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Synthesis of aliphatic α-ketoamides from α-substituted methyl ketones *via* a Cu-catalyzed aerobic oxidative amidation†

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α-Ketoamides are an important key functional group and have been used as versatile and valuable intermediates and synthons in a variety of functional group transformations. Synthetic methods for making aryl α-ketoamides as drug candidates have been greatly improved through metal-catalyzed aerobic oxidative amidations. However, the preparation of alkyl α-ketoamides through metal-catalyzed aerobic oxidative amidations has not been reported because generating α-ketoamides from aliphatic ketones with two α-carbons theoretically provides two distinct α-ketoamides. Our strategy is to activate the α-carbon by introducing an *N*-substituent at one of the two α-positions. The key to this strategy is how heterocyclic compounds such as triazoles and imidazoles affect the selectivity of the synthesis of the alkyl α-ketoamides. From this basic concept, and by optimizing the reaction and elucidating the mechanism of the synthesis of aryl α-ketoamides *via* a copper-catalyzed aerobic oxidative amidation, we prepared fourteen aliphatic α-ketoamides in high yields (48–84%).

Introduction

α-Ketoamides, founded in natural products and biologically relevant molecules such as a cytokine inhibitor,[1] an RARγ agonist,[1] an epoxide hydrolase inhibitor,[2] a PLA_2 inhibitor,[3] a histone deacetylase inhibitor,[4] a coronavirus inhibitor,[5] and an HCV protease inhibitor,[6] are an important key functional group, as shown in Fig. 1. These α-ketoamides have been used as versatile and valuable intermediates and synthons in a variety of functional group transformations and in total syntheses.[7] In the last decade, synthetic methods[8–13] for making aryl α-ketoamides in pharmaceutical research have been greatly advanced by the development of metal-catalyzed aerobic oxidative amidation reactions from phenylacetylene,[9] phenylacetaldehyde,[10] acetophenone,[11] propiophenone,[12] and 2-phenylpropanoic acid.[13] However, the preparation of alkyl α-ketoamides *via* a metal-catalyzed aerobic oxidative amidation has not been reported.[1]

Aerobic oxidative amidation or esterification reactions are the most attractive and powerful strategy for oxidizing the α-carbons of ketones with molecular oxygen. According to previous works on the preparation of aryl α-ketoamides or α-ketoesters, as shown in Scheme 1, the mechanisms of the aerobic oxidative amidation and esterification are different according to the kind of aryl ketone used as the starting material. In the case of aryl methyl ketones without substituents on their α-carbons, the common major intermediate in Scheme 1(a) is phenylglyoxal, and no cleavage of the C(CO)–C(CO) bonds was observed in this process (Scheme 1(a)).[11,14] On the other hand, aerobic oxidative C–C σ-bond cleavage of symmetrical aryl-substituted-1,3-diones can smoothly convert them into α-ketoesters.[15] The C(CO)–C(alkyl) bond cleavage of aryl–alkyl–ketones as unsymmetrical ketones for the synthesis of aryl long-chain-alkyl esters *via* an aerobic oxidation and oxygenation process with molecular oxygen was reported by the Jiao group.[16] And when there are substituents on the α-carbon of the ketone, the desired oxygenation pathway competes with a C(CO)–C(CO) bond cleavage pathway in the aerobic oxidation mechanism. This competition is related with hydroperoxide formation and dioxetane formation. The Jiao group reported the synthesis of α-ketoamide from α-carbonyl aldehyde, which is in a higher oxidation state of the α-carbon *via* aerobic oxidation (Scheme 1(b)).[17]

Interestingly, the Schoenebeck group reported how to avoid the two competing pathways: the desired oxygenation (C–H α-hydroxylation) and C(CO)–C(CO) cleavage in the copper-catalyzed selective aerobic oxidation of the α-carbon of a 2-methyl cyclic ketone.[18] The Zhang group was also able to obtain diarylmethanones and arylmethanoic acid by controlling the oxygenation and C(CO)–C(CO) bond cleavage pathways, respectively, in the aerobic oxidation of 2-phenylacetophenone.[19]

