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Synthesis of Amidines and Its Application to Pyrimidouracil Synthesis †

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Abstract: An efficient and sustainable copper-catalyzed protocol has been developed for the preparation of amidines via nucleophilic addition of amines into nitriles. The reaction proceeded smoothly at 100 °C in the presence of CuCl, Cs_2CO_3, and 2,2/-bipyridine under oxygen (O_2) atmosphere in 2,2,2-trifluoroethanol (TFE) solvent. Moreover, a straightforward synthetic method for the synthesis of substituted pyrimidouracils via $PhI(OAc)_2$-mediated oxidative coupling of *N*-uracil amidines and methylarenes has been developed. The starting materials *N*-uracil amidines were synthesized from 6-chlorouracil and amidines via nucleophilic substitution reactions.

Keywords: amidine; transition metal; C–H activation; oxidative insertion; pyrimidouracils

1. Introduction

Amidines are important structural motifs, which have been widely used as antibiotics, diuretics, antiphogistic drugs, anthelmintics, and acaricides [1,2]. They represent an important pharmacophore in modern drug discovery [3]. It can be found in DNA and RNA binding diamidine diminazene [4], Acid Sensing Ion Channel (ASIC) inhibitor [5], muscarinic receptor agonists for the treatment of Alzheimer's disease [6], and recently, serine protease inhibitors [7]. Many *N*-arylamidines containing compounds have been used for the treatment of inflammation and pain [8–10]. In addition, they were also used as ligands for the preparation of transition metal complex [11,12]. Recent studies revealed that amidine substrates also can fix carbon dioxide [13]. In synthetic chemistry, amidines have been used as valuable precursors for the preparation of azaheterocycles of biological interest [14] like imidazoles [15], benzimidazoles [16,17], quinazolines [18], quinazolinones [19], triazine [20], triazoles [21] etc. These enormous significant applications have attracted the research community toward the development of simple and economically viable methods for the synthesis of amidines. Several synthetic methods have been developed for the preparation of amidines. Amongst these, the direct nucleophilic addition of an amine to nitrile is the most suitable and atom-economic method [22]. This one-step protocol for the synthesis of *N*-substituted amidines from nitriles and amines can be realized only if the nitriles are activated either by electron-withdrawing groups or by employing harsh conditions such as high temperature or pressure in the presence of Lewis acids [23] such as anhydrous $AlCl_3$ [23], $ZnCl_2$ [23], $CaCl_2$ [24], SmI_2[25], Ln(III) salt [26], and Ytterbium amide [27], or with aluminum amides [28] or stoichiometric amounts of CuCl [29] for unactivated nitriles. Alternatively, *N*-substituted amidines can also be accessed by nucleophilic amino substitution of thioamides or imidates [30]. Recently, new synthetic protocols based on a transition metal catalyst were developed that eliminates the activation of nitrile with a stoichiometric reagent [31–34]. Larhed and co-workers [31] have reported the palladium catalyzed synthesis of

