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Simple and Efficient Copper-Catalyzed Approach to 2,4-Disubstituted Imidazolones

Xiaoyu Gong,[†] Haijun Yang,[†] Hongxia Liu,[‡] Yuyang Jiang,[‡] Yufen Zhao,[†] and Hua Fu*[,†]

Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China, and Key Laboratory of Chemical Biology (Guangdong Province), Graduate School of Shenzhen, Tsinghua University, Shenzhen 518057, P. R. China

fuhua@mail.tsinghua.edu.cn

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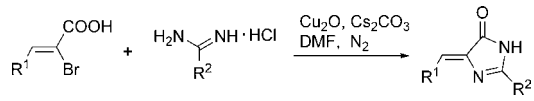
ABSTRACT



Some imidazolone derivatives are biological and pharmaceutical active molecules and the chromophores of the fluorescent proteins. In this communication, a simple and efficient approach to 4-arylidene-2-alkyl-4,5-dihydro-1*H*-imidazol-5-ones (2,4-disubstituted imidazolones) has been developed, and the protocol uses readily available 2-bromo-3-alkylacrylic acids and amidines as the starting materials without addition of any ligand or additive. The reactions were performed under mild conditions. Therefore, the present method will be of wide application in organic chemistry and medicinal chemistry.

The imidazolone motif appears in natural products. For example, bis(indole) alkaloids rhopaladins **A**−**D** (Figure 1), showing antibacterial activity against *Sarcina lutea* and *Corynebacterium xerosis* and inhibitory activity against cyclin-dependent kinase 4 and *c-erbB*-2 kinase, were isolated from the Okinawan marine tunicate *Rhopalaea* sp.[1] Imidazolones were applied as intermediates in the synthesis of natural products, such as biotin,[2] slagenins,[3] axinohydantoins,[4] and oroidin-derived alkaloids.[5] The imidazolone substructures were found to act as the chromophores of the fluorescent proteins, such as **E**[6] and **F**[7] for green fluorescent protein (GFP), **G** for the Y66F mutant of GFP, **H** for cyan fluorescent protein (CFP) representing the Y66W mutant of GFP, **I** for blue fluorescent protein (BFP) representing the Y66H mutant of GFP,[7] and **J** for red fluorescent protein (RFP) (Figure 1).[8] Imidazolones show various biological and pharmaceutical activities. For example, they are antagonists of many receptors including the neurokinin-1 receptor,[9] the CGRP receptor,[10] the dopamine receptors,[11] the angiotensin

[†] Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education).

[‡] Key Laboratory of Chemical Biology (Guangdong Province).

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II receptor,[12] and the β_3-adrenergic receptor.[13] They are also used as potent PDE4 inhibitors[14] and GABAA receptor ligands.[15] In addition, 2-imidazolones can be transferred into imidazoles that display wide biological and pharmaceutical activity.[16] Herein, we are interested in preparation of 4-arylidene-2-alkyl-4,5-dihydro-1*H*-imidazol-5-ones (2,4-disubstituted imidazolones) considering their wide applications in life science and medicinal chemistry. Only several approaches to 2,4-disubstituted imidazolones were reported until now,[7,17,18] and the protocols used reactions of oxazolones with amines[17,18a] or ammonia[18b] and coupling of imidates with amino acid esters.[18c] Recently, there has been great progress in copper-catalyzed N-arylations,[19] and the N-arylation strategy has been used to make N-heterocycles.[20] We have also developed some efficient methods for copper-catalyzed cross couplings[21] and synthesis of N-heterocycles.[22] In this communication, we report a simple and efficient copper-catalyzed synthesis of 4-arylidene-2-alkyl-4,5-dihydro-1*H*-imidazol-5-ones (2,4-disubstituted imidazolones) without addition of any ligand or additive under mild conditions.