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†Electronic supplementary information (ESI) available: Experimental procedures, and characterization for desired products (α-ketoamides), starting materials (α-*N*-heteroaryl ketones), and compounds trapped by TEMPO. See DOI: 10.1039/d1ob00129a

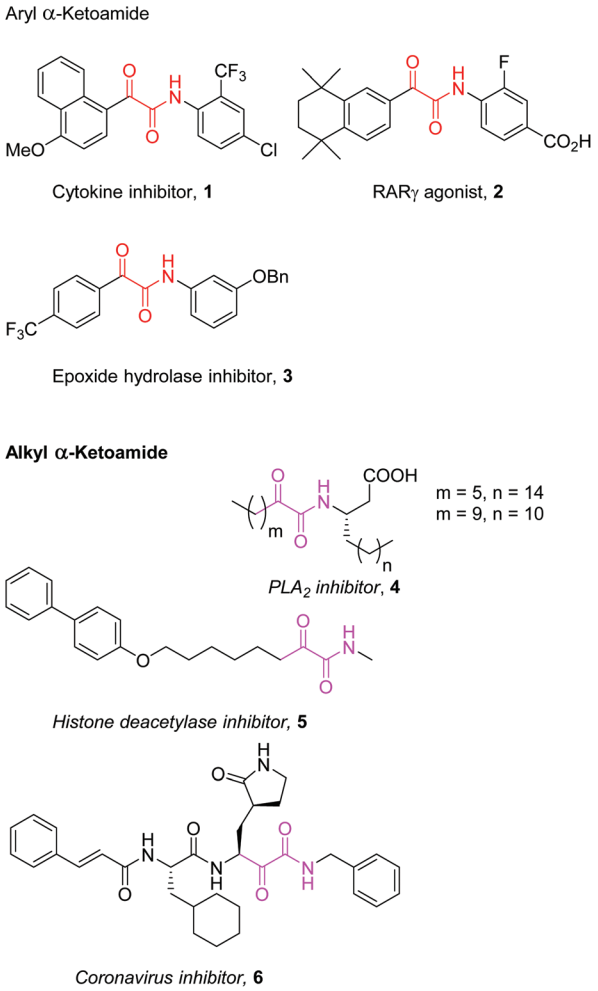
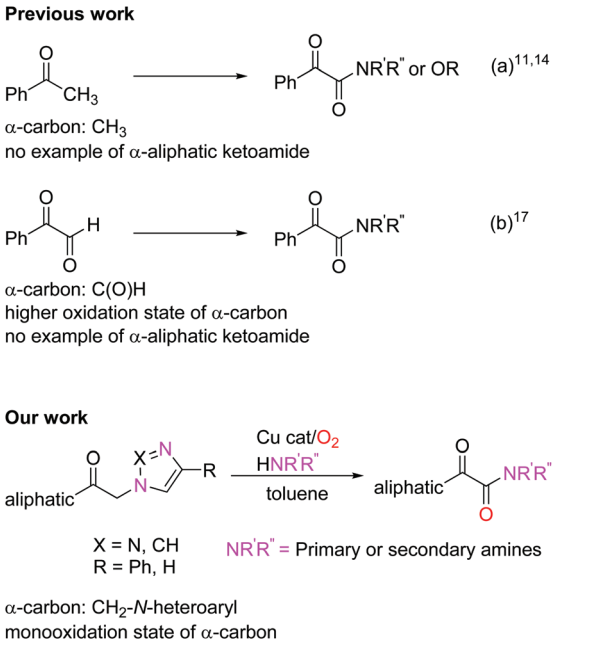
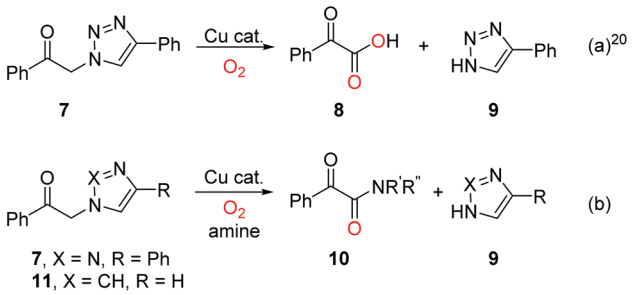


Fig. 1 Various α-ketoamides.[1–6]



Scheme 1 Cu-Catalyzed aerobic oxidative coupling to prepare α-ketoamides from ketones.