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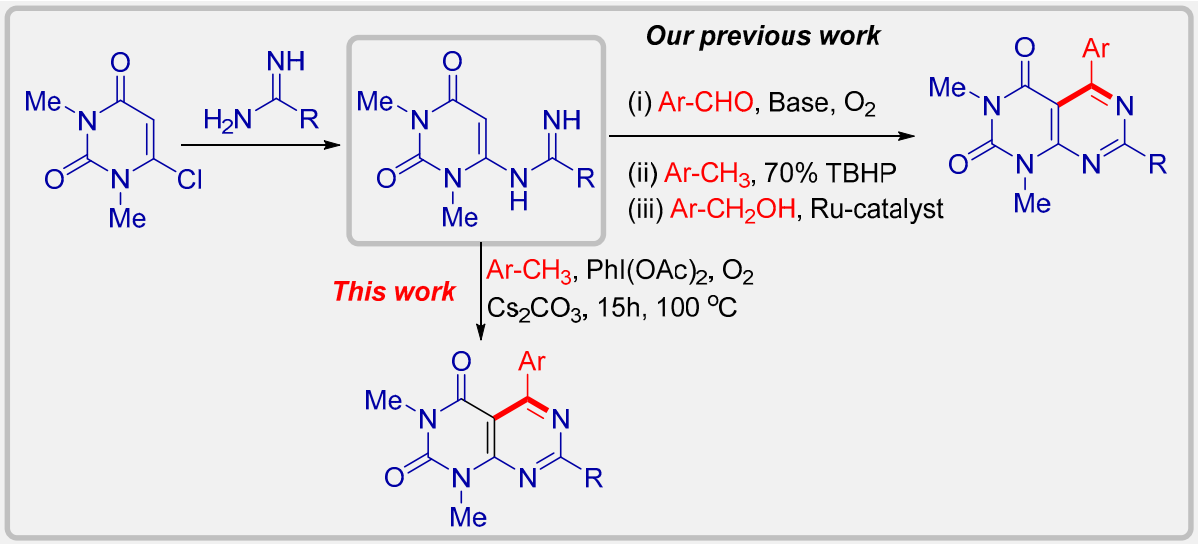
N-arylamidines from aryltrifluoroborates and cyanamides under microwave irradiation conditions. Recently, Bert et al. [32] have developed a new procedure for the synthesis of *N*-substituted amidines from arylboronic acids, isocyanides, and anilines catalyzed by palladium-catalyst under oxidative reaction conditions. Alternatively, *N*-substituted amidines can also be prepared via arylation of amidines with aryl halides or aryl triflates under transition metal catalysis conditions [33]. Other transition metal-catalyzed approaches such as palladium-catalyzed isocyanide insertion have also been explored in amidine synthesis [34]. However, such Pd(0)-initiated protocol typically requires phosphorus containing ligands, inert gas atmosphere, and basic reaction conditions, and hence, prevents the usage of substrates having base sensitive functional groups. Thus, the search for a new protocol for the synthesis of amidines via transition metal-catalyzed strategy under sustainable reaction conditions would be of high importance. Under these backgrounds, we have developed a new synthetic protocol for the preparation of *N*-substituted amidines using copper-salt as catalyst and O_2 as green oxidant. Under the oxidative conditions, various *N*-substituted amidines were obtained in good to excellent yields from nitriles and amines.

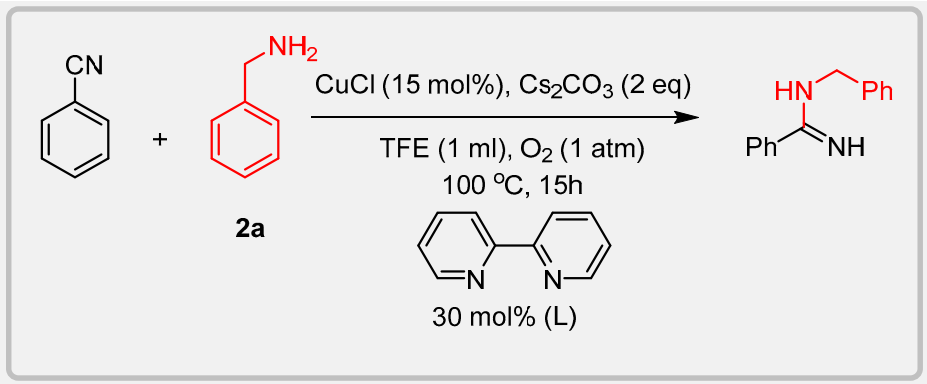
Of late, several research groups have given attention to the oxidative transformation of amidine derivatives toward azaheterocycles. In this regard, Brasche and Buchwald reported the synthesis of benzimidazoles via copper-catalyzed C–H amination of amidines [17]. Similarly, Sheng et al. [35] utilized 3-iodochromones and amidines as the substrates for the synthesis of chromento[2,3-*d*]imidazol-9(1*H*)-ones. Chiba and co-workers also carried out the molecular transformation of aliphatic amidines to imidazoles via Cu-catalyzed oxidation of amidine moieties [36–39]. Recently, Zhu and coworkers also reported the synthesis of 2-alkyl substituted benzimidazoles through the hypervalent iodine(III)-promoted intramolecular oxidative C-H imidation of *N*-arylamidines [16]. Very recently, we also observed that pyrimidopyrimidines could be prepared starting from *N*-uracil amidines and benzaldehydes under metal free conditions [16]. However, the use of aldehydes as the coupling partner has several limitations such as (i) the oxidation of some reactive aldehyde groups under the reaction conditions, and therefore, to prevent this, the inert atmosphere is required [40]; (ii) decarbonylation of some reactive aldehydes under the high reaction temperature [41]; and (iii) moreover, some aldehydes such as heteroaryl ones are costly and not easily available. For these reasons, the synthesis of variable products using aldehyde as a coupling partner is restricted. To alleviate these shortcomings, we have developed another synthetic protocol for the preparation of tetrasubstituted pyrimidopyrimidines via TBHP-mediated direct oxidative coupling of *N*-uracil amidines and methyl arenes [42]. Very recently, we observed that pyrimidouracil synthesis could also be accomplished by ruthenium-catalyzed oxidative insertion of aryl methanols into *N*-uracil amidines [43]. In the continuation of our efforts toward the synthesis of nitrogen heterocycles (Scheme 1), an efficient synthetic procedure for the synthesis of pyrimidouracils via $PhI(OAc)_2$ mediated oxidation insertion of methylarenes into *N*-uracil amidines was developed. The preliminary findings on the preparation of amidines and its application toward the synthesis of pyrimidouracils are presented in this communication.



