ORGANIC LETTERS

2011
Vol. 13, No. 14
3694–3697

Copper-Catalyzed Aerobic Oxidative Intramolecular Alkene C–H Amination Leading to *N*-Heterocycles

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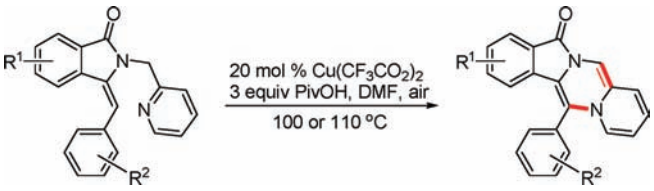
Received May 18, 2011

ABSTRACT



A copper-catalyzed aerobic oxidative intramolecular alkene C–H amination has been developed using readily available substituted 3-benzylidene-2-pyridin-2-ylmethyl-2,3-dihydro-isoindol-1-ones as the starting materials, and the corresponding *N*-heterocycles were obtained in good to excellent yields. This method should provide a new and useful strategy for constructing *N*-heterocycles.

N-Heterocycles are ubiquitous in a variety of natural products and biologically active molecules,[1] and they have been assigned as privileged structures in drug development because *N*-heterocyclic moieties often exhibit improved solubility and can facilitate the salt formation property, both of which are important for oral absorption and bioavailability.[2] The isoindolinone skeleton is the core unit of numerous naturally occurring substances,[3] and their derivatives have shown interesting biological properties.[4] The 1,4-dihydropyrazine ring is a key structural feature of some redox-active biological molecules (such as 1,5-dihydroflavin coenzymes[5]) and marine luciferins.[6] Pyrazine derivatives have been widely used in the fields of medicinal chemistry for the elaboration of the skeletons of biologically active sites.[7] However, synthesis of the combined molecules of isoindolinone and 1,4-dihydropyrazine frameworks (Figure 1) is not reported thus far. Therefore, we want to make this kind of poly *N*-heterocycles using readily available starting materials, and the synthesized new molecules can be potentially biologically activity.

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10.1021/ol2013395
Published on Web 06/22/2011

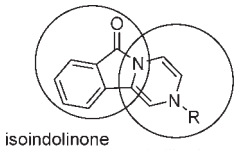
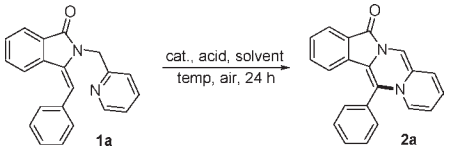


Figure 1. Structure of conjugate containing isoindolinone and 1,4-dihydropyrazine frameworks.

The development of transition-metal-catalyzed reactions for the formation of heterocycles continues to be an active area of research.[8] However, the precursors in the traditional methods needed possession of the corresponding functional groups or prefunctionalization before the synthesis of *N*-heterocycles. Recently, the direct functionalization of C−H bonds has made progress,[9] and some *N*-heterocycles, such as carbazoles,[10] benzimidazoles,[11] indazoles,[12] indolines,[13] and *N*-methoxylactams,[14] have been constructed through a C−H activation/C−N bond-forming strategy, and most of the methods used expensive palladium-, rhodium-, and ruthenium-based catalysts although they were very efficient. The use of transition-metal electrophiles in alkene heterocyclization reactions is attractive because facile cleavage of the metal−carbon bond often enables the metal electrophile to be regenerated and used catalytically, and palladium-catalyzed "Wacker-type" heterocylizations represent prominent examples of this principle and find many uses in the synthesis of oxygen and nitrogen heterocycles.[15] During the past decade, there have been remarkable advances in copper-catalyzed organic synthesis, and a wide scope of applications have been investigated because of the low cost and toxicity of copper catalysts and good functional tolerance of copper-catalyzed methods.[16] Recently, several examples for efficient copper-catalyzed sp^2 C−H amination have been reported,[17] and the heterocycles have been constructed via copper-promoted[18] or copper/iron-cocatalyzed[19] arene sp^2 C−H activation strategy using ideal dioxygen as the oxidant.[20] Herein, we report a novel copper-catalyzed aerobic oxidative intramolecular alkene C−H amination leading to *N*-heterocycles under air.

