Direct synthesis of 2-oxo-acetamidines from methyl ketones, aromatic amines and DMF via copper-catalyzed C(sp³)–H amidination†

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A convenient method for the synthesis of 2-oxo-acetamidines from methyl ketones using aromatic amines and DMF as nitrogen sources is reported via copper-catalyzed C(sp³)–H amidination. Various methyl ketones react readily with aromatic amines and DMF, producing 2-oxo-acetamidines in yields of 47 to 92%. This protocol features the simultaneous formation of C–N and C≡N bonds using DMF and aromatic amines as two different nitrogen sources. It thus provides an efficient approach to construct acyclic amidines via three C(sp³)–H bond amidination. Based on the preliminary experiments, a plausible mechanism of this transformation is disclosed.

Introduction

Amidines are important structural motifs in natural products, bioactive molecules and functional materials.1 They have profound applications in diverse areas such as medicinal chemistry, synthetic intermediates, catalyst design, material science, supramolecular chemistry, and coordination chemistry.2 Therefore, the direct and convenient construction of amidines is an important and popular research field, particularly for the synthesis of 2-oxo-acetamidines due to the wide applications of their carbonyl group as a versatile intermediate in the synthesis of a broad range of acetamidine derivatives.3 Recently, transition metal and metal-free catalyzed C–N bond formation has arisen as an excellent synthetic method to build complex structures because it reduces prefunctionalization while improving atom economy and energy efficiency.4 These protocols used nitriles,5 isonitriles,6 organic azides,7 and amines8 as nitrogenous sources, which are considered important pathways to construct cyclic and acyclic amidines. Amides are key building blocks of proteins and are broadly found in natural and manufactured organic molecules.9 Meanwhile, amides are also often used as precursor molecules to synthesize amidines.10 The general method of synthesizing amidines by amides is mainly divided into the following two strategies: (1) direct amidination of the amide and amine scaffolds without decarbonylation of amide, providing cyclic amidines as the final product (eqn (a)–(c) in Scheme 1);10 (2) decarbonylation of the amide to semicyclic amidines (Scheme 1, eqn (d)).11 Although significant progress has been made in this field, direct and efficient methods for the synthesis of acyclic amidines from amide are still highly desired.

As our continuing interest in carbon–nitrogen coupling fields,12 and inspired by the above-mentioned studies, we herein report a copper-catalyzed amidination of methyl ketones, aromatic amines and DMF to acyclic amidines, 2-oxo-acetamidines (Scheme 1, eqn (e)). Even though the reactions of methyl ketones with amines or amides are known to achieve the synthesis of α-ketoamides by using metal and metal-free approaches,13 the synthesis of acyclic amidines using amides and aromatic amines as two different nitrogen sources has not been described previously. This approach allows direct amidination of three C(sp³)–H bonds and affords C–N bond and C≡N bond simultaneously. This protocol provides a versatile approach to 2-oxo-acetamidines with good functional group

Scheme 1 Methods for the synthesis of amidines.
Results and discussion

Initially, the reaction of acetophenone 1a, aniline 2a and DMF catalyzed by copper salts was performed to optimize the reaction conditions. The results were listed as shown in Table 1. To our delight, under CuCl₂ conditions, reaction of 1a, 2a with DMF afforded mainly oxidative amidination product 4aa in 15–85% yield (entries 1–8, Table 1). Subsequently, a number of other oxidants including DTBP, TBHP, BPO, AIBN were explored. Only the DTBP and TBHP effected the reaction, among which DTBP proved to be superior oxidant, giving 4aa in 75% yield (entries 1–4; Table 1). Gratifyingly, further improvement of the process was achieved when the reaction conducted under the ligand of phen (1,10-phenanthroline monohydrate), affording 4aa in 85% yield (entry 5; Table 1). Copper salts exhibited unique ability in this transformation, as the reaction did not occur without copper catalyst (entry 6; Table 1). After a series of copper salts were tested (entries 9–13; Table 1), CuCl₂ was demonstrated to be the best choice. Further studies indicated that base can promote this transformation, PhCOOK is optimal (entries 14–17; Table 1). Under the nitrogen atmosphere, 1a and 2a could not react to form 4aa (entry 8; Table 1). This fact implied that oxygen was essential for this reaction. Reaction temperature and reaction time were also scanned to improve the yield, and 120 °C and 36 h were determined as optimum for the oxidative amidination reaction (entries 18–22; Table 1). After screening on different parameters, the highest yield of 4aa (85%) was achieved when the reaction was carried out with CuCl₂ (0.1 mmol), phen (0.1 mmol), PhCOOK (0.5 mmol) and DTBP (2 mmol) at 120 °C under the atmosphere of oxygen in DMF (entry 9; Table 1).