Scheme 1. Direct oxidative and oxidative imidoylative amination of *N*-uracil-amidines.

2. Materials and Methods

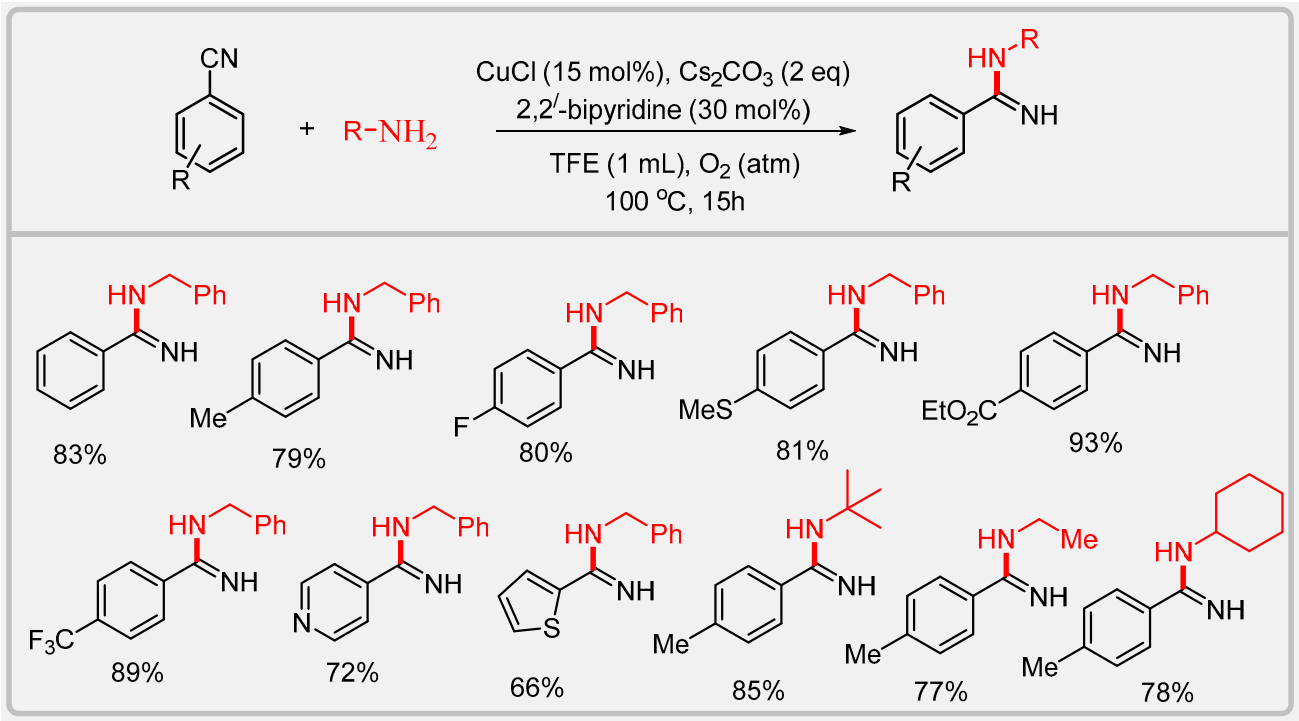
Initially, we have selected benzonitrile and benzylamine as a model substrate to examine the possibility of amidine synthesis by using commercially available Cu-salts as the catalyst (Scheme 2). The reactions were performed at 100 °C for 15 h using 15 mol % of different Cu-salts in the presence of Cs_2CO_3 (2 equiv) as a base and 2,2′-bipyridine (30 mol%) as the ligand in DMSO solvent. Amongst the tested copper catalysts, CuCl gave the best results and the desired *N*-benzylbenzamidine was obtained in 58% yield. Looking at the scope for improvement in the yield, screening of solvents, ligands, and bases was carried out. No improvement in the yield of the product was observed when the reaction was carried out either in DMF or THF, whereas only a small quantity of desired product was obtained in less polar toluene. Surprisingly, changing the solvent system to high polar ethanol gave the amidine product in 75% yield, and more polar TFE showed an increased yield (83%) of the product. This result encouraged us to choose this TFE as a solvent. Next, we examined the effect of temperature on this transformation, and it was observed that the optimum reaction temperature was 100 °C. The reaction at a higher temperature did not have any noticeable effect on the yield of the product. Furthermore, the reaction did not occurred without the copper catalyst.