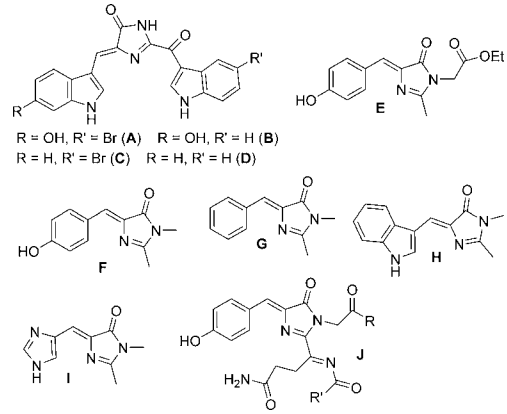
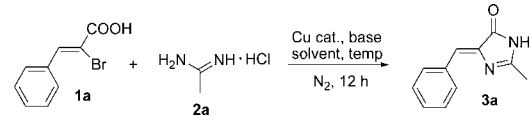


Figure 1. 2,4-Disubstituted imidazolone motif occurring in the natural products and the fluorescent proteins.

Table 1. Copper-Catalyzed Cascade Synthesis of (*Z*)-4-Benzylidene-2-methyl-4,5-dihydro-1*H*-imidazol-5-one (**3a**) via Coupling of 2-Bromo-3-phenylacrylic Acid (**1a**) with Acetamidine Hydrogen Chloride (**2a**): Optimization of Conditions[a]



entry	cat.	base	solvent	temp (°C)	yield (%)[b]
1	CuI	Cs_2CO_3	DMF	80	35
2	CuBr	Cs_2CO_3	DMF	80	27
3	CuCl	Cs_2CO_3	DMF	80	32
4	**Cu_2O**	**Cs_2CO_3**	**DMF**	**80**	**53**
5	CuO	Cs_2CO_3	DMF	80	15
6	$Cu(OAc)_2$	Cs_2CO_3	DMF	80	26
7	-	Cs_2CO_3	DMF	80	trace[c]
8	Cu_2O	K_2CO_3	DMF	80	37
9	Cu_2O	Na_2CO_3	DMF	80	43
10	Cu_2O	K_3PO_4	DMF	80	trace
11	Cu_2O	Cs_2CO_3	DMSO	80	40
12	Cu_2O	Cs_2CO_3	dioxane	80	0
13	Cu_2O	Cs_2CO_3	NMP	80	28
14	Cu_2O	Cs_2CO_3	DMF	r.t.	0
15	Cu_2O	Cs_2CO_3	DMF	60	trace

[a] Reaction conditions: 2-bromo-3-phenylacrylic acid (**1a**) (0.7 mmol), acetamidine hydrogen chloride (**2a**) (0.5 mmol), catalyst (0.1 mmol), base (1 mmol), and solvent (2 mL) under nitrogen atmosphere. [b] Isolated yield. [c] In the absence of copper catalyst.

2-Bromo-3-phenylacrylic acid (**1a**) and acetamidine hydrogen chloride (**2a**) were first used as the model substrates to optimize reaction conditions including optimization of the catalysts, bases, solvents, and temperature under nitrogen

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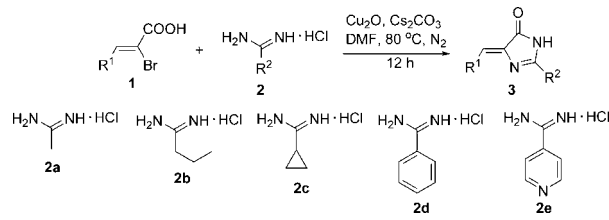
Table 2. Copper-Catalyzed Cascade Synthesis of 2,4-Disubstituted Imidazolones[a]



entry	1	3	yield (%)[b]	entry	1	3	yield (%)[b]
1	1a	3a	53	12	1c	3l	75
2	1a	3b	66	13	1c	3m	68
3	1a	3c	55	14	1c	3n	87
4	1a	3d	61	15	1c	3o	82
5	1a	3e	75	16	1d	3p	60
6	1b	3f	44	17	1d	3q	62
7	1b	3g	52	18	1d	3r	62
8	1b	3h	86	19	1e	3s	48[c]
9	1b	3i	71	20	1e	3t	45[d]
10	1b	3j	76	21	1e	3u	94
11	1c	3k	70	22	1e	3v	67[d]

