Tetrahedron Letters 56 (2015) 4638-4641

Contents lists available at ScienceDirect

Tetrahedron Letters

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

TBAI-catalyzed synthesis of α -ketoamides via sp³ C–H radical/radical cross-coupling and domino aerobic oxidation



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ARTICLE INFO

ABSTRACT

Article history: Received 13 May 2015 Revised 4 June 2015 Accepted 9 June 2015 Available online 14 June 2015

Keywords: TBAI-catalyzed α -Ketoamides Radical/radical cross-coupling Aerobic oxidation sp³ C-H bond

experiments suggested a possible oxidative coupling mechanism. © 2015 Elsevier Ltd. All rights reserved.

A TBAI-catalyzed one-pot synthesis of α -ketoamides via sp³ C-H radical/radical cross-coupling and dom-

ino aerobic oxidation was developed. This synthesis is suitable for abroad range of substrates. The control

 α -Ketoamides are key structural motifs in many natural products, biological compounds, pharmaceuticals, and synthetic intermediates.^{1,2} Traditionally, they are synthesized by condensation of their corresponding α -keto acids or α -keto acyl halides with amines.³ Recently, more convenient oxidation methods were developed, including the direct oxidation of the corresponding α hydroxyamides,⁴ arylacetamides,⁵ or α -amino- α -cyanoketones,⁶ the oxidative coupling of arylacetaldehydes, aryl methyl ketones, β -diketones or terminal alkynes with amines,⁷ and decarboxylative or decarbonylative acylation of formamides.⁸

N,*N*-Dimethylformamide as a ubiquitous solvent and multipurpose reagent has widely been used in many organic reactions.⁹ With the development of green and sustainable chemistry, utilization of DMF as a precursor may have important affection on the practical transformations. Compared with the corresponding amines, DMF showed less pollution, odor, and toxicity. Recently, more and more chemists focused on the research of using DMF as amine or amide sources. Although a lot of successful syntheses of α -ketoamides using DMF⁸ were developed, these transformations did not comply with the atom economy, in which at least one carbon atom was wasted in decarboxylation or decarbonylation. Herein, we present a TBAI-catalyzed one-pot synthesis of α -ketoamides via sp³ C–H radical/radical cross-coupling and domino

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aerobic oxidation, in which water was only by-product, without CO or CO_2 emissions (Scheme 1).

Initially, we chose toluene (**1a**) and DMF (**2a**) as model substrates to optimize the reaction conditions and the results are summarized in Table 1. Firstly, the well-established $nBu_4NI/TBHP$ catalytic system⁸ was chosen for this oxidative coupling. Unexpectedly, the desired compound (**3a**) was isolated in very poor yield (Table 1, entry 1). Further reaction attempts with other oxidants (Table 1, entry 2). Further reaction attempts with other oxidants (Table 1, entry 2). However, when two equiv additive of K_2CO_3 was added, the yield of **3a** increased to 43% (Table 1, entry 6). Among the examined other bases, Cs_2CO_3 showed the best performance, which increased the yield to 69% (Table 1, entries 7–10). Upon elevating the temperature to 120 °C, the yields were remarkably increased to 83%. The use of other catalysts or increasing the amount of loading catalyst, led no significant improvement on the yield (Supporting information, SI-Tables 1 and 2).

Having optimized the conditions, we explored the utility of this approach for this transformation. At the beginning of our investigation, most of the methylarenes were employed to react with DMF, giving the corresponding products in moderate to good yields (3a-3t). The reaction showed a good tolerance to many functional groups, including electron-donating and electron-withdrawing groups (e.g., OMe, Cl, Br, F, and CF₃). However, the substrates with electron-withdrawing groups gave some lower yields (3b > 3c and 3d, 3e > 3f, 3g and 3h, 3i > 3j and 3l). The connection position of the substrates on the benzene ring had little significant influence on the reaction $(3b \times 3e$ and 3i, $3c \times 3h$ and 3j). O-tBu substitute







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Scheme 1. Synthesis of α -ketoamides using formamides.





^a Reaction conditions: **1a** (0.5 mmol), **2a** (4 mL), TBAI (10 mol %), oxidant, additive, at 80 °C, under Ar atmosphere for 12 h.

^b Reaction at 120 °C.

^c Isolated yield.

(**3k**) gave no product due to the big steric hindrance. Satisfactorily, 2-methylfuran and 2-methylthiophene also proceeded smoothly to give the target products **3m** and **3n** in 48% and 53%, respectively. However, non-aromatic substrates showed no activity (**3o** and **3p**). Next a series of *N*,*N*-dialkylformamides were explored, but the results did not show an evident difference with DMF (**3m**-**3p**) (Scheme 2 and Table 2).

To understand the role of each compound in the formation of these α -ketoamides, control experiments were performed (see SI-Scheme 1 in the Supporting Information). Firstly, **1a** and **2a** reacting under standard conditions in the absence of Cs₂CO₃ gave no **3a**, and 63% yield of *N*,*N*-dimethyl-2-phenyl-acetamide (**3a**') was afforded (Eqs. 1 and 2). Subsequently, addition of 1.5 equiv TEMPO inhibited the reaction. These results suggest the formation of **3a**' involving a radical process.^{7.8} Secondly, **3a**' could be

converted to **3a** under standard conditions in 82% yield (Eq. 3), which suggests **3a**' as an important intermediate for the transformation.⁵ Finally, **1a** reacted under standard conditions with or without Cs_2CO_3 not affording any phenylmethanol and benzalde-hyde. Based upon the experimental and literatures' results,^{5,7,8} a plausible radical/radical cross-coupling and domino aerobic oxidation mechanism is proposed in Scheme 3.

In summary, we present a TBAI-catalyzed one-pot synthesis of α -ketoamides via sp³ C–H radical/radical cross-coupling and domino aerobic oxidation, in which water was only by-product, without CO or CO₂ emissions. This synthesis is suitable for a broad range of substrates. The control experiments suggested a possible oxidative coupling mechanism. Further studies concerning the detailed mechanism and the broader scope of substrates are currently underway in our laboratory.



Scheme 2. Control experiments.

Table 2Screening the utility of this approach





Scheme 3. The possible mechanism.

Acknowledgments

This work was supported financially by grants from the National Natural Science Foundation of China (Grants 21302066) and Young Program, SCF of Jiangsu Province (BK20130129).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.06. 021.

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