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Solvent- and Halide-free Synthesis of Pyridine-2-yl Substituted Ureas through Facile C–H Functionalization of Pyridine *N*-oxides

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Abstract

A novel solvent- and halide-free atom-economic synthesis of practically useful pyridine-2-yl substituted ureas utilizes easily accessible or commercially available pyridine *N*-oxides (PyO) and dialkylcyanamides. The observed C–H functionalization of PyO is suitable for the good-to-high yielding synthesis of a wide range of pyridine-2-yl substituted ureas featuring electron donating and electron withdrawing, sensitive, or even fugitive functional groups in any position at the pyridine ring (63–92%; 19 examples). In cases of 3-substituted PyO, the C–H functionalization occurs regioselectively providing a route for facile generation of ureas bearing 5-substituted pyridine-2-yl moiety.

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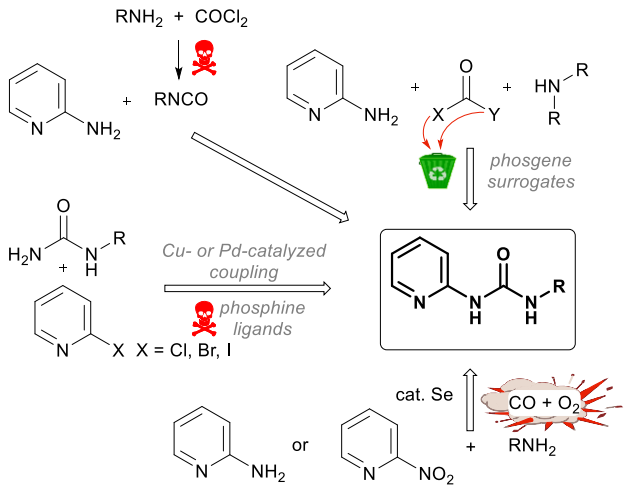
Introduction

Ureas, especially those functionalized with a heterocyclic moiety, are widely applied in drug design[1,2] and demonstrate antimicrobial,[3,4] antimalarial,[5–7] antivirus,[8] and anticancer[9–14] activities. Moreover, ureas act as kinase (LIM, VEGFR2, FGFR, FLT3) inhibitors,[15–20] they control gastric acid secretion,[21] and are used as plant grow regulators.[22,23] All known syntheses of ureas employ either various organic (in particular, chlorinated) solvents or heavy metals. In many instances, the reported methods start from toxic and/or halide-containing substrates or require special laboratory set up to perform the reaction under high pressure. The most straightforward approach to ureas includes reaction of amines with poisoning phosgene[24,25] or hazardous isocyanates[26–28] and led – apart from the target products – to huge amounts of halide-containing waste (Scheme 1).

Scheme 1. Environmentally unfriendly synthesis of pyridine-2-yl substituted ureas.



It is clear that the employment of volatile and highly toxic phosgene is a serious drawback of that method, especially for large-scale industrial processes. Therefore several "phosgene surrogates",[29] viz. trichloromethylchloroformate (diphosgene),[30] bis(trichloromethy1)carbonate (triphosgene),[31,32] diethyl carbonate,[33] *S*,*S*-dimethyl dithiocarbonate,[34,35] bis(4-nitrophenyl)carbonate,[36] carbonyldiimidazole,[37,38] methanol,[39] 1,1'-carbonylbisbenzotriazole,[40] have been applied for preparation of ureas (Scheme 1). Although the listed surrogates are less dangerous than phosgene itself, these solvent-involving methods could not be considered as atom-economic as they led to substantial amounts of waste and this contradicts with one of cornerstones of the green chemistry.[41]

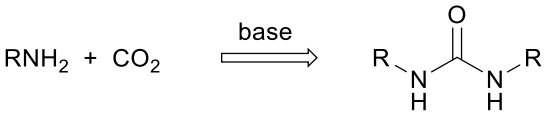
Another halide-involving synthesis of bisaryl-substituted ureas is based on metal-catalyzed cross-coupling of aryl halides and unsubstituted urea. Despite good yields of the target ureas, the

cross-coupling requires employment of a toxic heavy metal (i.e. palladium) and occurs either in DME, or in dioxane in the presence of toxic xanthene-based bidentate ligands (Scheme 1).[42–44]