With the optimized reaction conditions in hand, the scope with respect to the methyl ketones was firstly evaluated (Table 2). A wide variety of methyl ketones bearing electron-donating and electron-withdrawing functional groups gave the corresponding products in moderate to excellent yields (4aa–4ra). The position of the substituents on the aryl ring had a minor effect on the efficiency of this transformation. For example, not only methyl ketones 1d and 1i possessing para substituents but also substrates 1c,1e and 1b, bearing substituents in meta and ortho position, afforded the corresponding products in good yields. In addition, our newly developed protocol tolerated a variety of functionalities, including halogens (4ea, 4fa, 4ga and 4ha), methoxy (4ka), ethoxy (4la), ester groups (4ma), t-buty l (4na). Notably, reactive primary amine on the aromatic ring were also

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**Table 1** Optimization of the reaction conditions

| Entry | [Cu] (mol%) | Base         | Solvent | Oxidant (equiv.) | T (°C) | Yield (%) |
|-------|-------------|--------------|---------|------------------|--------|-----------|
| 1     | CuCl₂ (20)  | PhCOOK       | DMF     | DTBP(4)          | 120    | 75        |
| 2     | CuCl₂ (20)  | PhCOOK       | DMF     | TBHP(4)          | 120    | 15        |
| 3     | CuCl₂ (20)  | PhCOOK       | DMF     | BPO(4)           | 120    | 0         |
| 4     | CuCl₂ (20)  | PhCOOK       | DMF     | AIBN(4)          | 120    | 0         |
| 5    | CuCl₂ (20)  | Phen         | DMF     | DTBP(4)          | 120    | 85        |
| 6    | CuCl₂ (20)  | PhCOOK       | DMF     | DTBP(4)          | 120    | 0         |
| 7    | CuCl₂ (20)  | PhCOOK       | DMF     | DTBP(4)          | 120    | 36        |
| 8    | CuCl₂ (20)  | PhCOOK       | DMF     | DTBP(4)          | 120    | 0         |
| 9    | CuCl₂ (20)  | PhCOOK       | DMF     | DTBP(4)          | 120    | 56        |
| 10   | CuBr (20)   | PhCOOK       | DMF     | DTBP(4)          | 120    | 23        |
| 11   | CuI (20)    | PhCOOK       | DMF     | DTBP(4)          | 120    | 19        |
| 12   | CuClO₂(20)  | PhCOOK       | DMF     | DTBP(4)          | 120    | 50        |
| 13   | Cu(acac)₂(20) | PhCOOK   | DMF     | DTBP(4)          | 120    | 47        |
| 14   | CuCl₂ (20)  | PhCOOK       | DMF     | DTBP(4)          | 120    | 60        |
| 15   | CuCl₂ (20)  | CH₂COONa     | DMF     | DTBP(4)          | 120    | 55        |
| 16   | CuCl₂ (20)  | CH₂ONa       | DMF     | DTBP(4)          | 120    | 45        |
| 17   | CuCl₂ (20)  | Cs₂CO₃       | DMF     | DTBP(4)          | 120    | Trace     |
| 18   | CuCl₂ (20)  | PhCOOK       | DMF     | DTBP(4)          | 80     | 36        |
| 19   | CuCl₂ (20)  | PhCOOK       | DMF     | DTBP(4)          | 100    | 50        |
| 20   | CuCl₂ (20)  | PhCOOK       | DMF     | DTBP(4)          | 140    | 71        |
| 21   | CuCl₂ (20)  | PhCOOK       | DMF     | DTBP(4)          | 120    | 55        |
| 22   | CuCl₂ (20)  | PhCOOK       | DMF     | DTBP(4)          | 120    | 74        |

