Synthesis of Amidines and its application to pyrimidouracil synthesis

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Abstract: Amidines are the important classes of nitrogenous compounds, which have been widely used as antibiotics, diuretics, antiphogistic drugs, anthelmintics, and acaricides. They represent an important pharmacophore in modern drug discovery, and can be found in DNA and RNA binding diamidine diminazene, ASIC inhibitor, muscarinic agonists for the treatment of Alzheimer's disease, platelet aggregation inhibitors, and recently, serine protease inhibitors, to give some examples. These enormous significant applications have attracted the research community towards the development of simple and economically viable methods for the synthesis of amidines. In this paper, we have demonstrated a synthetic protocol for the preparation of amidines via copper catalyzed nucleophilic addition of amines into nitriles. The reaction proceeds smoothly at 100 °C in the presence of CuCl, Cs_2CO_3 and 2,2/-bipyridine as ligand in TFE solvent. Moreover, an efficient protocol for the synthesis of substituted pyrimidouracils via $PhI(OAc)_2$-mediated oxidative coupling of *N*-uracil amidines and methylarenes under metal-free conditions 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.

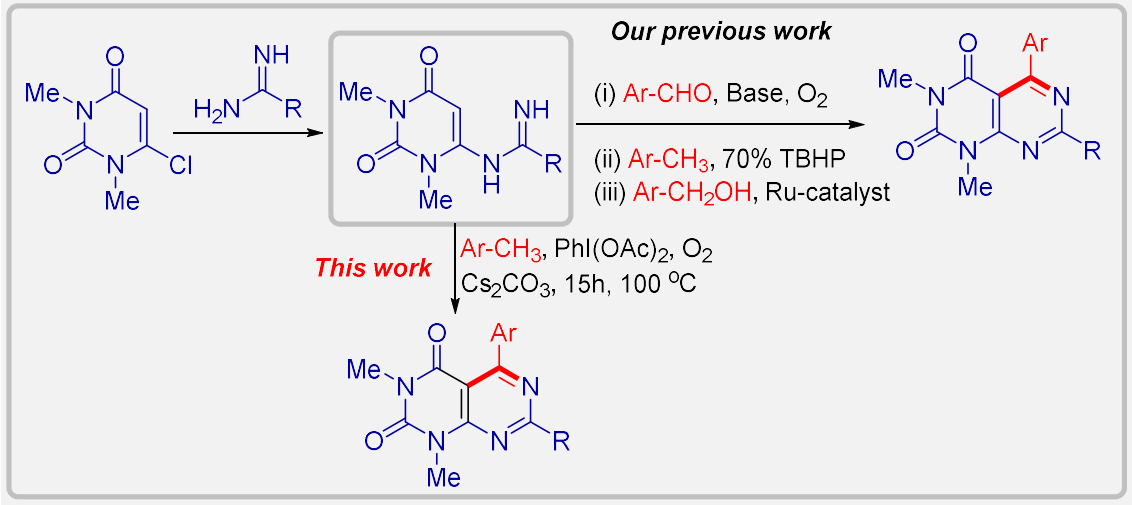
1. INTRODUCTION

Amidines[1] are important structural motifs in a wide range of molecules with numerous applications such as it represents an important pharmacophore in drug discovery[2-5]. It can be found in DNA and RNA binding diamidine diminazene [6], ASIC inhibitor [7], muscarinic agonists for the treatment of Alzheimer's disease [8], platelet aggregation inhibitors [9], and recently, serine protease inhibitors [10], to give some examples. Many compounds containing *N*-arylamidines have shown promise as treatment for inflammation and pain [11]. In fact, many of the top-selling pharmaceuticals of the fast few years feature an amidine as a key structural components [12]. In addition, they also serve as ligands for transition metals due to their unique structure [13]. Recent studies have demonstrated their capacity to fix carbon dioxide [14]. In synthetic chemistry, amidines have been used as valuable precursors for the preparation of azaheterocycles of biological interest like imidazoles [16], benzimidazoles [17], quinazolines [18], quinazolinones [19], pyrimidines [20], triazoles [21] *etc* . These enormous significant applications have attracted the research community towards development of simple and economically viable methods for the synthesis of amidines. Several synthetic methods have been developed, in which the nucleophilic addition of amine to nitrile is the most convenient and atom-economic method [22]. This one-step synthesis of *N*-substituted amidines from nitriles and amines can

