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Synthesis of quinazolines *via* CuO nanoparticles catalyzed aerobic oxidative coupling of aromatic alcohols and amidines†

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CuO nanoparticles were found to be efficient catalysts for the synthesis of quinazoline derivatives; twenty-four products were obtained with good to excellent yields *via* reaction of *N*-arylamidines and aromatic aldehydes or benzyl alcohol in air. Neither a base nor an organic oxidant was necessary, and CuO nanoparticles can be recycled without a significant decrease in catalytic activity.

Introduction

Quinazolines form the core of many biologically active compounds, such as HIV reverse transcriptase inhibitors, and they are present in many pharmaceuticals that exhibit anticonvulsant, antibacterial, antidiabetic, and anticancer properties.[1] In the past few decades, many approaches have been developed for the construction of quinazolines. Among them, the classic approach involves condensation of 2-aminobenzophenones with aldehydes,[2] acyl chloride and ammonium acetate,[3] or benzylamines.[4] In addition, quinazoline derivatives were also obtained using available amidines as substrates[5] since amidines are very important substrates in the synthesis of heterocyclic compounds.[6] Nevertheless, those methods suffer from limitations of operating difficulties or harsh reaction conditions involving a noble metal catalyst, base, microwave and organic oxidant. Thus, the development of an efficient reaction system with an inexpensive catalyst in the absence of bases and organic oxidants is highly desirable.

Recently, copper-catalyzed C–C, C–N, C–O, and C–S bond formations have evolved as major methods for the synthesis of novel heterocyclic compounds with obvious advantages of low cost and environmental friendliness.[7–10] For example, Jiang *et al.* have reported the synthesis of pyrazoles and indazoles *via* C–N bond formation with copper catalysts.[11] Furthermore, nanostructured copper catalysts with a large surface to volume ratio, varied morphology, and sustainable catalytic applications are of special interest.[12]

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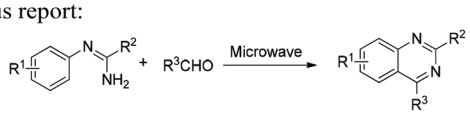
† Electronic supplementary information (ESI) available: Catalyst characterization, analytical data, images of ^{1}H and ^{13}C NMR of all products and other electronic format. See DOI: 10.1039/c4ob00569d

Previous report:



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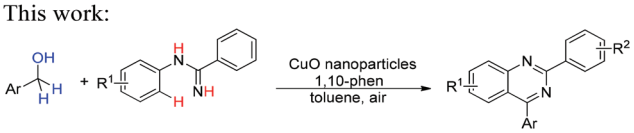


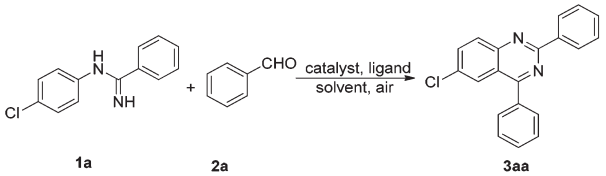
Scheme 1 Synthesis of quinazoline from amidines.

In the course of our ongoing efforts devoted toward studying copper-catalyzed C–H functionalization,[13] we discovered that, by virtue of nanostructured copper oxide as an inexpensive catalyst, quinazoline derivatives were able to be accessed directly by oxidative coupling of *N*-arylamidines and aldehydes or alcohols in air (Scheme 1). From a practical viewpoint, it should be one of the most straightforward and greener approaches for the preparation of quinazolines. During the preparation of our manuscript, Jiang also reported ruthenium-catalyzed dehydrogenative synthesis of 2,4,6-triaryl-1,3,5-triazines from aryl methanols and amidines.[14]

Results and discussion

In our initial optimization studies, *N*-(4-chlorophenyl)benzimidamide (**1a**) and benzaldehyde (**2a**) were selected as the model substrates. The results obtained from screening of the copper catalysts, ligands and solvents are summarized in Table 1. For example, the reaction of **1a** with **2a** in the presence of 5 mol% of CuO nanoparticles at 120 °C for 24 h in diglyme afforded

Table 1 Reaction optimization[a]



