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Metal-Free Synthesis of Pyridin-2-yl Ureas from 2-Aminopyridinium Salts

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ABSTRACT

An unprecedented base promoted domino approach has been developed for the synthesis of pyridin-2-yl urea derivatives *via* the reaction of 2-aminopyridinium salts and arylamines. The developed strategy tolerated a wide range of functional groups and afforded pyridin-2-yl ureas in moderate to good yields. The reaction was postulated to involve tandem cyclization, intermolecular nucleophilic addition, ring opening, and demethylation.

Urea derivatives have been investigated for an array of biological activities including antimicrobial,[1] antitubercular,[2] antimalarial,[3] antiviral,[4] and anticancer.[5] Substituted ureas with an attached heterocyclic ring system represent an important motif in medicinal chemistry.[6] In particular, ureas bearing a pyridin-2-yl ring (**I** and **II**) are key scaffolds in the development of glucokinase activators (GKAs) for the treatment of type-2-diabetes mellitus (T2DM) (Fig. 1).[7] Pyridin-2-yl substituted urea VU0463841 (**III**) was identified as a negative allosteric modulator (NAM) of metabotropic glutamate receptor subtype 5 ($mGlu_5$).[8] Omecamtiv mecarbil (**IV**) is being studied in Phase 3 clinical trials as a selective cardiac myosin activator of cardiac myosin to determine its effectiveness for the treatment of heart failure with reduced ejection fraction.[9] Pyridin-2-yl urea derivative **V** has been reported as a new class of antibacterial agent targeting bacterial topoisomerase binding targets.[10]

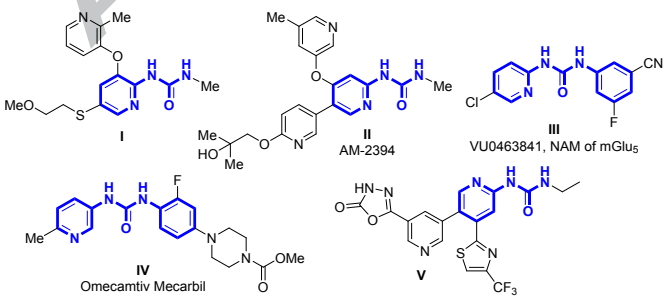

Figure 1. Representative bioactive pyridyl ureas.

Due to the valuable role of pyridyl ureas in drug discovery, there has been significant focus toward the development of efficient, practical and novel synthetic routes for the preparation of substituted ureas (Scheme 1). Traditionally, pyridyl ureas are synthesized *via* the reaction of aminopyridines and amines with phosgene[11] or isocyanates,[10] which are usually highly toxic, moisture sensitive and generate large amounts of halide containing waste. Later, transition metal-catalyzed cross coupling approaches were developed for the synthesis of pyridyl ureas *via* the reaction of halopyridines and unsubstituted urea.[12] Selenium-catalyzed oxidative carbonylation approaches were also developed for the synthesis of pyridyl ureas by employing a mixture of toxic carbon monoxide and oxygen.[13] Kukushkin and co-workers reported the methane sulfonic acid promoted synthesis of pyridin-2-yl substituted ureas from pyridine *N*-oxides (PyO) and dialkylcyanamides.[14] Recently, Mahajan and co-workers reported the synthesis of *N*-substituted ureas *via* the reaction of amines with potassium isocyanate in water without an organic co-solvent.[15] Although there has been marked progress towards the synthesis of substituted pyridyl ureas, their synthesis under environmentally benign and mild reaction conditions remains a topic of interest.

In continuation of our research interests toward developing synthetic transformations using 2-aminopyridinum salts,[16] herein, we report an unprecedented approach for the synthesis of pyridin-2-yl urea derivatives from 2-amino-1-ethoxycarbonyl-methylpyridium bromides (Scheme 1). The method involves tandem cyclization, intermolecular nucleophilic addition, ring opening, and demethylation to give pyridin-2-yl ureas in moderate to good yields under mild and transition metal-free conditions.