Yet another protocol employs Se-catalyzed oxidative carbonylation of amines with a mixture of CO and O_2 (Scheme 1). It is widely used for the preparation of symmetrically substituted ureas and for the synthesis of pyridine-2-yl unsymmetrically substituted ureas in toluene in the presence of selenium.[45] In most cases, the carbonylation of amines requires elevated temperatures and moderate to high pressures of CO. Not only is CO toxic, but a risk of explosion of the mixture of CO and O_2 should also be taken into account.[46] In another method, unsymmetrically substituted pyridyl ureas can be selectively obtained by Se- or SeO_2-catalyzed reductive carbonylation of nitropyridines with CO in the presence of various amines (Scheme 1).[47–50]

In view of the current ecological requirements, on the one hand, and the significance of ureas, on the other hand, development of solvent- and halide-free sustainable reactions giving these species is a challenging task. It is not surprisingly that a few efforts have recently been carried out to find out green chemical processes for the synthesis of ureas and the obtained results were published in this journal (Scheme 2).[51–53] The suggested routes start from amine and CO_2 and they were conducted under extremely high pressure of CO_2 (25–55 atm) and, in some instances, performed in highly reprotoxic solvent such as *N*-methylpyrrolidinone;[54] ureas were isolated in low yields and the scope of the reaction include only rather simple alkylamines such as butyl- or benzylamine. Although it is obvious that certain progress in elaboration of green routes to ureas has already been reached, the developed approaches still need further improvement.

Scheme 2. Attempted green synthesis of ureas.



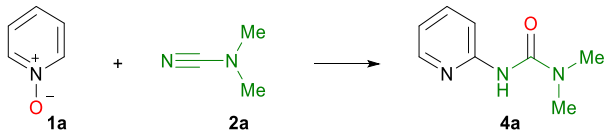
Upon our studies on gold-catalyzed generation of 2-amino-1,3-oxazoles from terminal alkynes and cyanamides in the presence of 2-picoline *N*-oxide,[55] we observed that when excess of 2-picoline *N*-oxide is used in the reaction, the heterocyclization is complicated with a side reaction furnishing 1,1-dimethyl-3-(6-methylpyridin-2-yl)urea. Being interested in understanding this unusual C–H functionalization of 2-picoline *N*-oxide, in this work, we found a way that turns the side reaction into high yielding green approach to pyridine-2-yl substituted ureas. We now report on solvent- and halide-free atom-economic synthesis of *N*,*N*-dialkyl-*N*'-pyridine-2-yl ureas based upon C–H functionalization between pyridine *N*-oxides and dialkylcyanamides.

Results and discussion

Toward environmentally benign conditions of the C–H functionalization

In our previous work,[55] we reported that the formation of 1,1-dimethyl-3-(6-methylpyridin-2-yl)urea from 2-picoline *N*-oxide and Me_2NCN proceeds under acid catalysis. This result indicates that the first step of the studied reaction is most likely activation of the cyanamide by protonation. To the best of our knowledge, acid- or metal-catalyzed addition of pyridine *N*-oxide to nitriles or cyanamides is yet unknown reaction and only alkylnitrilium salts react with pyridine *N*-oxide accomplishing different amide derivatives.[56,57] The optimization of the reaction conditions was performed with unsubstituted pyridine *N*-oxide (**1a**) and Me_2NCN (**2a**). Initially the reaction was performed in neat dimethylcyanamide (**2a**) (10 equiv) in the presence of 1.0 equiv of methane sulfonic acid, $MeSO_3H$ (**3**), at 60 °C for 3 h. Although we achieved full conversion of pyridine *N*-oxide (**1a**) (Table 1, entry 1) and isolated yield of urea **4a** was 93% (NMR based conversion is 100%), this approach does not meet requirements of green chemistry as it far from being atom-economic.