Scheme 2. Synthesis of *N*-benzylbenzamidine from benzylamine and benzonitrile catalyzed by copper salt.

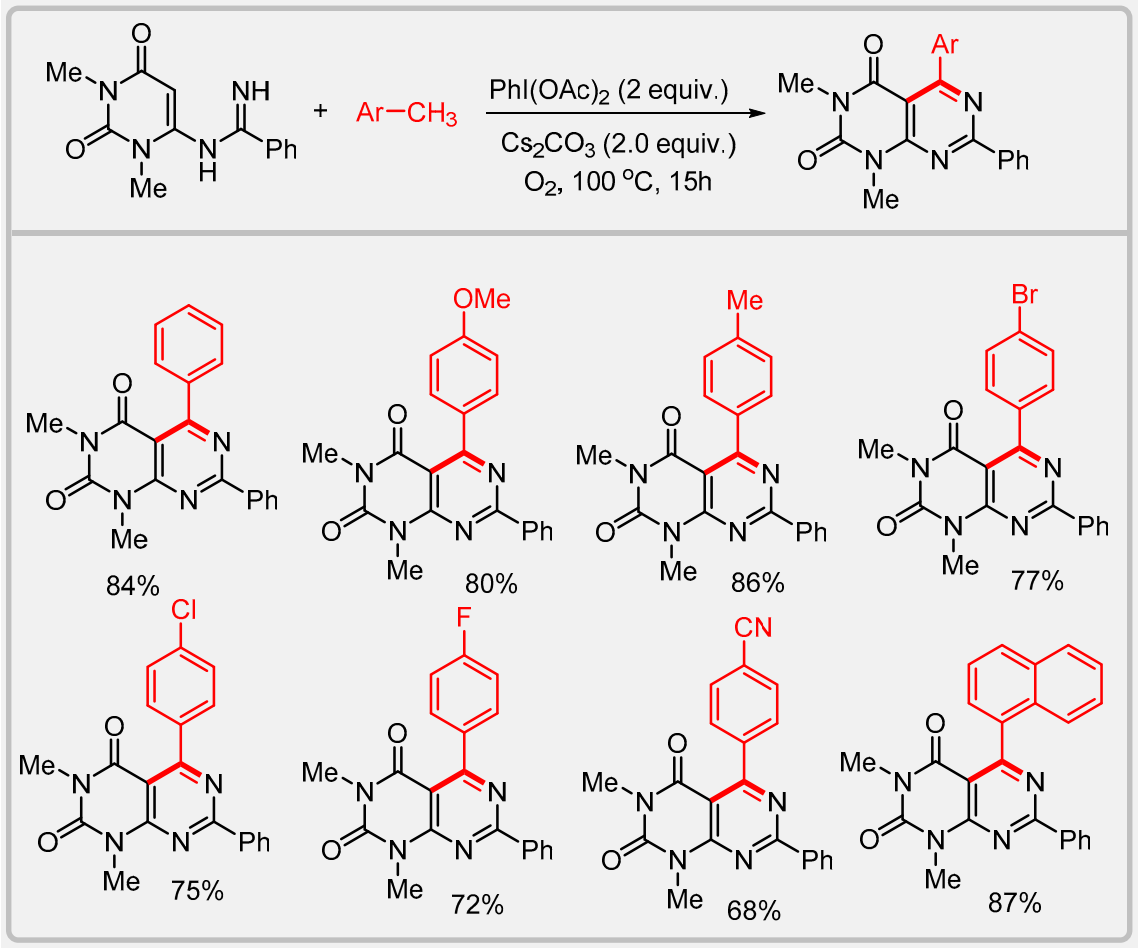
3. Results and Discussion

We then explored the substrate scope and limitations of the present protocol by performing the reactions of various benzonitriles and amines. From Scheme 3, it is clear that this protocol is effective for the synthesis of various *N*-substituted benzamidines in high yields (Scheme 3). It was observed that benzonitriles with electron-donating substituents produced respective amidines in lower yields compared to the benzonitriles bearing electron-withdrawing