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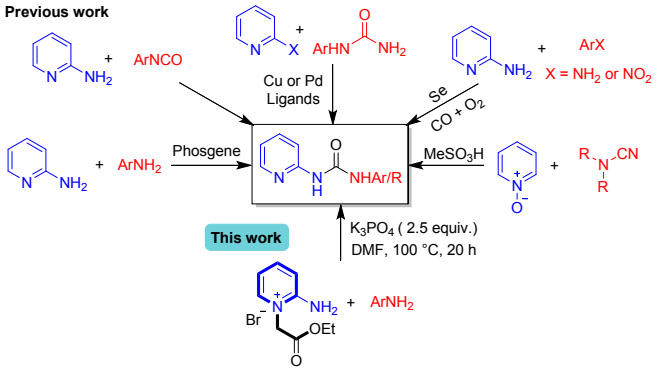
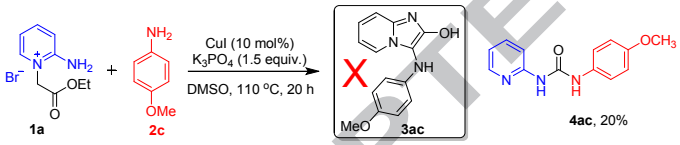


Scheme 1. Reported methods and our approach for the synthesis of pyridin-2-yl ureas.

Initially, we were interested in developing a novel method for the synthesis of 3-aminoaryl-imidazopyridines from 2-aminopyridinium salts. To test our hypothesis, 2-aminopyridinium salt (**1a**) and 4-methoxyaniline (**2c**) were treated with CuI (10 mol %) and K_3PO_4 (1.5 equiv.), at 100 °C in DMSO (3 mL). Surprisingly, instead of the expected 3-aminoarylimidazopyridine (**3ac**), we obtained 1-(4-methoxyphenyl)-3-(pyridin-2-yl) urea (**4ac**) in 20% yield (Scheme 2). The structure of **4ac** was established using ^{1}H, ^{13}C NMR, ESI-HRMS, and IR spectroscopic analysis (see ESI). The appearance of a strong peak at 1689 cm^{-1} (C=O stretch) along with two peaks at 3209 and 3124 cm^{-1} (N-H stretch) in the IR spectrum suggested the presence of an amidic/urea functional group. The presence of two singlets at 10.42 and 9.38 ppm for D_2O exchangeable protons along with other protons in the ^{1}H NMR spectrum and a peak at 155.4 ppm in the ^{13}C NMR spectrum also suggested the presence of disubstituted urea functionality. Finally, a peak at *m/z* 244.1084 in the ESI-HRMS analysis corresponding to the molecular formula $C_{13}H_{13}N_3O_2$ confirmed the structure of **4ac**.

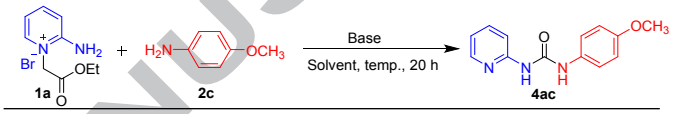


Scheme 2. Synthesis of 1-(4-methoxyphenyl)-3-(pyridin-2-yl) urea **4ac**.