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



Entry	Molar ratio of reagents			Conditions (Conversion,[b] %)
	2a	Acid		
1	10	$MeSO_3H$	1.0	60 °C, 3 h (100)
2	1.0	$MeSO_3H$	1.0	60 °C, 3 h (85)
3	1.5	$MeSO_3H$	1.0	60 °C, 3 h (98)
4	2.0	$MeSO_3H$	1.0	60 °C, 3 h (98)
5	1.5	$MeSO_3H$	0.1	60 °C, 3 h (46)
6	1.5	$MeSO_3H$	0.1	60 °C, 8 h (74)
7	1.5	H_3PO_4	0.1	60 °C, 3 h (7)
8	1.5	CF_3SO_3H	0.1	60 °C, 3 h (92)
9	1.5	$MeSO_3H$	1.0	40 °C, 3 h (56)
10	1.5	$MeSO_3H$	1.0	60 °C, 1 h (78)
11	1.5	$MeSO_3H$	1.0	60 °C, 2 h (98)

[a] – for more information related to optimization of the reaction condition see Supporting Information; [b] – conversion of the PyO was estimated by ^{1}H NMR

On the next step amount of dimethylcyanamide (**2a**) was reduced to 1.0, 1.5, and 2.0 equiv (Table 1, entries 2–4), and it appears that 1.5 equiv of **2a** is optimal for achieving almost full conversion of the starting pyridine *N*-oxide (**1a**) to substituted urea **4a** and the reaction takes 3 h. Further, we attempted the reaction with catalytic amounts of $MeSO_3H$. In the case of 0.1 equiv of methane sulfonic acid, conversion of **1a** was 46% and 74% after 3 h and 8 h, respectively (Table 1, entries 5 and 6). However, small amount of yet unidentified by-product (10 and 5% for entries 5 and 6, respectively) was detected in the reaction mixture.

We assumed that changing of the acid would effect on the reaction rate and probably would decreases the amount of the undesirable by-product. For rather weak H_3PO_4, the conversion of the pyridine *N*-oxide was only 7% after 3 h (Table 1, entry 7), although employment of the stronger CF_3SO_3H gave better result. Conversion of **1a** was 92% after 3 h and amount of the by-product was less than 6% (Table 1, entry 8). However, we continued our study with an equimolar amount of $MeSO_3H$, because employment of catalytic amount either methane sulfonic or trifluoromethane sulfonic acid led to formation of small amount of the by-product and required longer reaction time. The formed pyridinium salt can be easy transformed to the corresponding free base by treatment with potassium carbonate and thus formed CF_3SO_3K can be utilized in preparation of antiperspirants.[58]

The effect of temperature and reaction time was then studied. The reaction was slow at 40 °C and the conversion of **1a** was only 56% after 3 h (Table 1, entry 9). Higher temperatures were not tested insofar as our idea was to find out environmentally friendly conditions that do not anticipate elevated temperatures. With respect of the reaction time, we have found that keeping the mixture at 60 °C for 1 h resulted in poor conversion of **1a**, whereas stirring for 2 h is sufficient to achieve almost quantitative conversion of **1a** to urea **4a**, like in the case when the reaction was performed for 3 h (Table 1, entries 3, 10, and 11).

To demonstrate the possibility of the scale up synthesis of target urea **4a**, we carried out the reaction starting from 1.90 g of **1a** and the isolated yield of **4a** was 3.04 g (92%). We succeeded in recycling 550 mg (78% of excess Me_2NCN) of **2a** from the reaction mixture.

To summarize optimization of the reaction conditions, we found that employment 1.5 equiv of cyanamide and 1.0 equiv of methane sulfonic acid leads to the best synthetic results. Noteworthy that excess of the cyanamide was recycled by conventional vacuum distillation.

Reaction scope and limitation of the green synthesis of pyridine-2-yl substituted ureas

To verify the scope and limitations of the developed approach several pyridine *N*-oxides and dialkylcyanamides were tested (Scheme 3).