be realized only if the nitriles are activated either by electron-withdrawing groups [22] or by employing forcing conditions in the presence of Lewis acids [23] such as anhydrous $AlCl_3$ [23a], $ZnCl_2$ [23a], $CaCl_2$ [23b], SmI_2 [23c], Ln(III) salt [23d], and Ytterbium amide [23e], or with aluminium amides[23f,g] or stoichiometric amounts of CuCl [23h] for unactivated nitriles. Alternatively, *N*-substituted amidines can also be accessed by nucleophilic amino substitution of thioamides or imidates [24]. Recently, new synthetic approaches that do not require activation of nitrile with a stoichiometric reagent, based on a transition metal catalyst was developed [25-27]. Larhed and co-workers [25a] have reported the palladium catalysed synthesis of *N*-arylamidines from aryltrifluoroborates and cyanamides under microwave irradiation conditions. Recently, Bert *et al*. [25b] have developed a new procedure involving palladium-catalyzed oxidative synthesis of *N*-substituted amidines from arylboronic acids, isocyanides, and anilines under oxidative reaction conditions. Alternatively, *N*-substituted amidines can also be obtained starting from a free amidine *via* arylation with aryl halides or aryl triflates under transition metal catalysis [26]. Other transition metal-catalyzed approaches such as palladium-catalyzed isocyanide insertion has also been explored in the amidine synthesis [27]. However, such type of Pd(0)-initiated chemistry usually requires phosphine ligands, inert gas protection and basic reaction conditions, which increases the manipulation complexity and prevent the usage of base sensitive functional group substituted substrates. Thus, search for 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 procedure involving copper-catalyzed oxidative synthesis of *N*-substituted amidines. 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 paid their attention for the oxidative transformation of amidine derivatives towards the azaheterocycles. In this regard, Brasche and Buchwald reported the copper-catalyzed C-H amination to lead to benzimidazoles by using amidines as the substrates [28]. Similarly, Sheng et al. [29] have 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 [30] have also investigated the transformation of readily available amidine derivatives to imidazole derivatives initiated by Cu-catalyzed single-electron oxidation of amidine moieties. Recently, Zhu and co-workers reported [31] the synthesis of 2-alkyl benzimidazoles through the metal-free hypervalent iodine(III)-promoted intramolecular oxidative imidation of aromatic C-H bonds of *N*-arylamidines. Very recently, we have shown that pyrimido[4,5-*d*]pyrimidines could be achieved by the direct annulation of *N*-uracil amidines with benzaldehydes under transition metal free conditions [32]. However, the use of aldehydes as the coupling partners poses several shortcomings like- (i) some active aldehyde groups may undergo an oxidation reaction which can potentially form unwanted by-products, and therefore, for resisting this, inert conditions are required [33]; (ii) some reactive aldehydes may undergo a decarbonylation reaction under tough reaction conditions [34]; (iii) moreover, high cost or non-availability of some aldehydes

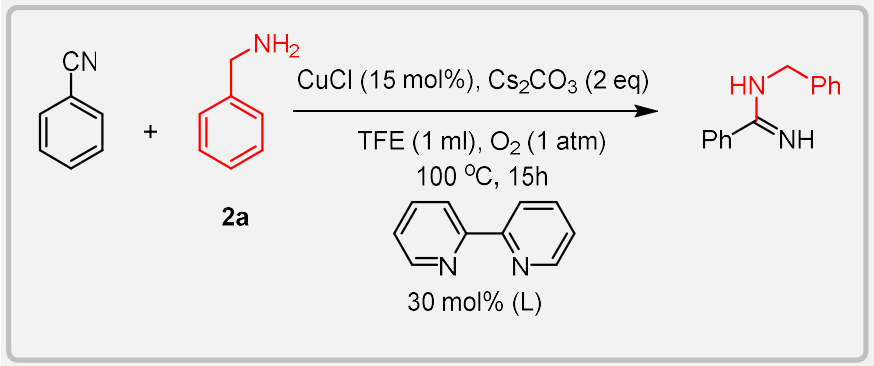
such as- heteroaryl ones, restricted the synthesis of variable products. In order to alleviate these shortcomings, we have developed another synthetic protocol for the preparation of 1,3,5,7-tetrasubstituted pyrimido[4,5-*d*]pyrimidines via TBHP-mediated direct oxidative coupling of *N*-uracil amidines and under metal-free conditions [35]. Very recently, we also observed that pyrimidouracils synthesis could also be accomplished by ruthenium catalyzed oxidative insertion of aryl methanols into *N*-uracil amidines [36]. In continuation of our efforts towards the synthesis of nitrogen heterocycles, an efficient synthetic procedure for the synthesis of pyrimidouracils via $PhI(OAc)_2$ mediated oxidation insertion of methylarenes into *N*-uracil amidines has been developed. The preliminary findings on the preparation of amidines and its application towards 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