1a 2a 3aa

Entry	Catalyst	Ligand	Solvent	Temp. (°C)	Yield (%)
1	CuO	phen	DGDE	120	35
2	CuO	phen	DMSO	120	45
3	CuO	phen	Toluene	110	88
4	CuO	Ph_3P	Toluene	110	<10
5	CuO	DMEDA	Toluene	110	60
6	CuO	TMEDA	Toluene	110	30
7	CuO	dipy.	Toluene	110	40
8[b]	CuO	phen	Toluene	110	60
9[c]	CuO	phen	Toluene	110	20
10[d]	CuO	phen	Toluene	110	61
11[e]	CuO	phen	Toluene	110	55
12[f]	CuO	phen	Toluene	110	25
13	$Cu(OAc)_2$	phen	Toluene	110	65
14	$CuSO_4$	phen	Toluene	110	15
15	$CuCl_2$	phen	Toluene	110	<10
16	$Cu(NO_3)_2$	phen	Toluene	110	30
17[g]	CuO	phen	Toluene	110	89
18	CuO	—	Toluene	110	<10
19	—	phen	Toluene	110	—
20[h]	CuO	phen	Toluene	110	55
21[i]	CuO	phen	Toluene	110	75
22[j]	CuO	phen	Toluene	110	85
23	CuO	phen	Toluene	100	80
24	CuO	phen	Toluene	90	69
25	CuO	phen	Toluene	60	Trace

[a] Reaction conditions: *N*-(4-chlorophenyl)benzimidamide (0.5 mmol), benzaldehyde (0.75 mmol), CuO nanoparticles (5 mol%), 1,10-phenanthroline (20 mol%), toluene (2 mL) under reflux in air for 24 h. [b] phen (10 mol%). [c] CuO (200 mesh). [d] CuO (nanorods). [e] CuO (nanoflowers). [f] CuO (nanospindles). [g] CuO (10 mol%). [h] Reaction time is 9 h. [i] Reaction time is 18 h. [j] Reaction time is 21 h.

the corresponding product 6-chloro-2,4-diphenylquinazoline (**3aa**) in 35% yield (Table 1, entry 1). To our delight, the amidine was transformed with full conversion in toluene, **3aa** was obtained in 88% yield (Table 1, entry 3), while other solvents just led to low yields (Table 1, entries 1 and 2). Further investigation revealed that the ligand played a critical role in this copper-catalyzed transformation. Among the examined ligands such as Ph_3P, DMEDA, TMEDA, 2,2-dipyridyl and 1,10-phenanthroline (phen), phen was the best (Table 1, entries 4–7). Decreasing the amount of ligand resulted in much lower yield (Table 1, entry 8). Other copper catalysts such as $Cu(OAc)_2$, $CuSO_4$, $CuCl_2$, $Cu(NO_3)_2$, CuO (200 mesh), CuO nanorods, CuO nanoflowers and CuO nanospindles gave relatively low yields of the quinazolines (Table 1, entries 9–16), CuO nanoparticles with 6.5 nm in diameter were found to be the best catalyst (Fig. 1). No significant improvement of the yield was observed by increasing the catalyst loading (Table 1, entry 17). The reaction did not proceed well in the absence of the catalyst or the ligand (Table 1, entries 18 and 19). The effect of reaction time and reaction temperature was also investigated, the yield

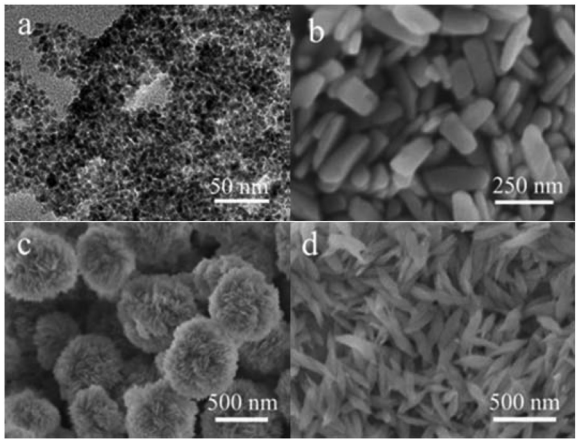


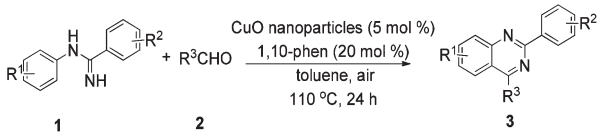
Fig. 1 CuO nanocatalysts employed for optimization of reaction conditions.

was reduced to 55% for 9 h, 75% for 18 h and 85% for 21 h (Table 1, entries 20–22). Furthermore, lower temperatures resulted in lower yields, only trace products were generated at 60 °C and 69% yield was obtained at 90 °C (Table 1, entries 23–25). Thus, the optimal reaction conditions were set to be 5 mol% of CuO nanoparticles in the presence of 20 mol% of phen in refluxing toluene for 24 h.