* Reaction conditions: 1a (0.5 mmol), 2a (0.5 mmol), catalyst (0.1 mmol), and base (0.5 mmol), oxidant, additive and solvent (2 mL) under O₂ atmosphere at 120 °C for 36 h. * Isolated yields. * Phen (0.1 mmol). * Air. * N₂ atmosphere. * 12 h. * 24 h. DTBP = di-tert-butyl peroxide, TBHP = tert-butyl hydroperoxide, BPO = benzoyl peroxide, AIBN = 2,2′-azobis(2-methylpropionitrile), phen = 1,10-phenanthroline monohydrate, DMSO = dimethyl sulfoxide, DMF = N,N-dimethylformamide, THF = tetrahydrofuran.
tolerated (4oa). Fortunately, when p-nitroaniline were used as substrates, the desired products were detected (4ja) in moderate yield. Heteroaryl methyl ketones were also investigated, and the corresponding products were obtained in moderate to excellent yields (4pa, 4qa, 4ra). Pyridine methyl ketones failed to participate in the reaction to obtain the desired product (4sa, 4ta).

Moreover, this methodology could be extended to alkyl methyl ketones as well, although in moderate yield (4ua).

Next, the scope of aromatic amines was explored (Table 3). A wide range of structurally diverse aromatic amines were suitable substrates for this transformation. For example, aryl amines bearing methyl groups could generate the corresponding 2-oxo-acetamidines 4ab–4ad in excellent yields. Under the optimal reaction conditions, the meta-halogen substrates (4ae–4ag) and the para-halogen substrates (4ah–4ak) are both completely tolerated. Also, functional groups such 4-isopropyl (4am), 3,5-dimethoxy (4an) were well tolerated under our reaction conditions. Fortunately, when p-nitroaniline were used as substrates, the desired products were detected (4al) in moderate yield. Moreover, heteroaryl amines were also investigated, and the corresponding products were obtained in moderate yields (4ao, 4ap). Unfortunately, pyridin-2-amine and 5-methylisoxazol-3-amine are not prone to this reaction (4aq, 4ar).

Meanwhile, quinolin-8-amine does not react (4as).

Then, the scope of amides was explored (Table 4). Unfortunately, this protocol was not general to a wide range of formamides including N,N-diethylformamide, N-methylformamide, N-methyl-N-phenylformamide, morpholine-4-carbaldehyde with piperidine-1-carbaldehyde, giving no desired products.

