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Silver triflate-copper(II) acetate cooperative catalysis in a cascade reaction for concise synthesis of 2-carbonyl *H*-pyrazolo[5,1-*a*]isoquinolines[†]

Zhiyuan Chen,*^a Liang Gao,^a Shengqing Ye,^b Qiuping Ding^a and Jie Wu*^b

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A cascade reaction of N'-(2-alkynylbenzylidene)hydrazide with allenoate in the presence of dioxygen co-catalyzed by silver triflate and copper(II) acetate under mild conditions is described, which provides an efficient approach to 2-carbonyl *H*-pyrazolo[5,1-*a*]isoquinolines.

The presence of the isoquinoline and pyrazolo[1,5-*a*]pyridine scaffolds in many biologically active compounds has stimulated the development of methods for their preparation.^{1,2} Recently, *H*-pyrazolo[5,1-*a*]isoquinoline which incorporates both isoquinoline and pyrazolo[1,5-*a*]pyridine skeletons was discovered to display promising activities for inhibition of CDC25B, TC-PTP, and PTP1B.³ With an expectation for the discovery of lead compounds, methods development for the efficient synthesis of diverse *H*-pyrazolo[5,1-*a*]isoquinolines is in great demand.

As a versatile building block, allene has been applied widely in organic synthesis, and the chemistry of allene has been extensively explored.⁴ Recently, we have been involved in the transformations of N'-(2-alkynylbenzylidene)hydrazides.^{3,5} By considering the features of our recent synthesis of H-pyrazolo[5,1-a]isoquinolines and the advancement of allene chemistry, we envisaged that an allenoate could take part in the reaction of N'-(2-alkynylbenzylidene)hydrazide. After an electrophilic 6-endo-cyclization and the subsequent [3+2] cycloaddition, an intermediate **B** would be formed (Scheme 1). It is well known that the utilization of molecular oxygen as an oxidant has attracted considerable attention because of its ready availability and its inexpensive and environmental benign character.6,7 Recently, Zhu and co-workers reported an intramolecular dehydrogenative aminooxygenation reaction, resulting in the formation of aromatic *N*-heterocycles substituted with a formyl group.⁸ It was found that the carbonyl oxygen in the aldehyde products was from dioxygen and the reaction proceeded through a peroxycopper(III) intermediate. Inspired by this result, we hypothesized

^b Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China. E-mail: jie_wu@fudan.edu.cn; Fax: +86 21 6564 1740; Tel: +86 21 6510 2412

† Electronic supplementary information (ESI) available. CCDC 868983. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc30413a that a peroxy–copper(III) intermediate could be introduced into the cycloaddition adduct **B** (Scheme 1) as well. Compound **B** would coordinate with a copper(II) catalyst, which then undergoes a single-electron transfer from copper(II) to dioxygen to produce the peroxy–copper(III) intermediate **C**. Formation of a carbon–oxygen bond occurs *via* an isomerization of the resulting peroxy–copper(III) intermediate **C**. Elimination of Cu^{II}–OH generates a carbonyl compound **E**, which undergoes spontaneous aromatization to yield *H*-pyrazolo[5,1-*a*]isoquinoline **3**. In the reaction process, Ag(I)/Cu(II) cooperative catalysis⁹ would be essential for the successful transformation. Herein, we describe the results of the above investigation for the preparation of 2-carbonyl *H*-pyrazolo[5,1-*a*]isoquinolines, co-catalyzed by silver triflate and copper(II) acetate in the presence of dioxygen.

Conditions for the Ag(I)/Cu(II) co-catalyzed cascade reaction of N'-(2-alkynylbenzylidene)hydrazide with allenoate in the presence of dioxygen were explored using N'-(2-alkynylbenzylidene)hydrazide **1a** and *n*-butyl buta-2,3-dienoate **2a** as the model substrates (Table 1). Since silver triflate was demonstrated as the choice for the 6-*endo*-cyclization of N'-(2-alkynylbenzylidene)hydrazide in dichloroethane (DCE), initially the reaction occurred in DCE/DMF at room temperature in the presence of 10 mol% of silver



Scheme 1 Proposed synthetic route for the generation of 2-carbonyl *H*-pyrazolo[5,1-*a*]isoquinolines in the presence of cooperative catalysis under oxygen.

^a Key Laboratory of Functional Small Organic Molecules, Ministry of Education and College of Chemistry & Chemical Engineering, Jiangxi Normal University, Nanchang, Jiangxi 330022, China

Table 1 Initial studies for the reaction of N'-(2-alkynylbenzylidene)hydrazide 1a with n-butyl buta-2,3-dienoate 2a under dioxygen in the presence of cooperative catalysis



| Entry | [Cu] catalyst | Base | Solvent | Yield ^a (%) | |
|---|--|--------------------------------|-------------|------------------------|--|
| 1 | | _ | DCE/DMF | nd | |
| 2 | $Cu(OTf)_2$ | _ | DCE/DMF | 33 | |
| 3 | CuCl ₂ | _ | DCE/DMF | 29 | |
| 4 | CuCO ₃ ·Cu(OH) ₂ | _ | DCE/DMF | 42 | |
| 5 | $Cu(NO_3)_2$ | _ | DCE/DMF | 39 | |
| 6 | $Cu(OAc)_2$ | _ | DCE/DMF | 43 | |
| 7 | $Cu(OAc)_2$ | Cs_2CO_3 | DCE/DMF | 39 | |
| 8 | $Cu(OAc)_2$ | K ₂ CO ₃ | DCE/DMF | 38 | |
| 9 | $Cu(OAc)_2$ | Et ₃ N | DCE/DMF | 55 | |
| 10 | $Cu(OAc)_2$ | K ₃ PO ₄ | DCE/DMF | 66 | |
| 11 | $Cu(OAc)_2$ | t-BuOK | DCE/DMF | 52 | |
| 12 | $Cu(OAc)_2$ | t-BuONa | DCE/DMF | 48 | |
| 13 | $Cu(OAc)_2$ | NaOAc | DCE/DMF | 53 | |
| 14 | $Cu(OAc)_2$ | K ₃ PO ₄ | DCE/THF | 23 | |
| 15 | $Cu(OAc)_2$ | K ₃ PO ₄ | DCE/DMA | 45 | |
| 16 | $Cu(OAc)_2$ | K ₃ PO ₄ | DCE/MeCN | 31 | |
| 17 | $Cu(OAc)_2$ | K_3PO_4 | DCE/toluene | 12 | |
| ^{<i>a</i>} Isolated yield based on N' -(2-alkynylbenzylidene)hydrazide 1a . | | | | | |