substituents such as *p*-CF_3 (89%) and *p*-CO_2Et (93%). Two representative heteroaromatic nitriles such as 3-pyridinecarbonitrile and 3-thiophenecarbonitrile were also tested. Delightfully, both reactions proceeded smoothly, producing the corresponding amidines in good yields. Interestingly, aliphatic amines such as *n*-hexylamine, secondary cyclohexylamine, and tertiary butylamine were also well tolerated with benzonitrile, giving corresponding benzamidines in good yields.



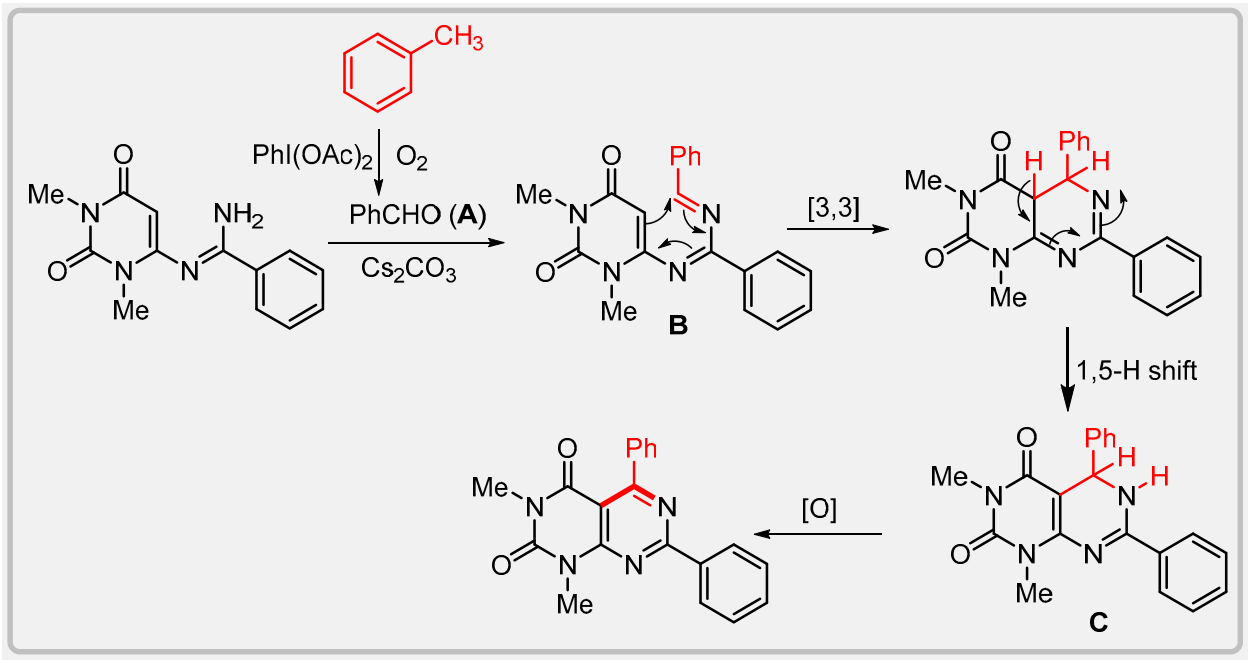
Scheme 3. Synthesis of *N*-substituted amidines from amines and benzonitriles catalyzed by CuCl.