Scheme 2 Model reaction of the Cu-catalyzed aerobic oxidation.

Despite the significance of these reports, there are two challenging tasks for new synthesis of aliphatic α-ketoamides: (1) controlling hydroperoxide formation and dioxentane formation in the oxygenation of unsymmetrical 2-substituted-ketone is still challenging and (2) while aryl ketones have one reaction site, alkyl ketones have two possible reaction sites, making their reactions more complicated.

Our work applies imidazole and triazole substituted at the α-carbon of the ketone as an unsymmetrical ketone to solve the challengeable tasks in the Cu-catalyzed aerobic oxidative amidation. Initially, factors of inducing major hydroperoxide formation were found, depending on whether the synthesis of aryl α-ketoamides was improved or not. Then, the optimized conditions were applied to synthesize the alkyl α-ketoamide. Finally, the predominant regioselectivity of introducing molecular oxygen at the doubly activated carbon of aliphatic ketone was proved with a TEMPO trapping experiment.

Recently, we reported a synthetic method to prepare 4-substituted-*NH*-1,2,3-triazoles *via* an aerobic oxidative *N*-dealkylation using copper(II) acetate from **7**.[20] The evidence for the formation of triazole **9** indicates that phenylglyoxylic acid was also formed (Scheme 2(a)), as shown in the plausible mechanism. We also proposed that phenylglyoxylic acid is formed when hydroxide attacks the key triazol-1-yl-1,2-diketo intermediate. If an amine or alcohol is present in that reaction, α-ketoamides or α-ketoesters would be formed, respectively. According to this hypothesis, α-triazolyl acetophenones are preferred and, as a result, aryl α-ketoamides could be obtained in a high yield (Scheme 2(b)). Thus, these results are also applicable to the preparation of alkyl α-ketoamides. Herein, this paper reports a new chemoselective, Cu-catalyzed aerobic oxidative amidation to synthesize aliphatic α-ketoamides from α-substituted methyl ketones using amines and molecular oxygen as the oxidant. As ketones have two α-positions, the synthesis of aliphatic α-ketoamides from ketones selectively by aerobic oxidation is challenging; however, it has been achieved herein (Scheme 1, our work). We optimized the aerobic oxidation reaction selectively using an α-substituted acetophenone **7**, which has one α-position (see ESI, Tables S1 and S2†).

Then, based on the optimized conditions, we searched the optimized reaction conditions for aliphatic α-ketoamide.

Results and discussion

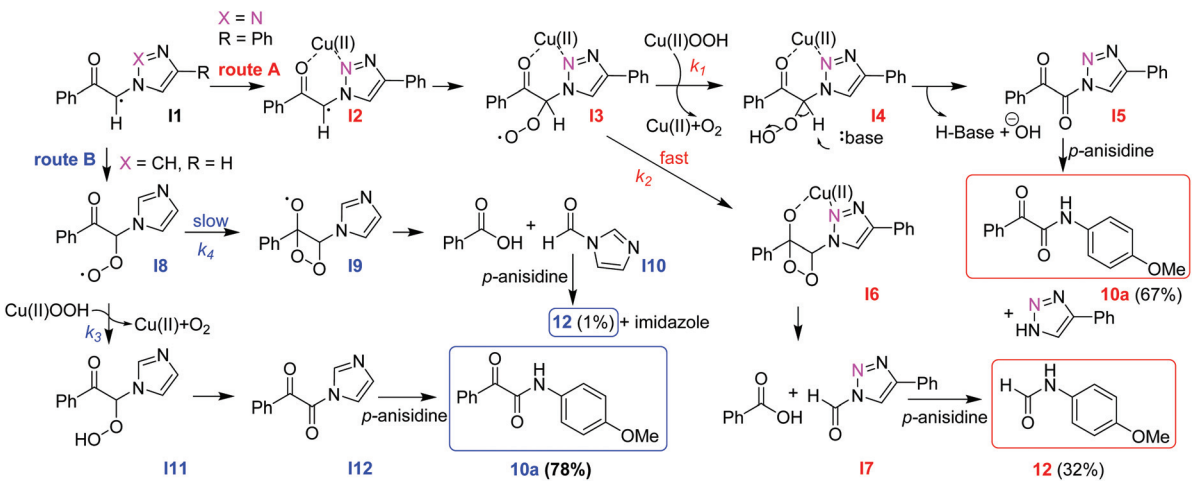
Preliminary investigation for the synthesis of α-ketoamide by using isotope $^{18}O_2$, and a plausible mechanism

