ppm): 12.03 (s, 1H, NH), 8.31 (d, J = 8.4 Hz, 2H, ArH), 8.16 (d, J = 7.8 Hz, 2H, ArH), 7.65–7.58 (m, 3H, ArH), 7.08 (d, J = 8.0 Hz, 2H, ArH), 7.02 (s, 1H, CH), 3.84 (s, 3H, OCH_3).

Anal calcd. For $C_{17}H_{14}N_2O_2$, C, 73.37; H, 5.07; N, 10.07; found C, 73.30; H, 5.17; N, 9.98%.

2-Phenyl-4-((thiophen-2-yl)methylene)-1H-imidazol-5(4H)-one (3i). IR (KBr): 3116, 3061, 2985, 1698, 1634, 1457, 1419, 1320, 1256, 1200, 1121, 922, 891, 788, 692 cm^{-1}.

^1H NMR (400 MHz, DMSO) (δ, ppm): 12.06 (s, 1H, NH), 8.16 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 2H, ArH), 7.92 (d, J = 5.2 Hz, 1H, ArH), 7.74 (d, J = 2.7 Hz, 1H, ArH), 7.64–7.60 (m, 3H, ArH), 7.39 (s, 1H, CH), 7.21–7.18 (m, 1H, ArH).

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{10}N_2OS$: 255.0587; found: 255.0580.

Anal calcd. For $C_{14}H_{10}N_2OS$, C, 66.12; H, 3.96; N, 11.02; found C, 66.19; H, 3.90; N, 11.11%.

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