Under the optimized reaction conditions, we employed *N*-arylamidines with different substituents **1a–m** and benzaldehyde as substrates, and representative results are listed in Table 2. No significant substitute effect was observed, excellent yields were obtained for *N*-arylamidines with both electron-donating and electron-withdrawing substituents (Table 2, entries 1–14). However, the position of the substituent has obvious effect on the reaction (Table 2, entries 7–9). In addition, a variety of aromatic aldehydes were examined under the optimized reaction conditions. The result showed that several functional groups, such as methyl, methoxy, chloro, nitro and cyan, were well-tolerated and gave the corresponding products in moderate to good yields (Table 2, entries 15–22). In general, the presence of electron-donating and weak electron-withdrawing groups on the *para* position of benzaldehydes showed slightly better efficiencies than those with electron-withdrawing substitutes. However, in the case of 2-ethyoxyl benzaldehyde, only 73% yield was obtained because of the influence of steric hindrance (Table 2, entry 21). This methodology worked equally well with heteroaromatic aldehydes and good yield was observed (Table 2, entry 18). Unfortunately, the reaction does not work well with aliphatic aldehydes, which is in accordance with Buchwald's report.[5d] We believe that the formation of imine from the condensation of aliphatic aldehydes and amidines may not as easy as that from aromatic aldehydes and amidines.

Recently, there has been great progress about the formation of aldehydes *via* catalytic alcohol oxidation in air.[15] Among them, the use of nanoparticles as catalysts caught our attention.[16]

Table 2 Scope of the synthesis of quinazolines[a]



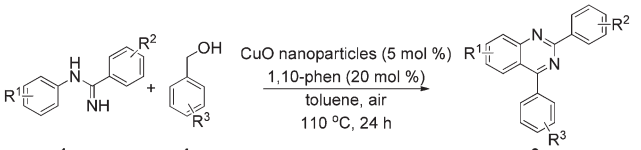
1 2 3

Entry	1	2	3	Yield (%)
1	**1a** R^1 = *p*-Cl, R^2 = H	**2a** R^3 = C_6H_5	**3aa**	88
2	**1b** R^1 = *p*-F, R^2 = H	**2a**	**3ba**	86
3	**1c** R^1 = R^2 = H	**2a**	**3ca**	84
4	**1d** R^1 = *p*-CH_3, R^2 = H	**2a**	**3da**	98
5	**1e** R^1 = *o*-CH_3, R^2 = H	**2a**	**3ea**	94
6	**1f** R^1 = *p*-OCH_3, R^2 = H	**2a**	**3fa**	87
7	**1g** R^1 = H, R^2 = *p*-CH_3	**2a**	**3ga**	98
8	**1h** R^1 = H, R^2 = *m*-CH_3	**2a**	**3ha**	95
9	**1i** R^1 = H, R^2 = *o*-CH_3	**2a**	**3ia**	92
10	**1j** R^1 = H, R^2 = *p*-Cl	**2a**	**3ja**	93
11	**1k** R^1 = H, R^2 = *o*-Cl	**2a**	**3ka**	89
12	**1l** R^1 = *p*-CH_3, R^2 = *p*-Cl	**2a**	**3la**	92
13	**1m** R^1 = *p*-Cl, R^2 = *p*-CH_3	**2a**	**3ma**	90
14	**1n** R^1 = *m*-CH_3, R^2 = *p*-Cl	**2a**	**3na**	91
15	**1c**	**2b** R^3 = *p*-ClPh	**3cb**	95
16	**1c**	**2c** R^3 = *p*-CNPh	**3cc**	91
17	**1c**	**2d** R^3 = *p*-NO_2Ph	**3cd**	83
18	**1c**	**2e** R^3 = Furan-2-yl	**3ce**	78
19	**1c**	**2f** R^3 = *p*-CH_3Ph	**3cf**	96
20	**1c**	**2g** R^3 = *p*-OCH_3Ph	**3cg**	85
21	**1c**	**2h** R^3 = *o*-OEtPh	**3ch**	73
22	**1a**	**2b**	**3ab**	92

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), CuO nanoparticles (5 mol%), phen (20 mol%) in toluene (2 mL) under reflux in air for 24 h.

We believe that alcohols could be used as latent aldehydes for the synthesis of quinazolines. A series of substituted benzyl alcohol were examined, moderate to good yields were obtained under the optimized reaction conditions (Table 3). Also, in the absence of amidines, intermediate aldehydes were successfully obtained in good to excellent yields (Table S1†). In the present alcohol oxidation reactions, CuO nanoparticles have proven to be efficient heterogeneous catalysts with more remarkable efficiency than other CuO nanocatalysts and commercial CuO.