To elucidate the mechanism, some control experiments were performed (Scheme 2). At first, the reaction of acetophenone 1a with aniline 2a was carried out without CuCl₂, and the desired product 4aa was not detected (Scheme 2 [eqn (1)]). When the reaction was done in the absence of O₂, 4aa was also not detected (Scheme 2 [eqn (1)]). These results suggested that both CuCl₂ and O₂ were necessary for the reaction. When 2.0 equiv. of BHT (2,6-di-tert-butyl-4-methylphenol) was added under the standard conditions, the reaction was inhibited substantially (Scheme 2 [eqn (1)]). The result suggests that the reaction may involve a radical reaction. Our reaction may be involved dimethylamine generated in situ from DMF.¹⁴ To verify this pathway, dimethylamine 5 was then used instead of DMF under the same conditions (Scheme 2 [eqn (2)]), and only a little amount of 4aa was detected. This result implies that an aminal radical, not an amine, was the intermediate in the transformation process. Accordingly to the literatures and experimental results,¹⁵ we predicted that acetophenone 1a may be oxidized to phenylglyoxal intermediate, and then form Schiff base to complete the transformation process. Therefore, we conducted a control experiment in which phenylglyoxal monohydrate 6 and imine 7...
were used as substrates under standard conditions (Scheme 2 [eqn (3) and (4)]). The experimental results show that the target product is obtained in a lower yield, indicating that 6 and 7 may not be the key intermediates in the reaction. As shown in eqn (5), the reactions between 2a and 2-(dimethylamino)-1-phenylethan-1-one 8 were investigated. Under the optimized conditions, the product 4aa could be furnished in 80% yields (Scheme 2 [eqn (5)]). The results demonstrated that the reaction may have undergone 8 intermediate process. Notably, 2-oxo-N,N,N-diphenylacetamide 9 and 1-phenyl-2-(phenylamino)ethan-1-one 10 both were not suitable substrates for the reaction (Scheme 2 [eqn (6) and (7)]). When the reaction was carried out in the absence of acetophenone 1a, N,N-dimethyl-N'-phenylformimidamide 11 and 1,2-diphenyldiazene 12 were detected (Scheme 2 [eqn (8)]). This result indicated the cationic aniline radicals maybe formed in this reaction.16

On the basis of the above results, a plausible mechanism for the copper-catalyzed aerobic oxidative coupling is illustrated in Scheme 3. In the first step, the tert-butoxy radicals trapped hydrogen from the aryl methyl ketone and DMF respectively to form radical B13,17 and aminyl radical A.18 Then, decarboxylation of A produced aminyl radical C, which reacted with radical B to generate intermediate D. D was then

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**Table 4** Scope of N,N-disubstituted formamides<sup>a</sup>

| Reaction conditions: 1a (0.5 mmol), 2a (0.5 mmol), CuCl₂ (0.1 mmol), PhCOOK (0.5 mmol), DTBP (2 mmol), phen (0.1 mmol), DMSO (2 mL), O₂ (1 atm), 36 h, 120 °C. | N.D. = not detected. | GC yields. |
|---|---|---|
| 4aa | 14% | 80% |
| 4aa | 17% | 20% |
| 4aa | 0% | 8% |
| 4aa | 30% | 98% |

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**Scheme 2** Different control experiments.

**Scheme 3** A proposed mechanism for the direct transformation.
converted to E in the presence of tert-butylperoxy radical. Meanwhile, a single-electron oxidation of anilines mediated by Cu(II) occurred, affording corresponding radical cations F. Cationic radical F coupled with radical E to obtain G. Hydrogen ion of G was removed by base to give the product H. Finally, H is oxidized under standard conditions to form the desired product I (Scheme 3).

Conclusions

In conclusion, the copper-catalyzed oxidative amidination of methyl ketones with aromatic amines and DMF has been developed. Acyclic 2-oxo-acetamidines could be obtained with moderate to good yields. This protocol features with acyclic amidines formation using DMF and aromatic amines as two different nitrogen sources. Further investigations on reaction scope and synthetic application are underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (a) R. J. Young, Bioorg. Med. Chem. Lett., 2000, 10, 597; (b) E. M. Stone, T. H. Schaller, H. Bianchi, M. D. Person and W. Fast, Biochemistry, 2005, 44, 13744; (c) R. G. Doveston, R. Steendam, S. F. Jones and R. J. K. Taylor, Org. Lett., 2012, 14, 1122; (d) C. Maccallini, A. Patruno, N. Besker, J. Ali, A. Ammazzalorso, B. D. Filippis, S. Franceschelli, L. Giampietro, M. Pesce and M. Reale, J. Med. Chem., 2009, 52, 1481; (e) C. Maccallini, A. Patruno, F. Lannutti, M. Fantacuzzi, S. Franceschelli, L. Giampietro, S. Masella and M. Felaco, Bioorg. Med. Chem. Lett., 2010, 20, 6495; (f) A. Patruno, S. Franceschelli, M. Pesce, C. Maccallini, M. Fantacuzzi, L. Speranza, A. Ferrone, M. A. De Luitis, E. Ricciott and R. Amoroso, Biochim. Biophys. Acta, 2012, 1820, 2095; (g) F. T. Edelmann, Chem. Soc. Rev., 2009, 38, 2253; (h) Y. Luo, B. Knuckley, Y. H. Lee, M. R. Stallcup and P. R. Thompson, J. Am. Chem. Soc., 2006, 128, 1092; (i) Q. Dai, Y. Jiang, J.-T. Yu and J. Cheng, Chem. Commun., 2015, 51, 16645.