triflate without the addition of copper(II) salt under dioxygen. In addition, no base was presented at the outset since DMF could act as a Lewis base in the reaction mixture. As predicted, no desired product 3a was detected (Table 1, entry 1). Only a trace amount of product was observed when the reaction was performed under nitrogen (data not shown in Table 1). 2-Carbonyl H-pyrazolo[5,1-a]isoquinoline 3a could be isolated in 33% yield when 20 mol% of copper(II) triflate was added in the reaction (Table 1, entry 2). The structural elucidation of compound 3a by X-ray diffraction analysis is presented in Fig. 1 (see the ESI⁺). Different copper(II) salts including CuCl₂, CuCO₃·Cu(OH)₂, Cu(NO₃)₂, and Cu(OAc)₂ were screened (Table 1, entries 3–6). It was found that the reaction worked efficiently when Cu(OAc)₂ was used as the co-catalyst, which afforded the corresponding product in 43% yield (Table 1, entry 6). Next, various bases were added in the reaction (Table 1, entries 7–13). From the results, K_3PO_4 was the best choice, which led to the desired product in 66% yield (Table 1, entry 10). In the meantime, the solvent effect was investigated (Table 1, entries 14-17). However, no better results were obtained. The reaction was retarded when the amount of



Fig. 1 X-Ray ORTEP illustration of H-pyrazolo[5,1-a]isoquinoline 3a (30% probability ellipsoids).

Table 2 Reactions of N'-(2-alkynylbenzylidene)hydrazides 1 with allenoate 2 in the presence of dioxygen co-catalyzed by silver triflate and copper(II) acetate



| Entry | Substrate 1 | Allene 2 | Yield ^a (%) |
|-------|------------------------------|------------------------------------|------------------------|
| 1 | Ph la | == ^{CO2ⁿBu 2a} | 66 (3a) |
| 2 | 1a | H ₃ C 2b | 45 (3b) |
| 3 | 1a | Ph CO2Et 2c | 60 (3c) |
| 4 | N-NHTs ⁿ Bu 1b | 2a | 53 (3d) |
| 5 | 1b | 2c | 68 (3e) |
| 6 | 1c | 2a | 55 (3f) |
| 7 | 1c | 2c | 45 (3g) |
| 8 | Ph 1d | 2a | 70 (3h) |
| 9 | 1d | 2c | 63 (3i) |
| 10 | | 2c | 71 (3j) |
| 11 | Meo Ph 1f | 2a | 42 (3 k) |
| 12 | CIN_NHTs Ph lg | 2a | 58 (3 I) |
| 13 | F Ph 1h | 2a | 62 (3m) |
| 14 | 1h | 2b | 42 (3n) |
| 15 | F Bu" 1i | 2c | 63 (3 0) |
| 16 | Ph Ji | 2a | 50 (3p) |

^a Isolated yield based on N'-(2-alkynylbenzylidene)hydrazides 1.

silver triflate or copper acetate was reduced. The result could not be improved when the temperature was elevated.

We next explored the reaction scope under the optimized conditions (10 mol% of silver triflate, 20 mol% of copper acetate, DCE/DMF, rt). Table 2 shows the summary of results for the evaluation of various substituted N'-(2-alkynylbenzylidene)hydrazides with allenoate under dioxygen. The presence of carbonyl group adds flexibility to further elaborate the final products. Not only aldehyde but also ketone could be formed, depending on the allenoates utilized. For example, when methyl or phenyl-substituted allenoate was employed in the reaction of N'-(2-alkynylbenzylidene)hydrazide 1a under the standard conditions, the corresponding ketone was obtained as expected (Table 2, entries 2 and 3). Moreover, incorporation of the alkyl substituents into the triple bond does not hamper the efficiency of the process. For instance, the reactions proceeded smoothly when N'-(2-alkynylbenzylidene)hydrazide **1b** or **1c** was used in the reactions of allenoate under dioxygen (Table 2, entries 4-7). The nature of the substituents on the aromatic ring of the N'-(2-alkynylbenzylidene)hydrazides can include methyl, methoxy, chloro, and fluoro groups. Furthermore, heteroaromaticsubstituted N'-(2-alkynylbenzylidene)hydrazide 1k also underwent this transformation, leading to the desired product 3p in 50% yield (Table 2, entry 16).

In summary, a cascade reaction of N'-(2-alkynylbenzylidene)hydrazide with allenoate in the presence of dioxygen co-catalyzed by silver triflate and copper(II) acetate under mild conditions is described, which provides an efficient approach to 2-carbonyl H-pyrazolo[5,1-a]isoquinolines. The silver triflate–copper(II) acetate cooperative catalysis is essential for the successful transformation. A possible mechanism is illustrated, which indicates that the reaction proceeds through a peroxy– copper(III) intermediate. Activation of dioxygen by using the strategy of cooperative catalysis in other transformations is in progress in our laboratory, and the results will be reported in due course.

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