Table 1. Copper-Catalyzed C−H Amination of 3-Benzylidene-2-pyridin-2-ylmethyl-2,3-dihydro-isoindol-1-one (**1a**) Leading to *N*-Hetercycle (**2a**) under Air: Optimization of Conditions[a]



entry	cat.	acid	solvent	temp (°C)	yield (%)[b]
1	CuI	PivOH	DMF	100	54
2	CuBr	PivOH	DMF	100	52
3	CuCl	PivOH	DMF	100	48
4	Cu_2O	PivOH	DMF	100	trace
5	$Cu(OAc)_2$	PivOH	DMF	100	40
6	$Cu(O_2CCF_3)_2$	PivOH	DMF	100	68
7	$CuSO_4 \cdot 5H_2O$	PivOH	DMF	100	63
8	$CuCl_2$	PivOH	DMF	100	trace
9	$CuBr_2$	PivOH	DMF	100	trace
10	CuO	PivOH	DMF	100	trace
11	Cu	PivOH	DMF	100	33
12	–	PivOH	DMF	100	0
13	**$Cu(O_2CCF_3)_2$**	**PivOH**	**DMF**	**110**	**83**
14	$CuSO_4 \cdot 5H_2O$	PivOH	DMF	110	69
15	$Cu(O_2CCF_3)_2$	PivOH	DMSO	110	71
16	$Cu(O_2CCF_3)_2$	AcOH	DMF	110	78
17	$Cu(O_2CCF_3)_2$	CF_3COOH	DMF	72	0
18	$Cu(O_2CCF_3)_2$	–	DMF	110	0

[a] Reaction conditions: 3-benzylidene-2-pyridin-2-ylmethyl-2,3-dihydroisoindol-1-one (**1a**) (0.5 mmol), catalyst (0.1 mmol), acid (1.5 mmol), solvent (2 mL), reaction time (8 h) in a flask under air. [b] Isolated yield.

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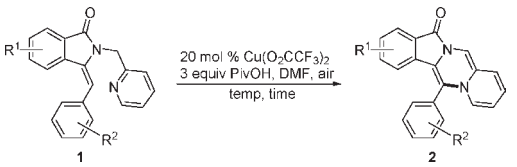
Table 2. Copper-Catalyzed Aerobic Oxidative Intramolecular Alkene C−H Amination Leading to *N*-Heterocycles[a]



1 2

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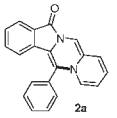
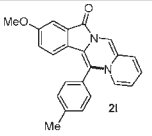
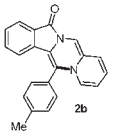
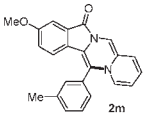
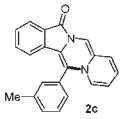
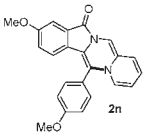
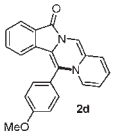
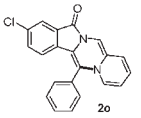
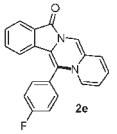
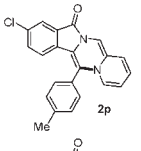
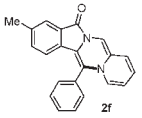
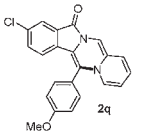
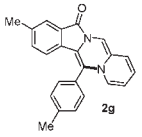
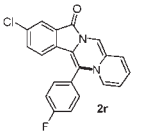
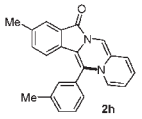
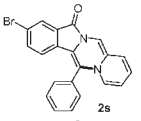
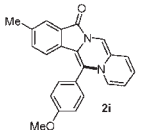
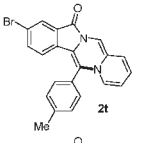
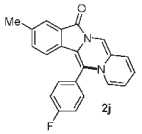
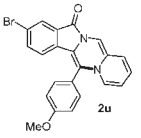
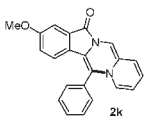
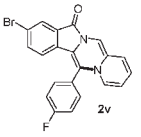
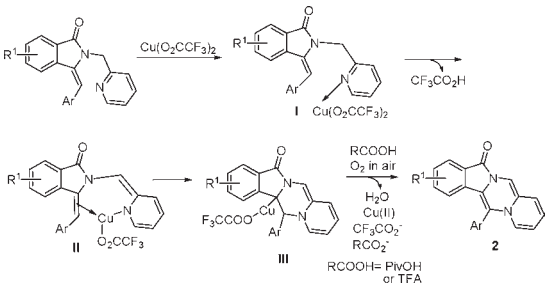
1	110 °C, 8 h	 2a	83	12	110 °C, 18 h	 2l	72
2	110 °C, 8 h	 2b	85	13	110 °C, 18 h	 2m	78
3	110 °C, 8 h	 2c	83	14	110 °C, 18 h	 2n	77
4	110 °C, 8 h	 2d	88	15	100 °C, 48 h	 2o	65
5	110 °C, 18 h	 2e	74	16	100 °C, 48 h	 2p	71
6	110 °C, 8 h	 2f	78	17	100 °C, 48 h	 2q	69
7	110 °C, 8 h	 2g	80	18	100 °C, 48 h	 2r	63
8	110 °C, 8 h	 2h	80	19	100 °C, 48 h	 2s	68
9	110 °C, 8 h	 2i	85	20	100 °C, 48 h	 2t	70
10	110 °C, 18 h	 2j	76	21	100 °C, 48 h	 2u	62
11	110 °C, 18 h	 2k	71	22	100 °C, 48 h	 2v	65