To prove the mechanism of incorporation of O_2 in the hypothesis (Scheme 2(b)), previously reported reaction conditions[20] with the addition of *p*-anisidine as a probe and bpy as a ligand were tested in the presence of $^{18}O_2$, instead of molecular oxygen $^{16}O_2$. This result is **^{16}O/^{18}O-10a** (73%) and **^{18}O/^{18}O-10a** (20%) in the isotopic ratio of **10a** (GC-MS spectrum, see ESI†). Furthermore, investigation that **10a** was left under previously reported reaction conditions with the addition of $H_2{}^{18}O$ (2 equiv.) and bpy under an argon atmosphere resulted in **^{18}O/^{16}O-10a** (58%) and **^{16}O/^{16}O-10a** (42%) in the isotopic ratio of **10a** (GC-MS spectrum, see ESI†). This result means that the reason for **^{18}O/^{18}O-10a** formation is isotope scrambling of the **^{16}O/^{18}O-10a** product with the ^{18}O-water that is generated after the formation of **^{16}O/^{18}O-10a**. The evidence that only a one oxygen atom from molecular oxygen O_2 is incorporated into α-carbon of ketone is related to selective aerobic oxidative amidation as the ultimate goal. Based on the experimental results (see ESI, Table S1†) and the literature,[20] a plausible mechanism that explains the different outcomes when using triazolyl and imidazolyl groups is proposed, as shown in Scheme 3. The mechanism of the formation of **Intermediate 1** (**I1**), as proposed in a previous report,[20] was determined by trapping with TEMPO. TEMPO-trapped α-triazolyl-acetopheone was proved by single-crystal X-ray diffraction studies.[20] From **I1**, two key intermediates, **I3** and **I8**, can be generated from 7 (triazole group) and **11** (imidazole group), respectively. **I3** can chelate with Cu(II) ions between the oxygen of the ketone and the N2-nitrogen of the triazole, while **I8** cannot. Consequently, the dioxygen radical in **I3** will attack the carbonyl carbon faster (k_2) than that of **I8** (k_4) because the carbonyl carbon of **I3** will be activated by the copper(II) ion, resulting in a greater partial positive charge on the carbon compared to that of **I8**. In comparing the reaction rates (k_1 and k_2), products **10a** and **12** were formed in a ratio of 67% and 32%, respectively. In the case of **I8**, the formation of **12** *via* **I9** was completely suppressed, while the desired product **10a** was obtained selectively in a high yield. To understand what the new function of imidazole under the optimized conditions for selective aerobic oxidation is, further investigation is needed in comparison to pyridine as the base.

Synthesis of aliphatic α-ketoamides from aliphatic ketones under optimization of the conditions

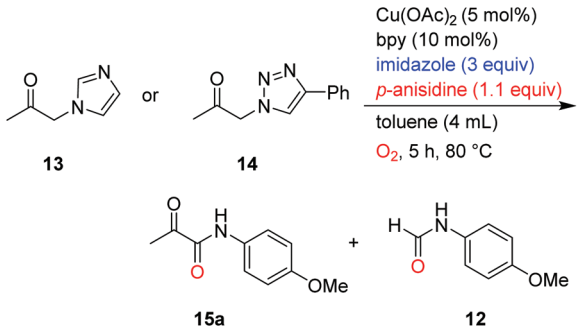
Theoretically, preparing α-ketoamides from aliphatic ketones with two α-carbons can afford two distinct α-ketoamides. Our strategy is to activate the α-carbon by introducing an *N*-substituent at one of the two α-positions. As we have developed a copper-catalyzed aerobic oxidative C–N bond cleavage reaction, a triazole group would be a good substituent to activate one of the α-carbons. The key to this strategy is determining how heterocyclic compounds such as triazoles and imidazoles affect selectivity in the synthesis of aliphatic compounds. When discussing the two α-positions of the ketone, we consider one carbon to be *singly activated* and the other carbon bearing the heterocycle to be *doubly activated*.[21] In a similar manner to the results (see ESI, Table S1†) for preparing aryl α-ketoamides, the key question is whether the carbon of the aliphatic ketone doubly activated by the heterocyclic moiety could be regioselectively oxidized. To the best of our knowledge, this is the first finding that aliphatic-α-ketoamides are prepared regioselectively on doubly activated carbon, when triazole or imidazole is attached into the α-carbon of the aliphatic ketone to conduct a Cu-catalyzed aerobic oxidative amidation reaction.