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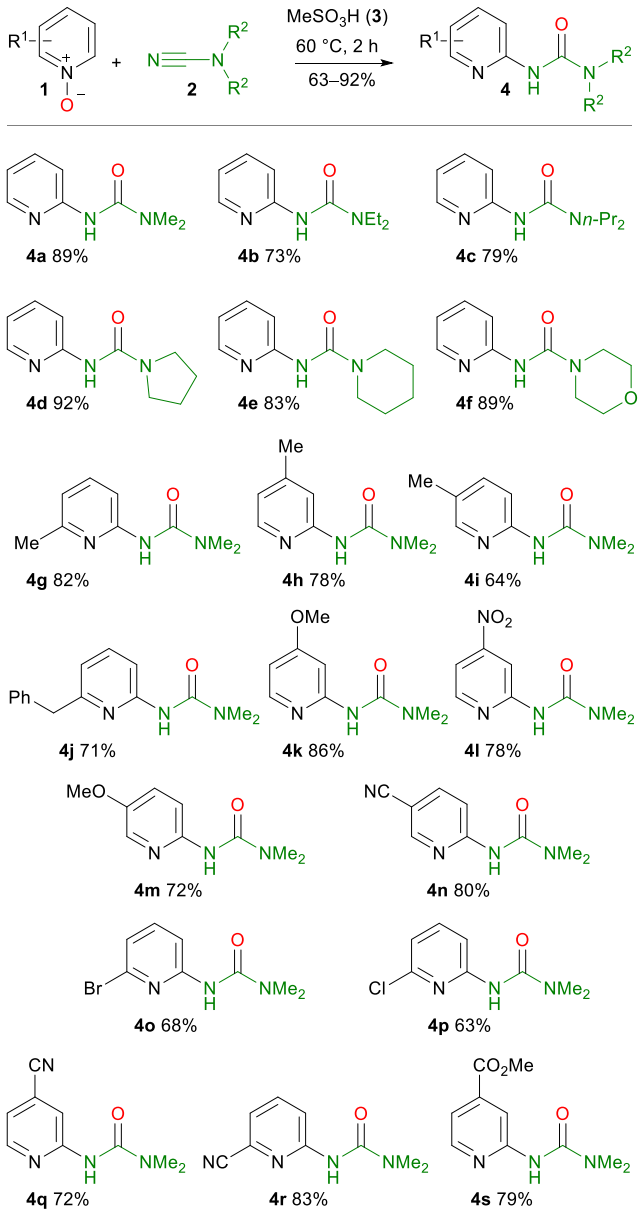
Scheme 3. Reaction scope with various pyridine *N*-oxides and cyanamides.



In most cases, pyridine *N*-oxides **1** were prepared by oxidation of the corresponding pyridine with a mixture of hydrogen peroxide and acetic acid according to conventional protocol.[59] Alternatively, green oxidation of *N*-heteroaromatic amines based on lipase–glucose oxidase system can also be applied in these syntheses.[60] Firstly, we tested several dialkylcyanamides, whose intriguing chemistry becomes increasingly popular in recent years.[61–68] In all cases, target ureas **4a-s** were obtained in 73–92% yields (Scheme 3). Even for 4-morpholinecarbonitrile, urea **4f** was isolated in 89% yield. To check an effect of substitution in the pyridine rings and to demonstrate stability of a wide range of functional groups under the reaction conditions, several *N*-oxides were tested. Firstly, we checked 2- and 4-substituted pyridine *N*-oxides and no significant difference between unsubstituted pyridine *N*-oxide (**1a**) and its derivatives bearing strong electron donating (4-MeO **1k**),

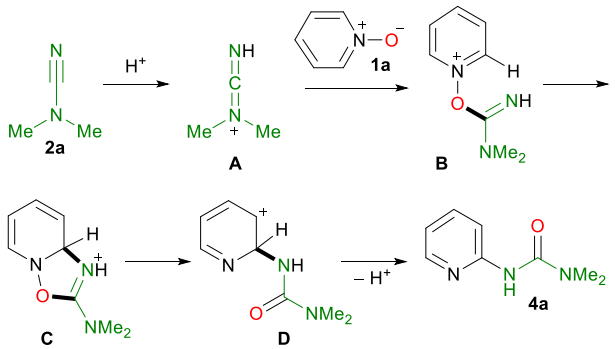
weak electron donating (4-Me **1h**, 2-Me **1g**, 2-$PhCH_2$ **1j**), and strong electron withdrawing (4-NO_2 **1l**) groups was observed. In the case of 3-substituted pyridine derivatives the situation was slightly different. Thus, 3-cyanopyridine *N*-oxide (**1n**) reacts similarly to the other substituted pyridine *N*-oxides and target urea **4n** was isolated in 80% yield. At the same time 3-methoxypyridine *N*-oxide (**1m**) reacted slower and full conversion of **1m** was achieved only after stirring of the reaction mixture at 60 °C for 5 h. The isolated yield of urea **4m** was 72%.

Surprisingly, in the case of 3-substituted pyridine *N*-oxides (3-Me **1i**, 3-MeO **1m**, and 3-CN **1n**), only 2,5-disubstituted pyridine ureas were formed in good yields. We were unable to detect by ^{1}H NMR even traces of the isomeric 2,3-disubstituted pyridine urea in the reaction mixture. It means that the C–H functionalization proceeds regioselectively and could be used for the synthesis of 5-substituted ureas **4** starting from *meta*-substituted derivatives of pyridine *N*-oxides.

