

Original article

Base mediated direct C–H amination for pyrimidines synthesis from amidines and cinnamaldehydes using oxygen as green oxidants

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ABSTRACT

A direct metal-free C–H amination reaction of cinnamaldehydes and amidines to realize the synthesis of polysubstituted pyrimidines was developed in the presence of base. This greener synthetic methodology provides a straightforward approach to the synthesis of a variety of pyrimidine derivatives under mild reaction condition using oxygen as sole oxidants.

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1. Introduction

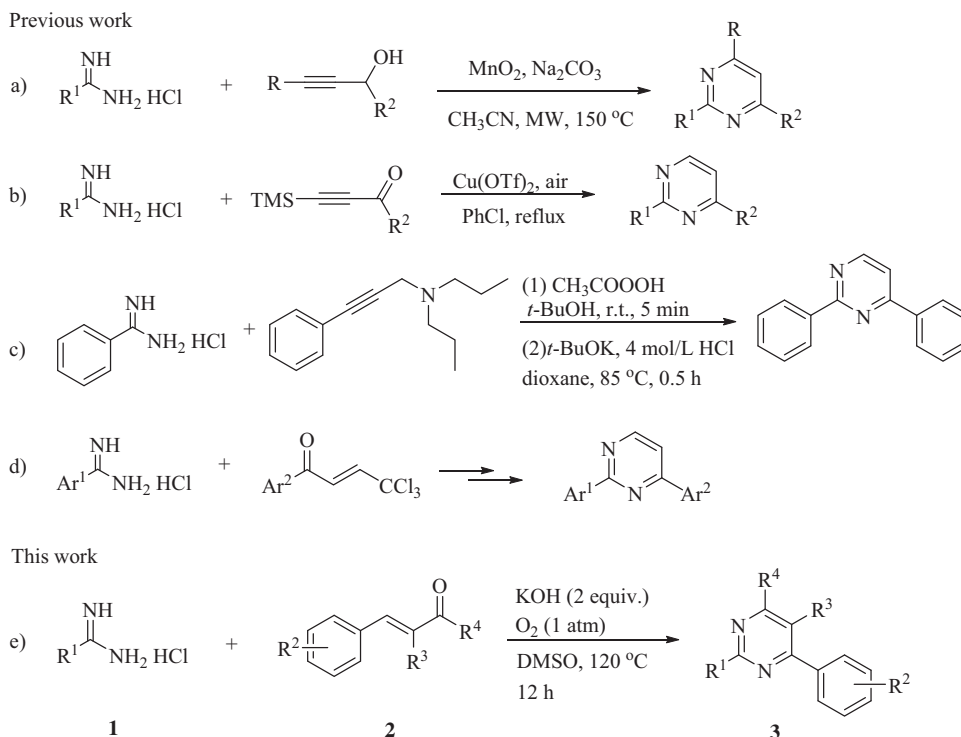
Pyrimidines are very important heterocycles featuring prominently in the synthesis of pharmaceuticals, agrochemicals, and functional materials as well [1]. Particularly, they represent an increasing valuable goal because of their large range of applications as anti-plasmodial agents, antimalarial agents, cytotoxic inhibitors and photophysical materials [2]. While there exist various synthetic methods for the useful heterocycles via cyclization–oxidation processes, amidines are frequently used to prepare multiple-nitrogen-containing heterocycles because of their innate structural advantages [3]. Numbers of synthetic routes have also been developed for the synthesis of pyrimidines through the cascade condensation cyclization–oxidation of amidines with 1,3-dicarbonyl derivatives or α,β -unsaturated ketones [4]. Bagley and co-workers successfully demonstrated a tandem oxidation/heterocyclocondensation of a propargylic alcohol and benzamidine for the synthesis of pyrimidines using BaMnO_4 under microwave irradiation [5] (Scheme 1, a). Lin developed a $\text{Cu}(\text{OTf})_2$ -catalyzed tandem reaction of propargylic alcohols with amidine, providing a general approach to pyrimidines [6] (Scheme 1, b). Recently,

Guirado published a chloroform elimination of 2,4-diaryl-6-trichloromethyl-1,6-dihydropyrimidines to 2,4-diarylpyrimidines starting from 2,2,2-trichloroethylidene-acetophenones and benzamidines [7] (Scheme 1, c). The condensation of propargylamine and benzamidine to give pyrimidine was also developed by Chen and co-workers [8] (Scheme 1, d). However, most of the mentioned methods suffered from harsh reaction conditions (special reaction medium, microwave irradiation, transition-metals) and the use of relatively unavailable starting materials. Hence, the development of a simple and efficient procedure for acquisition of pyrimidines from easily available starting materials under mild conditions continues to attract the interest of organic chemists due to their remarkable application value.