To prepare aliphatic α-ketoamides, α-heteroaryl acetones **13** and **14** were subjected to the optimal reaction conditions for preparing aryl α-ketoamides (see ESI, Table S1†). From



Scheme 3 Plausible mechanism and difference between the triazolyl and imidazolyl group.

Table 1 Optimization studies for the synthesis of pyruvic amide[a]



Entry	sm	Variation from the standard conditions	15a[b] (%)	12[b] (%)
1	**13**	None	68	0
2	**14**	None	32	38
3[c]	**14**	Imidazole (0 equiv.)	11	43
4	**14**	Pyridine (1 equiv.) instead of imidazole (3 equiv.)	0	59

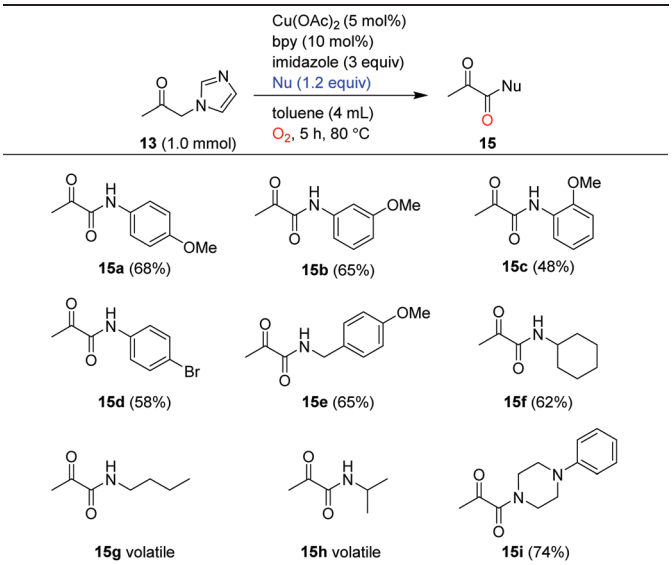
[a] Reaction conditions: ketone (1.0 mmol scale), O_2 balloon, 0.5 N HCl (aq) work-up. [b] Isolated yield. [c] Reaction time = 24 h.

α-imidazol-1-yl acetone **13**, the desired product, pyruvic amide **15a**, was isolated in a moderate yield (68%, Table 1, entry 1), while the undesired side product, formamide **12**, was not isolated (0%). In the case of α-triazolyl acetone **14**, the side product was isolated in 38% yield, which was due to the cleavage of a C–C bonding in the starting material (Table 1, entry 2). Without imidazole as a base, the reaction time increased to 24 h (full consumption of the starting material), and the selectivity for **15a** decreased (entry 3). When we used pyridine as the base instead of imidazole, the yield of the side product **12** increased and that of the desired product **15a** decreased (entry 4). We considered the heteroaryl group substituted on the α-carbon of acetone to be a key factor in determining the regioselectivity of the incorporation of the oxygen. Among the heterocycles tested, the imidazole group induced a better regioselectivity than was achieved with the triazole group.

The scope of various amines, including anilines, in the copper-catalyzed aerobic oxidative amidation was investigated as shown in Table 2. Products **15a–d** from anilines, **15e–h** from primary amines and **15i** from secondary amines were obtained in quite good yields. In the case of *ortho*-anisidine, which could have steric hindrance, the desired compound **15c** was obtained in a slightly lower yield (48%). Secondary amines can easily react with α-imidazol-1-yl acetone to afford the corresponding α-ketoamide product **15i** (74%).

