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Copper-catalyzed annulation of amidines for quinazoline synthesis†

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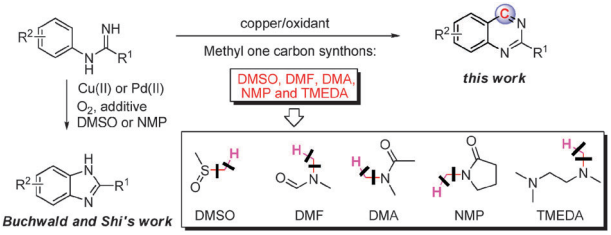
An efficient Cu-catalyzed synthesis of quinazolines *via* the C–N bond formation reactions between N–H bonds of amidines and C(sp^3)–H bonds adjacent to sulfur or nitrogen atoms in the commonly used solvents, such as DMSO, DMF, DMA, NMP or TMEDA, followed by intramolecular C–C bond formation reactions was developed for the first time.

Nitrogen functionality is prevalent in synthetic and natural small molecules with a high level of biological activities,[1] which motivates the development of methodologies to introduce nitrogen atoms into organic molecules. Among various C–N bond construction methods, the direct C–N bond formation reaction between C–H and N–H bonds is the most powerful methodology because of avoiding prefunctionalization of the substrates, minimum environmental impact and fewer synthetic steps.[2] In the area of C–H bond direct amination reaction, a significant breakthrough was achieved arising from the discovery of metal nitrenes.[3] As a result, the substrates studied underwent efficient nitrene insertion into various C–H bonds, especially aliphatic C(sp^3)–H bonds. Copper-nitrene intermediates have long been proposed as reactive intermediates in a number of copper-catalyzed alkane amination and alkene aziridination reactions.[4] Recently, a very interesting work suggested that in the presence of a copper catalyst and O_2, amidines (containing two N–H bonds) might be directly used as nitrogen-centred radicals or nitrene nitrogen sources,[5] which suggested the potential application of amidines to be used as a copper-nitrene nitrogen source.[6] In this communication, we developed a novel copper-catalyzed synthesis of quinazolines from amidines. Remarkably, the C–N bond formation reactions between N–H bonds of amidines and methyl C(sp^3)–H bonds of DMSO, DMF, *N*,*N*-dimethylacetamide (DMA), *N*-methylpyrrolidone (NMP) or N_1,N_1,N_2,N_2-tetramethylethane-1,2-diamine (TMEDA) were realized for the first time (Scheme 1).

Recently, with benzylic methyl sp^3 carbon as the one carbon synthon, starting from *N*-*para*-tolylamides, we realized the construction of benzoxazine derivatives *via* dehydrogenative cross-coupling reaction between benzylic methyl C(sp^3)–H and aromatic C(sp^2)–H bonds, and subsequent intramolecular C–O bond formation reaction.[7] As part of our continuing interest in the construction of C–N bonds directly from C–H bonds,[8] amidines were selected as nitrogen sources and sp^3 carbon in DMSO was used as a one carbon synthon to perform the intermolecular annulation reactions. Initially, the reaction of *N*-*p*-tolylbenzimidamide **1a** with DMSO was tested. After careful screening (see the ESI†), we were pleased to find that the annulation product 7-methyl-2-phenyl-3,4-dihydroquinazoline **2a** (CCDC 932059) could be obtained in 71% yield by employing 3.0 equivalents of Selectfluor as an oxidant and Cu(OTf)$_2$ as the catalyst (Table 1). Notably, under these conditions, the intramolecular cyclization product 7-methyl-2-phenyl-3,4-dihydroquinazoline was not obtained in the works of Buchwald and Brasche[6] and Shi *et al.*[9] (Scheme 1), in which DMSO or NMP was only used as solvent.



Scheme 1 Annulation reactions of amidines.

Quinazoline derivatives, widely distributed in natural products and synthetic pharmaceuticals, have been extensively studied for their biological and therapeutic activities,[10] which include protein tyrosine kinase, cellular phosphorylation inhibitors,[11] anticancer,[10a,d,12] antiviral,[13] and antitubercular agents.[14] Therefore, numerous efforts have been devoted to develop methods for the synthesis of quinazolines. Most of the synthetic routes to quinazolines depend on the use of anilines bearing an *ortho*-functional group.[15] Alternatively, synthesis of quinazolines from available *ortho*-unfunctionalized aniline,[16] such as amidine **1a**, is attractive. Amidines **1** were easily prepared by the reaction of anilines with nitriles in the presence of $AlCl_3$ or NaH.[6,9] With the optimal conditions in hand, we examined the scope of this novel annulation reaction. As described in Table 1, starting from substrates **1b–1e**, the desired annulation products