Next, we developed a synthetic protocol for the preparation of pyrimidouracils starting from 6-chlorouracil by using amidines as a reaction partner. For this purpose, we prepared the starting materials *N*-uracil amidines by the nucleophilic substitution reaction between 6-chlorouracil and amidines. These starting materials were applied for the preparation of structurally diverse pyrimidouracils via hypervalent iodine-mediated oxidative insertion of methylarenes into *N*-uracil amidine. The reaction proceeded smoothly at 100 °C in the presence of $PhI(OAc)_2$ (2 equiv.), Cs_2CO_3 (2 equiv.), and toluene for 15 h under an O_2 atmosphere. A variety of pyrimidouracils were obtained in good to excellent yields under the optimal reaction conditions (Scheme 4). The electron-withdrawing group (F and CN) substituted methylarenes gave the lower yield of the products compared to the methylarenes having electron-donating group (OMe, Me) and halogens (Cl, Br). Interestingly, 2-methylnaphthalene could also well tolerated under the reaction conditions, giving the corresponding pyrimidouracil in excellent yield.



Scheme 4. PhI(OAc)$_2$-mediated synthesis of pyrimidouracils from *N*-uracil amidines and arylmethanes.

A proposed reaction pathway for the formation of the product is predicted in Scheme 5. At the beginning of the reaction, an aldehyde (**A**) is formed by the oxidation of methylearene in the presence of hepervalent iodine reagent. The *insitu* generated aldehyde on condensation with amidine to form azadiene **B** [44,45]. The intermediate azadiene undergoes an intramolecular Aza-Diel's Alder type reaction, followed by a [1,5]-hydrogen transfer to give the isolable intermediate 5,6-dihydropyrimidopyrimidine (**C**). Finally, the pyrimidouracil is obtained by the oxidation of intermediate **C** with aerial oxygen.



Scheme 5. A plausible mechanism for the formation of pyrimidouracil.

4. Conclusions

In conclusion, we have developed an efficient and more sustainable protocol for the preparation of *N*-substituted benzamidines from aromatic/aliphatic nitriles and amines using CuCl as the catalyst in the presence of Cs_2CO_3, and 2,2′-bipyridine under O_2 atmosphere in TFE solvent at 100 °C. Various *N*-substituted benzamidines were obtained in high yields under oxidative reaction conditions. Moreover, we developed an efficient and operationally simple method for the preparation of substituted pyrimidopyrimidines from *N*-uracil amidines and methylarenes using $PhI(OAc)_2$ as an oxidative reagent. In this transformation, methylarenes are acted as the precursor of aldehyde. The main advantages of the protocol are that (i) it is operationally simple, (ii) methylarenes are cheap and more stable compared to aldehydes, and (iii) the use of green oxidant (O_2). We believe that this protocol would be highly useful for the preparation of various pyrimidouracils of biological interest.