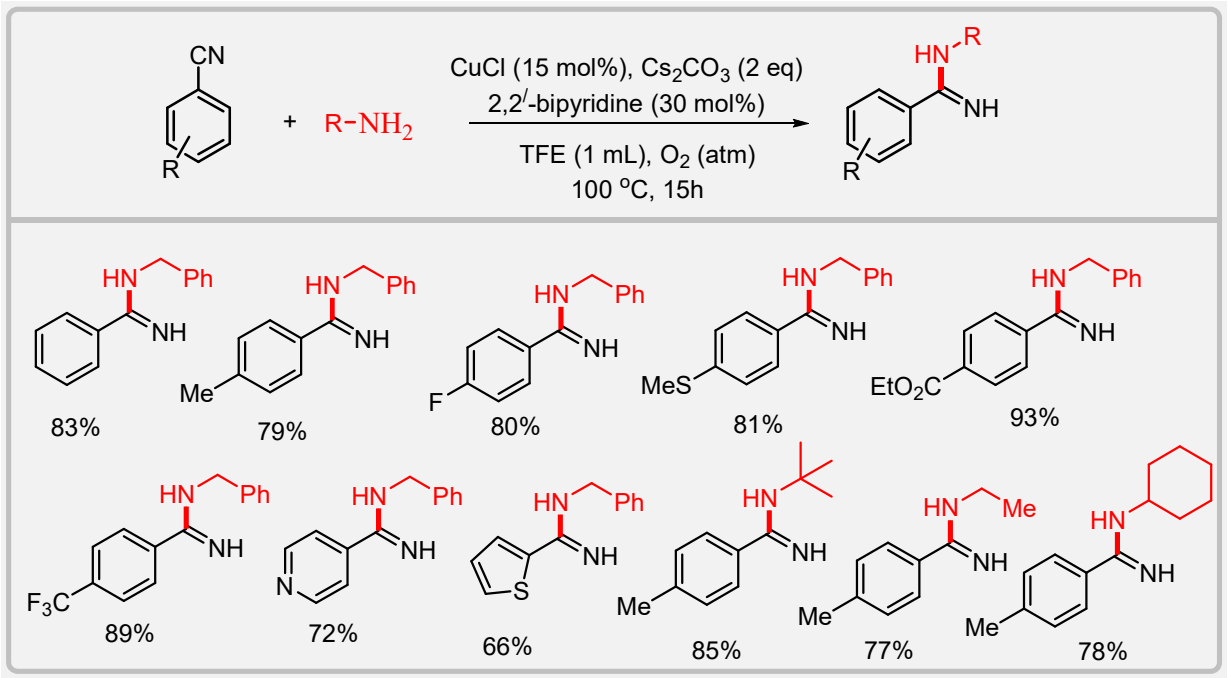
The possibility of direct synthesis of amidine has been examined by using commercially available Cu-salts as catalyst. Initially, benzonitrile and benzylamine were selected as a model substrate (Scheme 2). The reactions were carried out at 100 °C for 15 h using 15 mol % of different Cu-salts, 30 mol% of 2,2′-bipyridine as ligand and Cs_2CO_3 as base in DMSO solvent. In all the tested catalytic systems, CuCl gave the best results and 58% of the desired *N*-benzylbenzamidine was formed. Looking at the scope for improvement in the yield, screening of solvents, ligands and bases were 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 trace amount of desired product was obtained in less polar toluene. Surprisingly, changing the solvent system to high polar ethanol resulted into formation of the amidine product in 75% yield and more polar TFE showed a higher yield of the product. This surprise result encouraged us to choose this TFE as solvent. Next, the effect of temperature was studied, and it was observed that 100 °C is the optimum reaction temperature. Farther, increase in the reaction temperature did not have any noticeable effect on this transformation. No reaction occurred without copper catalyst.