2 (a) J. V. Greenhill and P. Lue, Prog. Med. Chem., 1993, 30, 203; (b) S. D. Guile, L. Alcaraz, T. N. Birkinshaw, K. C. Bowers, M. R. Edben, M. Furber and M. J. Stocks, J. Med. Chem., 2009, 52, 3123; (c) M. Y. Lee, M. H. Kim, J. Kim, S. H. Kim, B. T. Kim, I. H. Jeong, S. Chang and S. Y. Chang, Bioorg. Med. Chem. Lett., 2010, 20, 541; (d) G. Brasche and S. L. Buchwald, Angew., Chem. Int. Ed., 2008, 47, 1932; (e) S. Caron, L. Wei, J. Douville and A. Ghosh, J. Org. Chem., 2010, 75, 945; (f) R. Khan, M. Arfan, J. Mahmood, S. Anjum and M. I. Choudhary, Chin. Chem. Lett., 2010, 21, 905; (g) J. R. Harjani, C. Liang and P. G. Jessop, J. Org. Chem., 2011, 76, 1683; (h) M. A. McGowan, C. Z. McAvoy and S. L. Buchwald, Org. Lett., 2012, 14, 3890; (i) Y. F. Wang, X. Zhu and S. Chiba, J. Am. Chem. Soc., 2012, 134, 3679; J. Am. Chem. Soc., 2012, 134, 11980; (j) J. E. Taylor, S. D. Bull and J. M. J. Williams, Chem. Soc. Rev., 2012, 41, 2109; (k) M. Matzka, J. Janczak, M. Trzebiatsowa, A. Sieradzki, S. Pawlus and A. Pilk, Dalton Trans., 2017, 46, 8476; (l) J. Barker and M. Kilner, Coord. Chem. Rev., 1994, 133, 219; S. H. Oakley, D. B. Soria, M. P. Coles and P. B. Hitchcock, Dalton Trans., 2004, 537; F. T. Edelmann, Adv. Organomet. Chem., 2008, 57, 183.

3 (a) V. A. Mamedov, N. A. Zhukova, V. V. Syakaev, A. T. Gubaidullin, T. N. Beschastnova, D. I. Adganova, A. I. Samigullina and S. K. Latypov, Tetrahedron, 2013, 69, 1403; (b) D.-H. Wang, Y.-X. Yang, Y.-Q. Yang, T.-C. Zhao, X. Wu and S.-K. Wang, Sci. Bull., 2006, 51, 785; (c) A. Tantawy, A. E. Barghash, S. Badr and R. Gomaa, Heterocycl. Commun., 2013, 19, 125; (d) N. R. Perl and J. L. Leighton, Org. Lett., 2007, 9, 6399; (e) J.-L. Du, L.-J. Li and Y.-F. Li, Inorg. Chem. Commun., 2005, 8, 246; (f) H. C Chang, B. C. Son, G. Y. Song, J. Y. Shin, C. S. Ha, H. S. Suh and I. Kim, Macromol. Res., 2013, 21, 118; (g) V. A. Mamedov, A. M. Murtazina, N. A. Zhukova, T. N. Beschastnova, I. K. Rizvanov and S. K. Latypov, Tetrahedron, 2014, 70, 7567.