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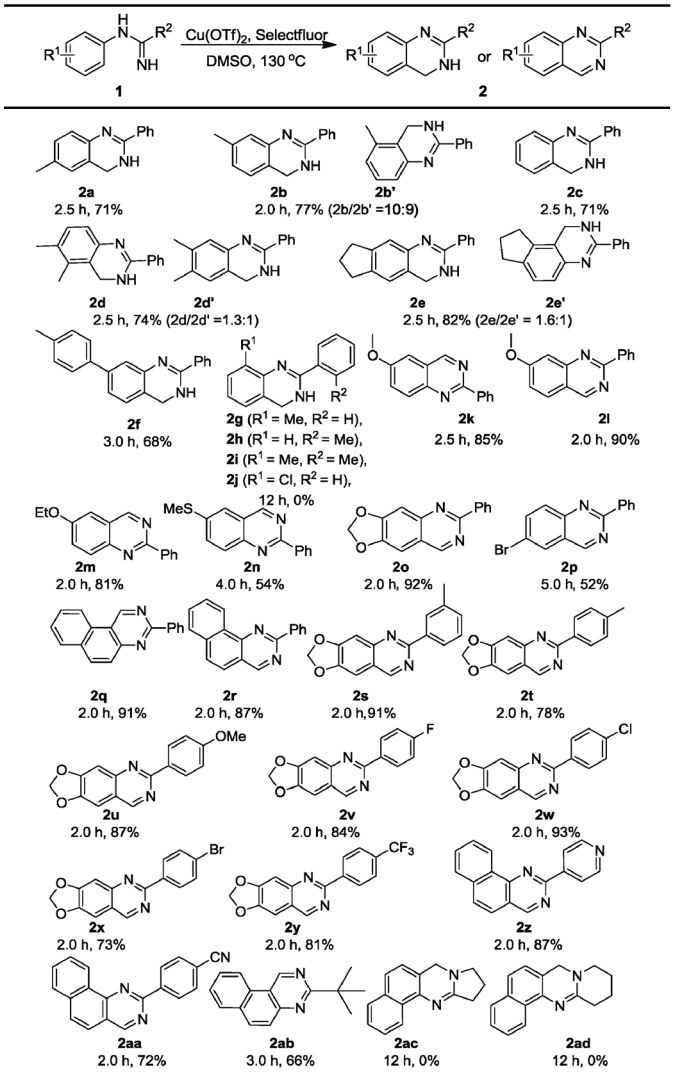
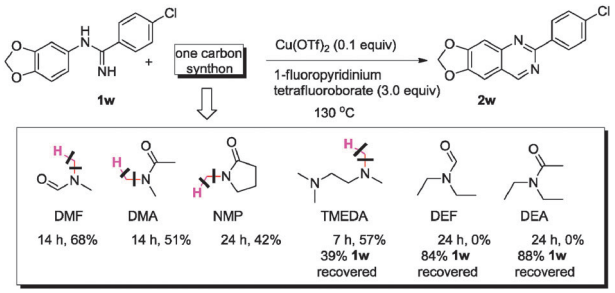
Table 1 Intermolecular annulation of amidines **1** with DMSO[a,b]



[a] Reaction conditions: **1** (0.3 mmol), $Cu(OTf)_2$ (0.03 mmol) and Selectfluor (0.9 mmol) in 2 mL DMSO at 130 °C. [b] Yield of the isolated product.

dihydroquinazolines **2b**/**2b′**, **2d**/**2d′** and **2e**/**2e′** were obtained in 74–82% yields with poor regio-selectivity. From 4-methylphenyl substituted amidine **1f**, the annulated product **2f** was afforded as a single regioisomer. However, no desired annulation products were obtained from *ortho*-substituted aniline moiety or *ortho*-substituted nitrile moiety containing substrates **1g–1j**. It should be noted that substrates **1k–1r** underwent the annulation/aromatization reaction smoothly to give quinazolines **2k–2r** in moderate to excellent yields. In addition, when dihydroquinazoline **2a** was treated under the optimal conditions for 3 h, 77% yield of aromatization quinazoline could also be obtained. The scope of the intermolecular annulation reaction was further examined with respect to various nitrile derivatives. Starting from nitrile derivatives containing both electron-withdrawing and electron-donating groups on the aromatic ring of nitrile moieties, quinazolines **2s–2ab** were obtained in good to excellent yields. **1ab** underwent annulation at the sterically more hindered 1-position of the naphthalene ring to give **2ab**, which can be attributed to the dominating electronic effect. The ability to incorporate C–Br and C–Cl bonds (**2p**, **2w** and **2x**) makes this method appealing, since it offers

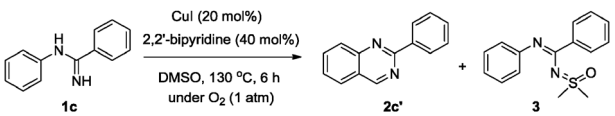


Scheme 2 Intermolecular annulation of amidine **1w** with various one carbon synthons.

an opportunity for further transformation. However, from the cyclic amidine substrates **1ac** and **1ad**, no reactions occurred.