Encouraged by the unexpected, but remarkable result for the reaction of **1a** and **2c**, we systematically screened other reaction parameters to improve the yield of **4ac** (Table 1). Interestingly, a slightly improved yield (35%) was obtained in the absence of CuI, indicating that the reaction is mediated only by the base and CuI has no role (Table 1, entry 1). Next, we screened different inorganic and organic bases (Table 1, entries 1-8) and found that K_3PO_4 was the most suitable base. We then investigated the effect of solvents on the reaction using K_3PO_4 as the base. To our satisfaction, **4ac** was obtained in 50% yield in DMF, whereas other organic solvents such as 1,4-dioxane, toluene, DCE, MeCN, and water gave lower yields (Table 1, entries 9-14). Next, we examined the K_3PO_4 loading (Table 1, entries 15-17). Increasing the amount of K_3PO_4 from 1.5 equivalents to 2.5 equivalents resulted in an increased yield. Further increasing the K_3PO_4 amount from 2.5 equivalents to 3.0 equivalents did not significantly effect the yield. Finally, the effect of the temperature was evaluated (Table 1, entries 18-19). Lower yields were obtained upon increasing or decreasing the reaction temperature.

With the optimized reaction conditions in hand (Table 1, entry 16), we then explored the substrate scope and generality of this reaction (Table 2). The reaction of **1a** with aryl amines (**2a-h**) possessing methyl, methoxy, fluoro, chloro, and bromo substituents afforded the corresponding ureas **4aa-ah** in moderate to good yields (32-68%). The yields were relatively lower for halogen-substituted aryl amines which can be attributed to their lower nucleophilicity. Similarly, the reaction of 2-aminopyridinium salts processing chloro, bromo, methyl, phenyl, 4-methoxyphenyl, and 4-chlorophenyl substituents on the pyridine ring (**1b-i**) with aniline (**2a**) afforded the corresponding ureas **4ba-ia** in 36-62% yield. Higher yields were obtained using 2-aminopyridinium salts possessing electron-donating groups on the pyridine ring. The reaction of substituted pyridinium salt **1d** with the substituted anilines 4-methoxyaniline (**2c**) and 4-bromoaniline (**2f**) gave ureas **4dc** and **4df** in 65% and 50% yields, respectively. Similarly, the reaction of other substituted pyridinium salt **1e** with **2c** and **2f** gave ureas **4ec** and **4ef** in 51% and 29% yield, respectively.

Table 1. Optimization of the reaction conditions.[a,b]



Entry	Base	Solvent	Temp. (°C)	Yield (%)[b]
1	K_3PO_4	DMSO	100	35
2	KOH	DMSO	100	22
3	K_2CO_3	DMSO	100	20
4	^{t}BuOK	DMSO	100	23
5	Cs_2CO_3	DMSO	100	33
6	DBU	DMSO	100	15
7	NEt_3	DMSO	100	Trace
8	Piperidine	DMSO	100	Trace
9	K_3PO_4	DMF	100	50
10	K_3PO_4	1,4-Dioxane	100	23
11	K_3PO_4	Toluene	100	17
12	K_3PO_4	DCE	100	24
13	K_3PO_4	MeCN	100	29
14	K_3PO_4	H_2O	100	25
15[c]	K_3PO_4	DMF	100	57
16[d]	**K_3PO_4**	**DMF**	**100**	**63**
17[e]	K_3PO_4	DMF	100	62
18[d]	K_3PO_4	DMF	120	42
19[d]	K_3PO_4	DMF	80	46

[a]Reagents and conditions: **1a** (1.2 mmol), **2c** (1.0 mmol), base (1.8 mmol), solvent (3 mL), 20 h.
[b]Isolated yield.
[c]2.4 mmol K_3PO_4 was used.
[d]3.0 mmol K_3PO_4 was used.
[e]3.6 mmol K_3PO_4 was used.

The structures of all the synthesized pyridin-2-yl ureas were established using IR, ^{1}H NMR, ^{13}C NMR, and ESI-HRMS analysis. The structure of **4ab** was further confirmed by single crystal X-ray (CCDC No. 1852803) analysis (Fig. 2).