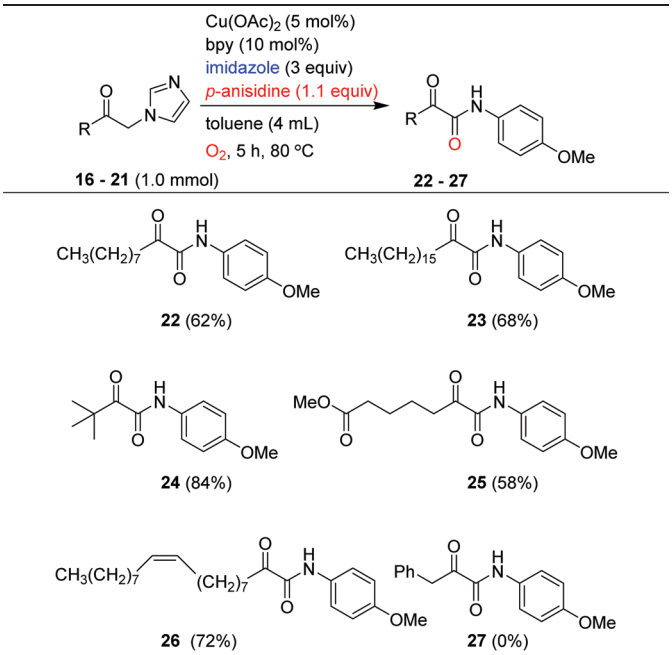
Long-chain alkyl ketones containing various substituents provided the corresponding α-ketoamides. Unfortunately, acyl amide could also be isolated as a side product. This side product was not observed with the previously tested substituents, such as aryl and methyl groups. Control reactions for the synthesis of long-chain α-ketoamides were conducted (Table 3). Intriguingly, α-imidazol-1-yl ketones **16** and **17** with simple, long-chain aliphatic substituents afforded simple long-

Table 2 The scope of amines in the copper-catalyzed aerobic oxidative amidation to prepare aliphatic α-ketoamides[a,b]



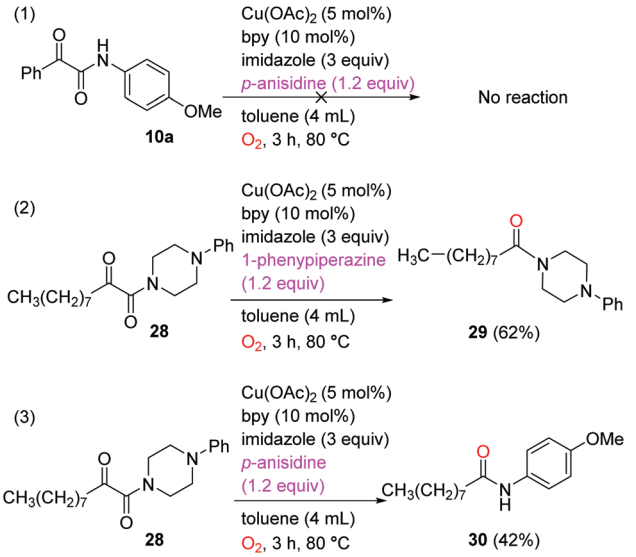
[a] Reaction conditions: ketone (1.0 mmol scale), O_2 balloon, 0.5 N HCl (aq) work-up. [b] Isolated yields.

Table 3 Preparation of various aliphatic α-ketoamides *via* copper-catalyzed aerobic oxidative amidation[a,b]



[a] Reaction conditions: ketone (1.0 mmol scale), O_2 balloon, 0.5 N HCl (aq) work-up. [b] Isolated yields.

chain α-ketoamides **22** (62%) and **23** (68%) in moderate yields. Although the long chains contained ester or olefin moieties, which could be converted into carboxylic acids and epoxides as side products, these reactions proceeded smoothly in moderate yields to afford **25** (58%) and **26** (72%). However, **21** did



Scheme 4 Three additional experiments to elucidate the reaction mechanism.

not afford the desired product because both α-carbons of the substrate were activated as benzyl groups, even though starting material **21** was completely consumed.