4 (a) B. Wang, H.-F. Du and Y. A. Shi, Angew. Chem., 2008, 120, 8348; Angew. Chem., Int. Ed., 2008, 47, 8224; (b) J. J. Neumann, S. Rakshit, T. Droge and F. Glorius, Angew. Chem., 2009, 121, 7024; Angew. Chem., Int. Ed., 2009, 48, 6892; (c) Y. Tan and J. F. Hartwig, J. Am. Chem. Soc., 2010, 132, 3676; (d) K. Shin, H. Kim and S. Chang, Acc. Chem. Res., 2015, 48, 1040; (e) J. Jiao, K. Murakami and K. Itami, ACS Catal., 2016, 6, 610; (f) W. Choi, J. Kim, T. Ryu, K.-B. Kim and P. H. Lee, Org. Lett., 2015, 17, 3330; (g) C. Du, P.-X. Li, X.-J. Zhu, J.-N. Han, J.-L. Niu and M.-P. Song, ACS Catal., 2017, 7, 2810; (h) Y. Park, Y. Kim and S. Chang, Chem. Rev., 2017, 117, 9247; (i) S. B. Laflèrè, R. Gil, D. Prim and J. Hannedouche, Molecules, 2017, 22, 1901; (j) Y. N. Timsina, B. F. Gupton and K. C. Ellis, ACS Catal., 2018, 8, 5732.

5 (a) G. Rousselet, P. Capdevielle and M. Mauny, Tetrahedron Lett., 1993, 34, 6395; (b) V. Y. Kukushkin and A. J. L. Pombeiro, Chem. Rev., 2002, 102, 1771; (c) J.-F. Wang, F. Xu, T. Cai and Q. Shen, Org. Lett., 2008, 10, 445; (d) S. Ueda and H. Nagasawa, J. Am. Chem. Soc., 2009, 131, 15080; (e) J. Savmarker, J. Rydflöjd, J. Gising, L. R. Odell and M. Larhed, Org. Lett., 2012, 14, 2394; (f) J. Rydflöjd, F. Svensson and A. Trejos, J. Am. Chem. Soc., 2013, 135, 13803.

6 (a) A. T. Khan, R. Sidick Basha, M. Lala and M. H. Mir, RSC Adv., 2012, 2, 5506–5509; (b) A. Kumar, D. Saxena and M. K. Gupta, Green Chem., 2013, 15, 2699; (c) T. Vlaar, RSC Adv., 2019, 9, 7203−7209 | 7207
Q. Sun and X.-P. Wan, *Sci. China: Chem.*, 2017, **60**, 1439, DOI: 10.1007/s11426-017-9096-7.

17 D. Wang, K. Zhang, L.-H. Jia, D.-T. Zhang, Y. Zhang, Y.-J. Cheng, C. Lin and B. Wang, *Org. Biomol. Chem.*, 2017, **15**, 3427.

18 (*a*) Z.-J. Liu, J. Zhang, S.-L. Chen, E.-B. Shi, Y. Xu and X.-B. Wan, *Angew. Chem., Int. Ed.*, 2012, **51**, 3231; (*b*) L. Y. M. Eymann, A. G. Tskhovrebov, A. Sienkiewicz, J. L. Bila, I. Živković, H. M. Rønnow, M. D. Wodrich, L. Vannay, C. Corminboeuf, P. Pattison, E. Solari, R. Scopelliti and K. Severin, *J. Am. Chem. Soc.*, 2016, **138**, 15126; (*c*) L.-W. Zheng, M. Griesser, D. A. Pratt and M. M. Greenberg, *J. Org. Chem.*, 2017, **82**, 3571; (*d*) D. Shimizu, K. Furukawa and A. Osuka, *Angew. Chem., Int. Ed.*, 2017, **56**, 7435.