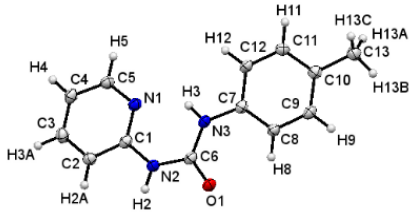
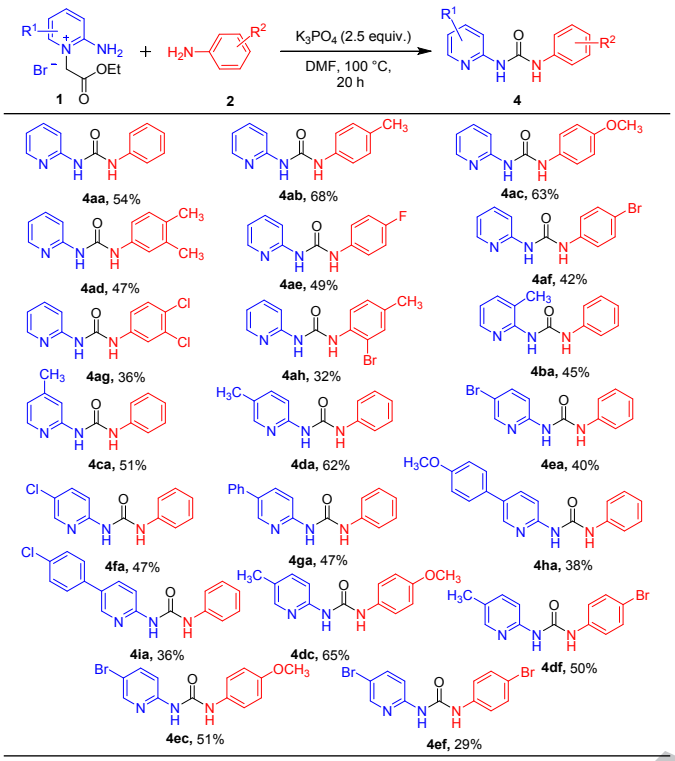


Figure 2. ORTEP diagram and the atomic numbering of **4ab**. Displacement ellipsoids are drawn at the 50% probability level.

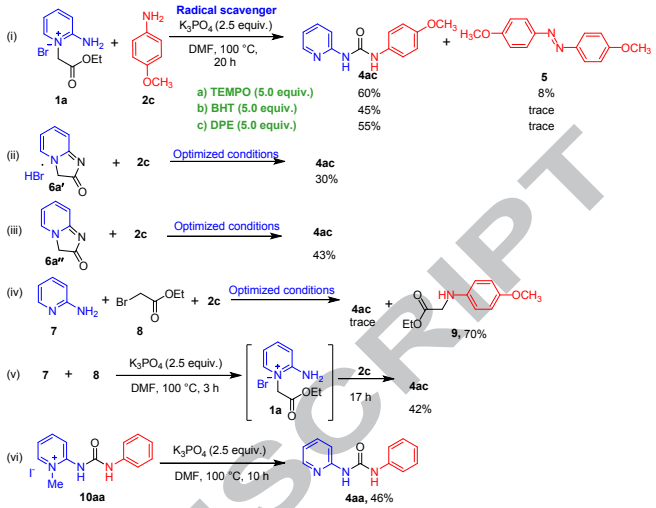
Table 2. Substrate scope for the synthesis of pyridin-2-yl ureas.[a,b]



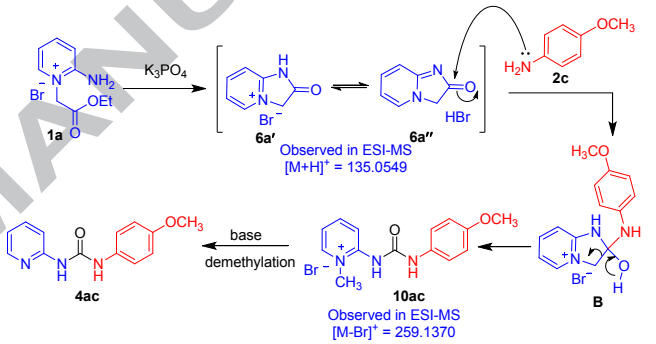
[a]Reagents and conditions: **1** (1.2 mmol), **2** (1.0 mmol), K_3PO_4 (3.0 mmol), DMF (3 mL), 100 °C, 20 h.
[b]Isolated yield.