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

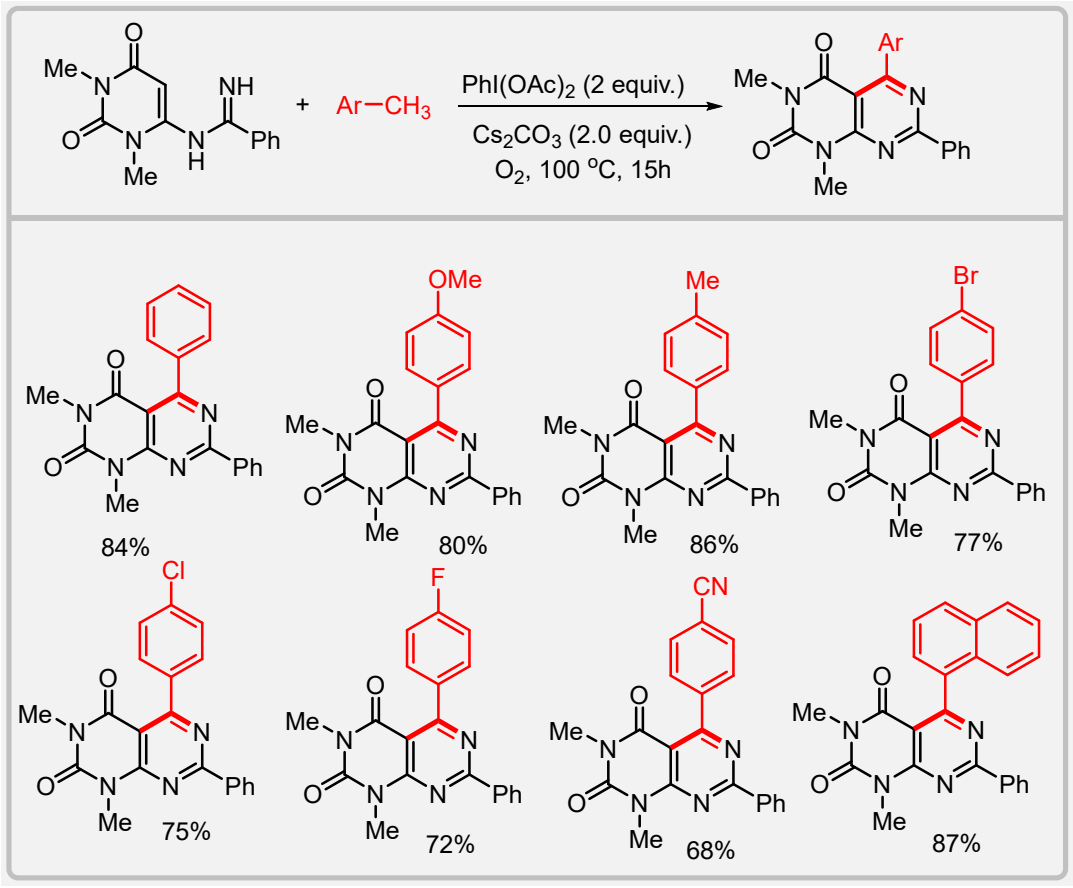
3. RESULTS AND DISCUSSIONS

With the optimized conditions in hand, the substrate scope and limitations of this protocol was explored by performing the reactions of various benzonitriles and amines. Various *N*-substituted benzamidines were synthesized in good to excellent yields under the optimized reaction conditions (Scheme 3). Both electron-withdrawing and electron donating substituents are well tolerated. It was observed that benzonitriles with electron-donating substituents produced respective amidines in lower yields as compared to the benzonitriles bearing electron-withdrawing substituents such as *p*-CF_3 (89%) and *p*-CO_2Et (93%). To extend the scope of the reaction, heteroaromatic nitriles such as 3-pyridinecarbonitrile, and 3-thiophenecarbonitrile were tested. Delightfully, both the reactions proceeded smoothly producing the corresponding amidines in good yields. Many aliphatic amines including primary *n*-hexylamine, secondary cyclohexylamine, and tertiary butylamine reacted well with benzonitrile giving corresponding benzamidines in comparable yields.