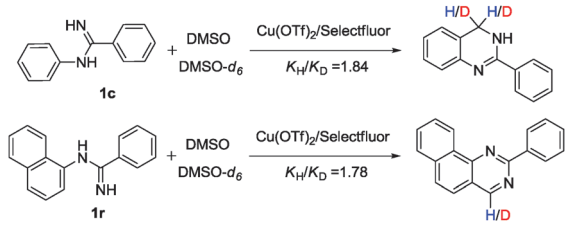
The efficient utilization of $C(sp^3)$–H bonds of DMSO in the transformation of **1** to **2** leads us to broaden this new type of reaction by testing the annulation of amidines **1** with similar $C(sp^3)$–H bonds adjacent to heteroatoms in some other solvents. After many investigations, satisfyingly, in the presence of $Cu(OTf)_2$ (0.1 equiv.) and 1-fluoropyridinium tetrafluoroborate (3.0 equiv.) instead of Selectfluor, the reaction of **1w** with DMF (2 mL) was performed at 130 °C for 14 h, and the desired product **2w** was afforded in 68% yield (Scheme 2). To our delight, other one carbon synthons, such as *N*,*N*-dimethylacetamide (DMA), *N*-methyl-2-pyrrolidone (NMP) and N_1,N_1,N_2,N_2-tetramethylethane-1,2-diamine (TMEDA) (3.0 equiv. of TMEDA was used with 2 mL of CH_3CN), were also effective in performing the annulation reaction to provide **2w** in 51%, 42% and 57% yield, respectively (Scheme 2). However, no reaction occurred with *N*,*N*-diethylformamide (DEF) and *N*,*N*-diethylacetamide (DEA) as the corresponding one carbon synthon.

The kinetic deuterium isotope effect (DMSO and DMSO-d_6 reacted with substrate **1c**/**1r**, both $k_H/k_D \approx 1.8$; Scheme 3) of the reaction was investigated under the optimal conditions, which indicated that the first $C(sp^3)$–H bond cleavage in DMSO might be involved in the rate-limiting step. In the work of Chiba and co-workers,[5a] the possible nitrene species starting from **1c** was trapped by DMSO to provide a sulfoxyimine product. Under the same conditions, when the reaction of **1c** was performed at 130 °C for 6 h, **2c′** was generated in 12% yield, along with sulfoxyimine **3** in 47% yield [eqn (1)]. This result showed that the *in situ* generated nitrene species could react with DMSO to form quinazoline **2c′**.

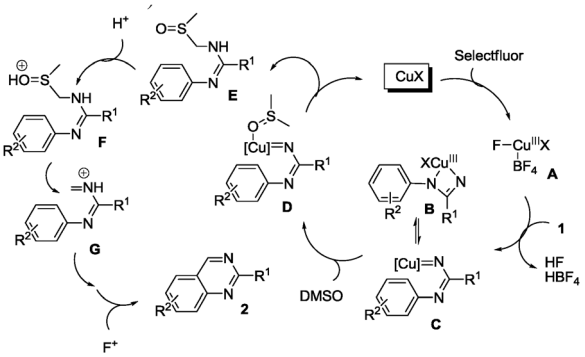


(1)

Although the mechanistic details of this transformation are not very clear at the moment, based on the experimental results and some related research,[5,6] a possible mechanism was proposed in Scheme 4. Initially, the oxidation of CuX with the F^+ oxidant (such as Selectfluor) provides the Cu(III) complex **A**,[7,8b,17] which reacts with amidine **1** *via* the elimination of HF and HBF_4 to provide a four-membered Cu(III) intermediate **B**. Then, a copper-nitrene intermediate **C** might be generated and at the same time stabilized by its equilibrium structure **B**.[18] The subsequent coordination of intermediate **C** with DMSO provides a copper–nitrene complex **D**, which



Scheme 3 The kinetic deuterium isotope effect of reactions between **1c**/**1r** and DMSO.



Scheme 4 Possible mechanism for the synthesis of quinazolines **2**.

undergoes a C–N bond formation reaction *via* nitrene insertion into the C(sp^3)–H bond of DMSO to give intermediate **E**. Finally, in the presence of H$^+$, the cleavage of the C–S bond[19] gives an iminium species **G**, which undergoes an electrophilic addition reaction or electrocyclization[20] with the aromatic ring to provide dihydroquinazolines **2a–2f** and in the presence of an oxidant, the following aromatization reaction gives the quinazoline products **2k–2ab**. Since the possible copper-nitrene species **C** (might exist with its equilibrium intermediate **B**) is sterically hindered, the steric effect might play an important role in the annulation reaction (no reaction occurs starting from **1g–1j** (Table 1) and DEF and DEA (Scheme 2)).

In summary, we have succeeded in developing an efficient Cu-catalyzed synthesis of quinazolines from amidines and DMSO, DMF, DMA, NMP or TMEDA through direct oxidative amination of N–H bonds and methyl C(sp^3)–H bonds followed by intramolecular C–C bond formation reactions. The generality and high selectivity of the annulation reaction towards various C(sp^3)–H bonds together with employing readily available amidines as the substrates made this method very attractive. Further studies utilizing this strategy for the construction of various C–N bonds are ongoing in our lab.

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