To understand the reaction mechanism, we performed the reactions shown in Scheme 4. When aryl α-ketoamide **10a**, the product of the aerobic oxidative amidation, was subjected to the optimized conditions, no reaction occurred. When aliphatic α-ketoamide **28**, the product of the aerobic oxidative amidation, was left under the optimized conditions, but in the presence of 1-phenylpiperazine instead of *p*-anisidine, 1-(4-phenylpiperazin-1-yl)nonan-1-one (**29**) was obtained in 62% yield. On the other hand, when aliphatic α-ketoamide **28**, the product of the aerobic oxidative amidation, was left under the optimized conditions, *N*-(4-methoxyphenyl)nonanamide (**30**) was obtained in 42% yield. In these two reactions, the aliphatic α-ketoamide could be transformed to **29** or **30**. The mechanism of this reaction should be studied further. The Baeyer–Villiger oxidation did not occur from the aryl α-ketoamide.

In the case of the aryl ketones in Scheme 3, there is only one radical formation at the one α-carbon, such as **Intermediate 1** (**I1**). Clarifying the selectivity of the radical formation at the two α-carbons in the aerobic oxidation of aliphatic ketones would be important for understanding the reaction mechanism. TEMPO has been widely used to determine if a radical pathway is active during a reaction.[22] It has also been reported that when TEMPO is introduced, an α-hydroxylated product can be obtained by an additional reduction.[23] Fig. 2 shows ^{1}H NMR spectra indicating the selectivity of the radical