Direct C–H diamination represents one of the most powerful synthetic protocols for the construction of *N*-heterocycles, avoiding the pre-installation of transformable functional groups and possessing atom economy and environmental sustainability [9]. Many elegant methods involving transition-metal catalization and the use of overstoichiometric amounts of oxidants have been dominated [10]. For green and sustainable chemistry, molecular oxygen is considered as an ideal oxidant due to its natural, inexpensive, and environmentally friendly characteristics, and therefore shows attractive academic and industrial prospects [11]. In the past few years, our group developed serials of C–H dioxygen activation reactions using molecular oxygen as the terminal oxidant [12], we therefore think about employment of the molecular oxygen as the

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Scheme 1. General approaches for the synthesis of pyrimidine derivatives.

oxidant for the pyrimidine synthesis. Herein, we further report a base mediated direct C–H amination of amidines and cinnamaldehydes to afford polysubstituted pyrimidines using molecular oxygen as sole oxidant (Scheme 1, e).

2. Experimental

All of the reagents were used directly as obtained commercially. Column chromatography was performed with silica gel (200–300 mesh) and analytical TLC on silica GF254. Melting points were measured using a melting point instrument and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer. IR spectra were obtained with an infrared spectrometer on either potassium bromide pellets or liquid films between two potassium bromide pellets. GC–MS data were obtained using electron ionization. HRMS was carried out on a high-resolution mass spectrometer (LCMS-IT-TOF).

2.1. General procedure for **3aa**

A mixture of benzamidine hydrochloride **1a** (0.25 mmol), cinnamaldehyde **2a** (0.30 mol) and KOH (0.50 mmol, 2 equiv.) was stirred in DMSO (1.0 mL) under 1 atm O_2 atmosphere at 120 °C for 12 h. After completion of the reaction (monitored by TLC), water (10 mL) was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The combined organic layers were then dried over MgSO_4 , filtered, and then concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give the desired product **3aa** as a white solid (using the mixture of petroleum ether and ethyl acetate as eluents). Yield: 0.045 g (78%), mp 63–65 °C; IR (KBr, cm^{-1}): ν 3064, 1563, 1422, 1383, 1182, 1068, 1030, 747, 691; ^1H NMR (400 Hz, CDCl_3): δ 8.78–8.77 (m, 1H), 8.59–8.58 (m, 2H), 8.19–8.18 (m, 2H), 7.52–7.49 (m, 7H); ^{13}C NMR (100 Hz, CDCl_3): δ 164.59, 163.87, 157.86, 137.91, 136.96, 131.01, 130.78, 128.97, 128.59, 128.36, 127.24,

114.54; MS (EI, 70 eV) m/z : 232.13, 129.11, 116.16, 102.08; HRMS (ESI) Calcd. $\text{C}_{16}\text{H}_{13}\text{N}_2$ $[\text{M}+\text{H}]^+$: 233.1073, found: 233.1070. The data of **3ab–3la** were available in Supporting information.

3. Results and discussion

We initiated our study by using benzamidine hydrochloride **1a** and cinnamaldehyde **2a** as model substrates under various conditions and the results are summarized in Table 1. In the absence of a base, the reaction between **1a** and **2a** gave a low yield of 2,4-diphenylpyrimidine **3aa** (Table 1, entry 1). When this reaction was performed in the presence of bases, such as NaHCO_3 , Li_2CO_3 , Na_2CO_3 , K_2CO_3 , CH_3COONa , CH_3COOK , CS_2CO_3 and KOH, the yield of **3aa** increased (Table 1, entries 2–9). Especially, the reaction performed with CS_2CO_3 gave the best result (89% GC yield) (Table 1, entry 9). Trace of **3aa** was detected in N_2 atmosphere (Table 1, entry 10). As a result, both the base and O_2 were found to be indispensable. Organic bases such as Et_3N , DBU, and DABCO exhibited poor results (Table 1, entries 11–13). Considering the costs of CS_2CO_3 and KOH, we used KOH to further optimize this transformation. Screening of different solvents revealed that DMSO was the best solvent for this process. Trace or No **3aa** were detected by GC–MS when using toluene or 1,4-dioxane as solvents (Table 1, entries 14–15). Therefore, the best conditions for this transformation involved 2 equiv. KOH, in DMSO at 120 °C for 12 h.

Under the established conditions, benzamidine hydrochloride **1a** and various cinnamaldehydes were explored as substrates, and the results are summarized in Fig. 1. A series of *para*-substituted cinnamaldehydes, including some with electron-donating groups and some with electron-withdrawing groups ($\text{R}' = \text{F}$, Cl , CF_3 , NO_2), proceeded smoothly and afforded the desired pyrimidine products in high yields (**3ab–3af**). Other substituted cinnamaldehydes, such as *meta*-, and *ortho*-substituted substrates, could also provide the desired product (**3ag–3ai**). These results showed that this transformation was tolerant towards the electronic and steric

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