[a] Reaction conditions: 2-bromo-3-alkylacrylic acid (**1**) (0.7 mmol), amidine hydrogen chloride (**2**) (0.5 mmol), Cu_2O (0.1 mmol), Cs_2CO_3 (1 mmol), and DMF (2 mL) under nitrogen atmosphere, reaction temperature of 80 °C, and reaction time of 12 h. [b] Isolated yield. [c] Reaction temperature of 100 °C. [d] 0.6 mmol of 2-bromo-3-(furan-2-yl)acrylic acid.

atmosphere. As shown in Table 1, six copper catalysts were investigated at 80 °C using 2 equiv of Cs_2CO_3 as the base (relative to amount of **2a**) in DMF (entries 1−6), and Cu_2O showed the best activity (entry 4). Only a trace amount of target product was found in the absence of copper catalyst (entry 7). Other bases, K_2CO_3, Na_2CO_3, and K_3PO_4, were tested, and Cs_2CO_3 was proven to be the most effective base (compare entries 4 and 8−10). The effect of solvents was

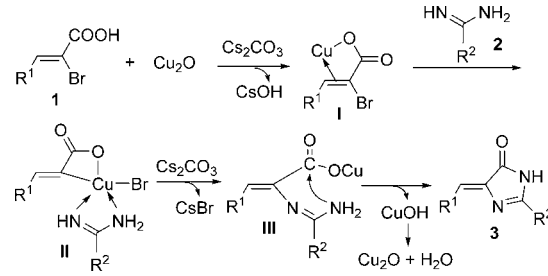
also investigated (compare entries 4 and 11−13), and DMF provided the highest yield (entry 4). Reaction temperature was also changed, and 80 °C was the best choice (compare entries 4, 14, and 15).

The scope of copper-catalyzed cascade reactions of 2-bromo-3-alkylacrylic acids with amidines was investigated under optimized conditions (20 mmol % of Cu_2O as the catalyst, 2 equiv of Cs_2CO_3 as the base, DMF as the solvent under nitrogen atmosphere). As shown in Table 2, all the substrates examined provided moderate to good yields at 80 or 100 °C. For various substituted 2-bromo-3-alkylacrylic acids, their reactivity did not show evident differences. In general, aromatic amidines showed slightly higher reaction activity than aliphatic ones. In addition, the cascade reactions could tolerate ether (entries 11−15 and 19−22) and the C−Cl bond (entries 16−18).

Since the suitable *ortho*-substituents could promote Ullmann-type couplings,[22a,d,23] a possible formation mechanism of 2,4-disubstituted imidazolones was proposed in Scheme 1 according to the results above. Coordination of 2-bromo-3-alkylacrylic acid with a Cu(I) ion first forms **I** in the presence of base (Cs_2CO_3). Oxidative addition of **I** and following complex of copper with amidine gives **II**, and reductive elimination of **II** provides **III**. Intramolecular nucleophilic attack[24] of amino to carbonyl in **III** affords 2,4-disubstituted imidazolone (**3**) freeing the copper catalyst.

In summary, we have developed a simple and efficient method for synthesis of 2,4-disubstituted imidazolones. The protocol uses readily available 2-bromo-3-alkylacrylic acids and amidines as the starting materials, and the corresponding target products were obtained in moderate to good yields without addition of any ligand or additive under mild conditions. The 2,4-disubstituted imidazolones are biological and pharmaceutical active molecules and the chromophores of the fluorescent proteins, and therefore, the present method will be of wide application in organic chemistry and medicinal chemistry.

Scheme 1. Possible Formation Mechanism of 2,4-Disubstituted Imidazolones



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Supporting Information Available: Synthetic procedures, characterization data, and ^1H and ^{13}C NMR spectra of these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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