Next, a set of control experiments was performed to investigate the mechanistic pathway (Scheme 3). Initially, we performed the reaction in the presence of radical scavengers such as TEMPO, BHT, and DPE under the optimized reaction conditions. Product **4ac** was obtained in 60%, 45% and 55% yield, respectively (Scheme 3, entry i). The fact that there was little or no significant change in the product yields indicated absence of a radical-mediated pathway. The reaction of cyclic amide **6a′** and **6a″** with **2c** under the optimized reaction conditions gave **4ac** in 30% and 43% yield, respectively (Scheme 3, entry ii and iii). Next, the one-pot, multicomponent reaction of 2-aminopyridine (**7**), ethyl bromoacetate (**8**) and **2c** under the optimized reaction conditions gave ethyl (4-methoxyphenyl)glycinate (**9**) in 70% yield along with trace amounts of the desired product **4ac** observed by TLC (Scheme 3, entry iv). The one-pot, sequential reaction of **7** with **8**, followed by the addition of **2c** gave the desired product **4ac** in 42% yield (Scheme 3, entry v). Finally, we prepared 1-methyl-2-(3-phenylureido)pyridin-1-ium iodide (**10aa**) *via* the reaction of **4aa** with methyl iodide following a literature method.[17] The reaction of **10aa** under the optimized conditions led to the formation of **4aa** in 46% yield (Scheme 3, entry vi). This further indicated that **10** may be a possible intermediate in this transformation.

Although a detailed mechanism for this reaction remains to be investigated, on the basis of control experiments and literature precedence[18] a plausible mechanism is depicted in Scheme 4. First, the 2-aminopyridinium salt undergoes intramolecular nucleophilic substitution in the presence of a base to form cyclic amide intermediate **6a′** (observed by ESI-MS). Intermediate **6a′** further undergoes intermolecular nucleophilic attack of aniline to form hemiaminal intermediate **B**, which may generate intermediate **10ac** (observed by ESI-MS) after ring opening. Intermediate **10ac** undergoes demethylation with the assistance of base[18] to give the desired product **4ac**.



Scheme 3. Control experiments



Scheme 4. Proposed mechanism.

An unprecedented transition metal-free strategy has been developed for the synthesis of pyridin-2-yl ureas from simple and nontoxic 2-aminopyridinium salts under mild reaction conditions. The developed method tolerated various functional groups and resulted in the formation of aryl substituted pyridin-2-yl ureas in moderate to good yields.

Acknowledgments

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Supplementary Material

Supplementary material [materials & methods, experimental procedures, NMR (^{1}H and ^{13}C), HRMS and X-ray data] for this article can be found online at https://doi.org/10.1016/j.tetlet……..

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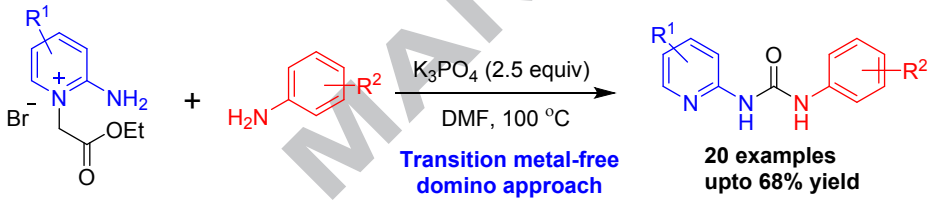

Highlights

- Metal-free, base mediated synthesis of pyridin-2-yl urea derivatives.

Graphical Abstract

- Good to moderate (29-66%) yields of pyridin-2-yl urea derivatives.
- Tandem intramolecular cyclization, nucleophilic addition and demethylation.