Table 3 Reaction of *N*-arylamidines and benzyl alcohol[a]



1 4 3

Entry	1	4	3	Yield (%)
1	**1c**	R^3 = H **4a**	**3ca**	84
2	**1c**	R^3 = *p*-Cl **4b**	**3cb**	85
3	**1c**	R^3 = *p*-OCH_3 **4g**	**3cg**	54
4	**1c**	R^3 = *p*-CH_3 **4f**	**3cf**	88
5	**1c**	R^3 = *p*-NO_2 **4d**	**3cd**	79
6	**1c**	R^3 = *m*-NO_2 **4j**	**3cj**	76
7	**1c**	R^3 = *o*-NO_2 **4k**	**3ck**	73
8	**1d**	**4a**	**3da**	95
9	**1j**	**4a**	**3ja**	91
10	**1f**	**4a**	**3fa**	84
11	**1g**	**4a**	**3ga**	94

[a] Reaction conditions: **1** (0.5 mmol), **4** (0.75 mmol), CuO nanoparticles (5 mol%), phen (20 mol%) in toluene (2 mL) under reflux in air for 24 h.

To discuss whether the CuO nanoparticles are the actual catalysts, or they simply serve as a reservoir of soluble [(phen)-Cu(II)] complexes of unknown composition, additional experiments were performed. The leaching of copper from CuO nanoparticles was examined by AAS. The oxidative coupling of benzaldehyde and *N*-(4-chlorophenyl)benzimidamide was carried out under the optimized conditions and the catalyst was removed from the mixture by centrifugation. Analysis of the solution revealed slight leaching of the catalyst with a concentration of 2.7 ppm. When the substrates were added into the 'catalyst-free' solution that contains leached copper, no reaction was observed. Also, when [(phen)Cu(II)] complexes were synthesized and used as catalysts, a trace of the target product was obtained. So, we believe that the CuO nanoparticles are the actual catalysts. The XRD pattern of the recovered catalysts after three cycles demonstrated that the catalysts were not changed during the reaction process (Fig. S1b†) and TEM revealed that the morphology of the catalysts was unaltered. Hence the used catalyst is successfully re-employed for a series of consecutive runs (see the ESI, Table S2†).

Conclusions

In conclusion, we have successfully developed an efficient method for the synthesis of quinazoline derivatives. With CuO nanoparticles as catalysts, the reactions of *N*-arylamidines and aromatic aldehydes or benzyl alcohol were readily facilitated to afford the desired products in good to excellent yields. The reaction shows high generality and functional group tolerance. Further study of related CuO nanoparticle-catalyzed aerobic reaction to synthesize heterocycles is in progress.

Experimental

General information

All the *N*-arylamidines used were synthesized according to ref. 5*e*. All the other reagents were purchased from commercial suppliers and used without further purification. The CuO nanoparticles were prepared by thermal dehydration of the freshly prepared $Cu(OAc)_2$ in solution.[16c] The as-prepared CuO products were characterized by X-ray powder diffraction (Shimadzu XRD-6000) with graphite monochromatized Cu-Kα radiation (λ = 0.154060 nm), employing a scanning rate of 0.02° s^{-1} in the 2θ range from 10° to 80°. The field-emission scanning electron microscopy (FE-SEM) images were taken with a Hitachi S-4800 scanning electron microscope. Transmission electron microscopy (TEM) images were recorded on a FEI Tecnai G^2 20 high-resolution transmission electron microscope performed at an acceleration voltage of 200 kV. NMR spectra were obtained at 25 °C on a Bruker Avance-300 at 300 MHz for ^1H, and at 75 MHz for ^{13}C NMR using TMS as the internal standard, chemical shifts for ^1H and ^{13}C were both referenced to $CDCl_3$. High resolution mass spectral (HRMS) data were obtained with an ionization mode of ESI on Agilent 6200 LC/MS TOF.

General procedure for the synthesis of quinazolines

N-Arylamidine (0.5 mmol), aldehyde (0.75 mmol), CuO nanoparticles (5 mol%), 1,10-phenanthroline (20 mol%) were stirred in toluene (2 mL) under reflux in air for 24 h. The resulting mixture was cooled to room temperature and then centrifuged. The organic phase was separated; the precipitate was washed thoroughly with EtOAc and then centrifuged. The organic phases were combined, washed with brine (3 × 10 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc–petroleum ether = 1/20) to afford the product.

Acknowledgements

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