5. Experimental

Instruments and reagents: All chemicals and reagents were purchased from Sigma-Aldrich, Alfa-Aesar, Spectrochem, TCI Chemicals and used as it received from company. Silica gel, 60–120 was used for normal chromatographic separation and silica gel 230–400 mesh was used for flash column chromatography. TLC plates were purchased from Merck and used for thin-layer chromatography (TLC). Silicon oil bath was used to determine the melting points of the synthesized compounds using open capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively using $CDCl_3$ or DMSO-d_6 solvents. Chemical shift values are given in parts per million (ppm, δ) with reference to tetramethylsilane (TMS) as the internal standard.

(a) **Procedure for the preparation of *N*-benzylbenzamidine from benzonitrile and benzylamine.**

The benzonitrile (0.5 mmol, 1.0 equiv), benzylamine (0.6 mmol), Cs_2CO_3 (1.0 mmol), 2,2′-bipyridine (30 mol%), and CuCl (7.4 mg, 0.075 mmol) were taken in a dry vial (10 mL). Dry TFE (1 mL) was added using a syringe and then, oxygen (O_2) gas was flushed into the vial for 1 min. Then, the vial was sealed and placed in a preheated oil bath at 100 °C. After 15 h stirring, the reaction mixture was cooled and then poured into NaOH (2M) so-

lution. The aqueous layer was extracted with dichloromethane (3 × 10 mL). Finally, DCM was washed with brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by chromatography using ethyl acetate–petroleum ether mixture (1:4) as eluent (ethyl acetate mixed with 7N NH_3 in MeOH in the ratio 19:1) to give the title compounds.

N-Benzylbenzenecarboximidamide: Yield: 83% (87 mg), White solid, mp 69–71 °C. ^{1}H NMR (400 MHz, DMSO): δ= 4.36 (s, 2H), 6.53 (br s, 2H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.38–7.43 (m, 5H), 7.82–7.84 (m, 2H). ^{13}C NMR (100 MHz, DMSO): δ= 49.7, 126.5, 127.0, 127.9, 128.4, 128.5, 129.8, 137.7, 142.4. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{15}N_2$ [M^++H]: 211.1236; found: 211.1235.

(b) **General procedure for the synthesis of *N*-uracil amidine derivatives**

An oven-dried 10 mL pressure vial was loaded with 1,3-dimethyl-6-chlorouracil (349 mg, 2 mmol, 1.0 eq.), benzamidine hydrochloride (3.0 mmol, 1.5 equiv.), and 1,8-diazabicyclo[5.4.0]undec-7-ene (660 μL, 4.4 mmol, 2.2 equiv.). The anhydrous *tert*-butanol (0.5 mL) was added to the vial. Then, the vessel was flushed with N_2 for 1 min. and sealed with a septum. The resulting mixture was placed in a preheated oil bath and stirred at 80 °C for 24 h. After completion of reaction, the reaction mixture was cooled to room temperature and then extracted with ethyl acetate. The combined ethyl acetate was washed with brine and the organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography using the ethyl acetate/petroleum ether mixture as the eluent.

(c) **Procedure for $PhI(OAc)_2$-mediated oxidative insertion of toluene into *N*-Uracil Amidines toward the synthesis of pyrimidouracils**

N-Uracil amidine (0.5 mmol, 1.0 equiv.), toluene (1 mL), $PhI(OAc)_2$ (1.0 mmol, 322 mg,) and Cs_2CO_3 (1.0 mmol, 325 mg) were added in a microwave vial. The vessel was flushed with O_2 and then sealed with septum. The reaction mixture was placed in an oil bath and stirred for 15 h at 100 °C. After completion of the reaction, the reaction mixture was stirred with ethyl acetate (10 mL) and brine for 10–12 min. The aqueous layer was extracted with ethyl acetate. The combined ethyl acetate layers were washed with brine and dried (Na_2SO_4), and filtered. The crude products were purified by column chromatography using a mixture of hexane-ethyl acetate as the eluent.

Institutional Review Board Statement:

Informed Consent Statement: Not applicable

Data Availability Statement: Not applicable

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Conflicts of Interest: The authors declare no conflict of interest.

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