[a] Reaction condition: **1** (0.5 mmol), catalyst (0.1 mmol), PivOH (1.5 mmol), DMF (2 mL) in a flask under air. [b] Isolated yield.

At first, the substituted 3-methyleneisoindolin-1-ones (**1**) were prepared through copper-catalyzed cascade reactions of 2-bromobenzamides with terminal alkynes in DMF in sealed Schlenk tubes at 80 °C according to the previous procedure,[21] and they were used as the substrates in this work. Here, 3-benzylidene-2-pyridin-2-ylmethyl-2,3-dihydro-isoindol-1-one (**1a**) was used as the model substrate to optimize reaction conditions including catalysts, acids (as additives), solvents, and reaction temperatures under air (1 atm). As shown in Table 1, various copper salts (0.2 equiv) were tested in the presence of 3 equiv of pivalic acid (relative to amount of **1a**) in DMF at 100 °C under air (entries 1−11), and $Cu(O_2CCF_3)_2$ and $CuSO_4 \cdot 5H_2O$ provided higher yields (entries 6 and 7). The yields increased when the temperature was raised to 110 °C from 100 °C, and $Cu(O_2CCF_3)_2$ displayed more efficiency (see entries 13 and 14). The yield decreased when DMSO replaced DMF as the solvent (entry 15). We attempted other acids, trifluoroacetic acid and acetic acid (entries 16 and 17), and they were inferior to pivalic acid (compare entries 13, 16, and 17). No target product was found in the absence of acid (entry 18).

The scope on the copper-catalyzed intramolecular C−H amination of **1** leading to *N*-hetercycles (**2**) was investigated under the optimized conditions using 20 mol % of $Cu(O_2CCF_3)_2$ as the catalyst, 3 equiv of pivalic acid as the additive (relative to amount of **1**), and DMF as the solvent. As shown in Table 2, the corresponding target products were obtained in good to excellent yields for the examined substrates at 100 or 110 °C. The reaction temperature remained at 100 °C when R^1 was halo substituents (entries 15−22), and a slightly lower temperature could reduce formation of side products. For R^1 and R^2 substituents, the substrates containing electron-donating groups provided slightly higher yields than those containing electron-withdrawing groups. The copper-catalyzed intramolecular C−H amination showed the tolerance of the functional groups in the substrates including ether (entries 4, 9, 11−14, 17, and 21), C−F bond (entries 5, 10, 18, and 22), C−Cl bond (entries 15−18), and C−Br bond (entries 19−22).

Scheme 1. Possible Mechanism for Copper-Catalyzed Aerobic Oxidative Intramolecular Alkene C−H Amination Leading to *N*-Heterocycles (**2**)



A possible mechanism for copper-catalyzed aerobic oxidative intramolecular alkene C−H amination is suggested in Scheme 1. Coordination of the pyridine ring in **1** with $Cu(O_2CCF_3)_2$ forms **I**, and isomerization of the pyridine ring[22] and the following complexation with Cu(II) yields **II** releasing CF_3COOH (TFA). Further intramolecular addition of the alkene C=C bond[23] in **II** provides **III**, and oxidation of **III** with oxygen in air in the presence of acid gives **2** leaving a Cu(II) catalyst.

In summary, we have developed an efficient copper-catalyzed aerobic oxidative intramolecular alkene C−H amination leading to *N*-heterocycles. The protocol uses cheap and readily available $Cu(O_2CCF_3)_2$ as the catalyst, substituted 3-methyleneisoindolin-1-ones as the starting materials, and economical and environment friendly air as the oxidant, and the corresponding *N*-heterocycles were obtained in good to excellent yields. To the best of our knowledge, this can be the first example of constructing *N*-heterocycles via copper-catalyzed aerobic oxidative intramolecular alkene C−H amination. This method should provide a new and useful strategy for constructing *N*-heterocycles.

Acknowledgment. The authors wish to thank the National Natural Science Foundation of China (Grant No. 20972083) and the Ministry of Science and Technology of China (2009ZX09501-004) for financial support.

Supporting Information Available. Synthetic procedures, characterization data, and ^1H, ^{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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