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

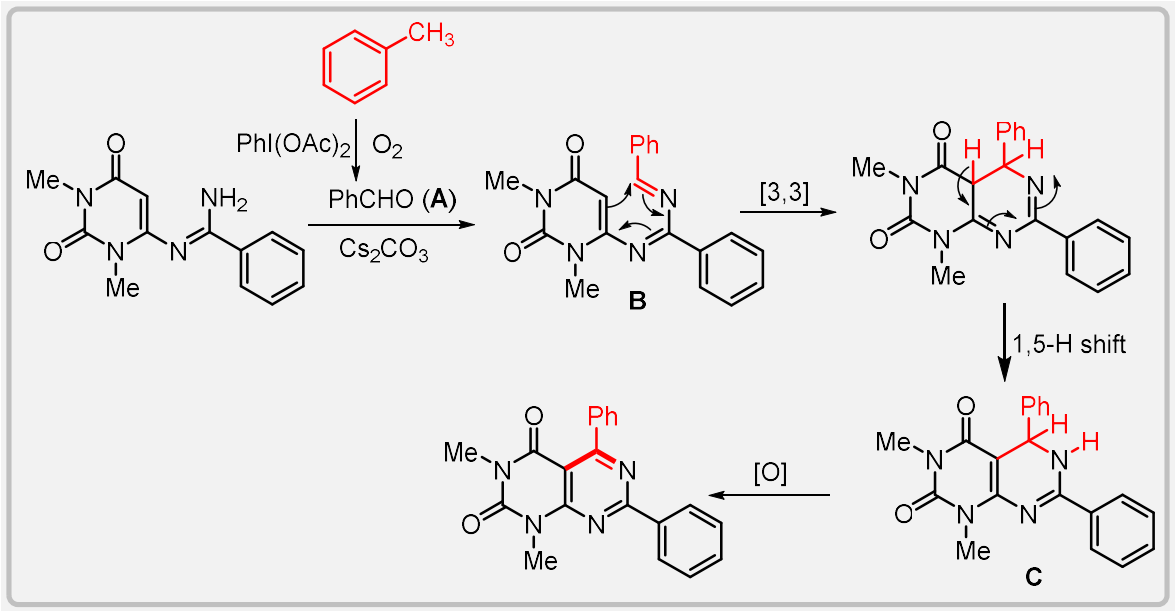
Next, we have developed a synthetic protocol for the preparation of pyrimidouracils starting from 6-chlorouracil by using amidines as reaction partner. For this purpose, we have prepared the starting materials *N*-uracil amidines by the S_NAE of the C6 halogen of 6-chlorouracil by amidines. These staring materials have been applied for the synthesis of structurally diverse pyrimidouracils via $PhI(OAc)_2$-mediated oxidative insertion of methylarenes into *N*-uracil amidine. The reaction proceeded smoothly with 2 equiv. of $PhI(OAc)_2$, Cs_2CO_3 (1.0 mmol, 2.0 equiv.), and toluene (1 mL) at 100 °C for 15 h under O_2 atmosphere. All the reactions using methylarenes furnished desired products in good to excellent isolated yields (Scheme 4). It was observed that methylarenes with electron-donating substituents such as OMe, Me, halogens (Cl, Br) produced respective pyrimidouracils in very good yields (75-86%) while methylarenes having electron-withdrawing substituents such as F, CN furnished slightly lower yield of the products. α-Methylnaphthalene could also be employed to react with *N*-uracil amidine under the optimal reaction conditions giving the corresponding product in 87% yield.



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

A plausible mechanism for the formation of product is proposed in Scheme 5. Initially, the reaction may proceeds with the formation of an aldehyde (**A**) by $PhI(OAc)_2$ mediated oxidation of toluene. Then, in situ generated aldehyde **A** condensed with *N*-uracil amidine to give azadiene **B** [37].

The intramolecular [4+2] cycloaddition reaction of azadiene followed by a [1,5]-hydrogen shift to form the intermediate 5,6-dihydropyrimido[4,5-d]pyrimidine (**C**), which on oxidation by aerial oxygen affords the desired product.



Scheme 5. Plausible mechanism for the formation of pyrimidouracil.