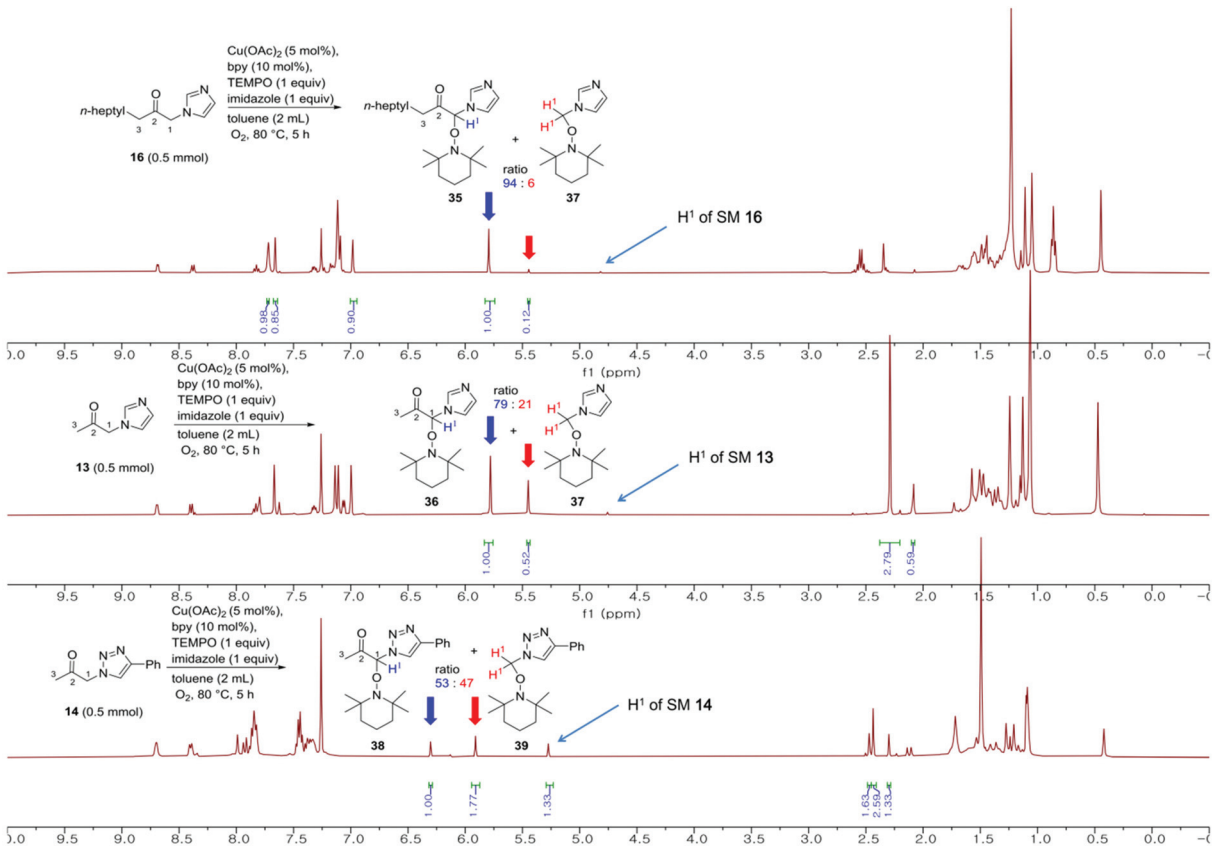


Fig. 2 ^{1}H NMR studies to determine the selectivity of the radical formation at the two α-carbons of three aliphatic ketones as starting materials by scavenging with TEMPO.

formation at the two α-carbons of three aliphatic ketone starting materials in the presence of TEMPO as a scavenger. From imidazole **16**, the ratio of product **35** to **37** was 94 : 6. From another imidazole, **13**, products **36** and **37** were produced at a ratio of 79 : 21. Because C3 in compound **16** is not only more sterically hindered but also bears a less acidic hydrogen due to the heptyl substituent compared with the C3 position of compound **13**, the generation of the C3 radical of compound **16** was not as favorable.

In the case of **14**, the product ratio of **38** to **39** was 53 : 47. The C1/C3 selectivity with triazolyl-substituted starting material **14** was lower than that of the previous two reactions, which started from imidazole-substituted compounds **16** and **13**. These results can be explained by the fact that imidazole **13** provided a better selectivity for the synthesis of the desired product than **14**, which has a triazolyl-substituent at the α-carbon, as shown in Table 1.

The chelation of the N2-nitrogen of the triazole and the oxygen of the ketone to the Lewis acidic copper ions[24,25] will activate the H3 hydrogen, providing the C3 radical intermediate. This chelate structure can be found in the literature in the analogous reaction of acylpyrazole with TEMPO.[25] In our triazole reaction, the chelation in **14** decreased the electron density on the C2 carbonyl carbon, which favored the C–C bond cleavage reaction, decreasing the selectivity of the aerobic oxidation.

Conclusions

In summary, we have developed a new copper-catalyzed aerobic oxidative amidation of aliphatic ketones for the synthesis of aliphatic α-ketoamides *via* the introduction of imidazole at the α-carbon of the aliphatic ketone and using extra imidazole as the base. First of all, aerobic oxidative amidation of α-(1,2,3-triazol-1-yl)acetophenone resulted in aryl α-ketoamides and formamides through formation of peroxide and C(CO)–C(CO) cleavage of the ketone, respectively. ^{18}O labeling experiments demonstrate that carbonyl oxygen atom of amide in the aryl α-ketoamide originated from molecular oxygen. This means that inhibiting the C(CO)–C(CO) cleavage pathway in the aerobic oxidative amidation of α-(1,2,3-triazol-1-yl)acetophenone is the major issue for the selective aerobic amidation. As a result, applying an α-imidazolyl acetophenone instead of α-(1,2,3-triazol-1-yl) acetophenone as the substrate, and imidazole as the base allowed the selective synthesis of aryl α-ketoamides. Based on these results, using α-imidazolyl-aliphatic ketones as the substrates gives rise to alkyl α-ketoamides, highlighting the *versatility* of this protocol. Moreover, the observation of acyl amides as side products in the synthesis of alkyl α-ketoamides provides insight into the stepwise pathway involving the imine from the air overoxidation of the alkyl α-ketoamide. However, the acyl amide was not observed in the synthesis of aryl α-ketoamides. The discovery of a stepwise pathway through the aerobic oxidative amidation of alkyl α-ketoamides provides a new platform for achieving the *selective* aerobic oxidation of long-chain lipid ketones.[26] In addition, scavenging *doubly activated carbon* with TEMPO in the unsymmetrical ketone showed the selectivity of the radical formation at the two α-carbons of three aliphatic ketones as starting materials. Further studies to understand the mechanism of the selective oxidative amidation and esterification, and the synthetic application, are in progress.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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