CONCLUSION

In conclusion, an efficient, one-step and environmentally benign protocol has been developed for the synthesis of *N*-substituted benzamidines from aromatic nitriles and amines using CuCl as catalyst, Cs_2CO_3 as base, and 2,2′-bipyridine as ligand under O_2 atmosphere in TFE solvent. A variety of *N*-substituted benzamidines were synthesized in good to excellent yields under oxidative reaction conditions. We have also developed an efficient and straightforward method for the synthesis of 1,3,5,7-tetrasubstituted pyrimidouracils from inexpensive and easily available methylarenes and *N*-uracil amidines employing a green oxidant under metal-free conditions. Methylarenes are performed as effective aldehyde precursors in the oxidation-imination-cyclization transformation. The present protocol has a number of advantages such as- inherent stability of methylarenes compared to aldehydes, operational simplicity, and use of green oxidant, making it a highly practical approach to access various pyrimidouracils of biological interest. This protocol is a significantly important complement to the existing synthetic methodologies.

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4. EXPERIMENTAL

Instruments and reagents: All the chemicals and reagents were commercially available and purchased from Sigma-Aldrich, Alfa-Aesar, Spectrochem, TCI Chemicals and used as received without further

purification. Silica gel, 60-120 and 230-400 mesh were purchased from Spectrochem, India and used for chromatographic separation. Flash column chromatography was performed over silica gel and 230-400 mesh. TLC plates were purchased from Merck and used for thin-layer chromatography (TLC). All solvents were distilled prior to use in extraction and purification purposes. Melting points were measured on silicon oil bath using open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker Ascend 400 MHz spectrometer (Brucker, Germany) at 400 MHz and 100 MHz, respectively using $CDCl_3$ or DMSO-d_6 solvents. Chemical shifts values are given in parts per million (ppm, δ) with reference to tetramethylsilane (TMS) as internal standard.

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

An oven-dried microwave vial (10 mL) equipped with a magnetic stirring bar was charged with 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). The vessel was flushed with O_2 and then sealed with septum. Dry TFE (1 mL) was added to the reaction vial using a syringe. The reaction mixture was heated at 100 ^{o}C and stirred for 15 h. The reaction mixture was allowed to reach room temperature. Then the reaction mixture was poured into NaOH (2M) solution (20 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water and then brine, and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (60-120 mesh) using ethyl acetate-petroleum ether mixture (20:80) as eluent (ethyl acetate mixed with 7N NH_3 in MeOH in the ratio 95:5) to give the title compounds.

***N*-Benzylbenzenecarboximidamide:** Yield: 83% (87 mg), White solid, mp 69-71 $^{\circ}C$. ^{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.), 1,8-diazabicyclo[5.4.0]undec-7-ene (660 µL, 4.4 mmol, 2.2 equiv.) and anhydrous *tert*-butanol (0.5 mL). The vessel was flushed with N_2 and then sealed with a septum. The resulting mixture was stirred at 80°C under N_2 atmosphere for 24 hours. The reaction mixture was extracted with ethyl acetate (3 x 15 mL), and the combined ethyl acetate was washed with water (20 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure. The resulting residue was purified by column chromatography using ethyl acetate/petroleum ether mixture as eluent.

(c) Procedure for $PhI(OAc)_2$-mediated oxidative insertion of toluene into *N*-Uracil Amidines towards 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 an oven-dried microwave vial (10 mL) equipped with a magnetic stirring bar. The vessel was flushed with O_2 and then sealed with septum. The reaction mixture was stirred in an oil bath at 100 °C for 15 hours. After completion of reaction, the mixture was cooled to room temperature. The mixture was then stirred with ethyl acetate (10 mL) and brine (10 mL) for 15 minutes. The aqueous layer was extracted with ethyl acetate (2 x 10 mL). Finally, the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated. The crude products were purified by either column chromatography on silica gel (60-120 mesh) or flash column chromatography (230-400 mesh) using a mixture of hexane-ethyl acetate as the eluent to afford the title compounds.

1,3-Dimethyl-5,7-diphenylpyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione:

White solid; Yield: 84%, 210 °C. 1H NMR (400 MHz, $CDCl_3$): δ= 3.41 (s, 3H), 3.85 (s, 3H), 7.48-7.57 (m, 6H), 7.64 (dd, J = 2.0 Hz, 8.4 Hz, 2H), 8.57 (d, J = 8.4 Hz, 2H). 13C NMR (100 MHz, $CDCl_3$): δ= 28.6, 29.9, 103.7, 127.7, 128.6, 129.1, 129.3, 130.0, 132.3, 136.1, 138.4, 151.3, 157.9, 159.6, 165.2, 170.4. HRMS (ESI): m/z calcd for $C_{20}H_{16}N_4O_2Na$ [M++Na]: 367.1165; found: 367.1158.

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