The halogen substituted pyridine *N*-oxides (2-Br **1o**, 2-Cl **1p**) gave appropriate ureas **4o** and **4p** in 68 and 63% yields. Pyridine *N*-oxides featuring cyano (3-NC **1n**, 4-NC **1q**, 2-NC **1r**) and methoxycarbonyl (4-MeO_2C **1s**) groups efficiently undergo the reaction and in all cases corresponding ureas were isolated in 63–83% yields. Important that obtained ureas **4n–s** potentially suitable for further modifications. Thus, halogen atom in the pyridine ring of **4o** and **4p** could be substituted with various nucleophiles through S_NAr[69–74] or metal-catalyzed reactions,[75–82] whereas the methoxycarbonyl group in **4s** could be convert to amides, esters, reduced to alcohols or aldehyde as well as undergo the Barton decarboxylation.[83]

Based on the above discussion a plausible mechanism for formation of the urea is given on Scheme 4.

Scheme 4. Plausible mechanism of formation of urea **4a**.



The first step of the reaction most likely includes the activation of the cyanamide by protonation (**A** in Scheme 4) followed by nucleophilic addition of pyridine *N*-oxide to cation **A** giving **B**, which then undergoes intramolecular cyclization furnishing **C**. In **C**, the heterolytic N–O bond cleavage results

in the ring opening giving **D**, which restores the aromaticity via proton elimination thus accomplishing target urea **4a**.

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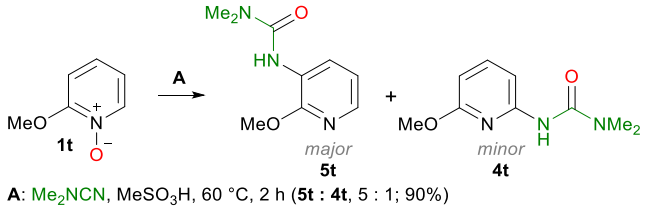
Unexpected reaction pathway for 2-methoxypyridine *N*-oxide

Interesting and unexpected result has been obtained when the C–H functionalization was performed with 2-methoxypyridine *N*-oxide (**1t**). Based on the LC-HRMS data two isomeric compounds were formed and the brutto-formula corresponds to desired urea **4t**. The ^{1}H and ^{13}C as well as ^{1}H–^{13}C HMBC and ^{1}H–^{13}C HSQC spectra clearly indicate that both isomers featuring the same fragments, but the position of the substituents in the pyridine ring need to be specified; the ^{1}H–^{15}N HSQC and ^{1}H–^{15}N HMBC NMR experiments allowed the identification of both products (Scheme 5). A mixture of ureas of **5t** and **4t** (molar ratio 5:1) was formed in 90% overall yield.

Scheme 5. Formation of ureas **5t** and **4t**.



A: Me_2NCN, $MeSO_3H$, 60 °C, 2 h (**5t : 4t**, 5 : 1; 90%)

Cross-peaks correspond to coupling between the urea nitrogen and the H-4 proton of the pyridine ring and also between the pyridine nitrogen and the H-5 and H-6 protons was observed in ^{1}H–^{15}N HMBC experiment for the major isomer. In the case of the minor isomer, we observed cross-peaks corresponding to coupling of the pyridine nitrogen and the H-3 and H-5 protons of the pyridine ring (for more details see ESI). Moreover, for the major isomer, the signal of the H-5 proton (6.84 ppm) appears as a doublet of doublet (J = 5.0, 7.8 Hz), whereas for the minor isomer the signal of the H-4 proton (7.39 ppm) appears as a triplet (J = 7.9 Hz). These data agree with well-known fact that for pyridines value for H-2/H-3 coupling constant is smaller than for H-3/H-4 (for pyridine: $^{3}J_{\text{H-2/H-3}}$ = 4.88 Hz and $^{3}J_{\text{H-3/H-4}}$ = 7.67 Hz).[84] Unfortunately column chromatography on silica did not allow the separation of a mixture of ureas **5t** and **4t**, because of their similar retention. We isolated pure urea **5t** (328 mg, 42%) by the repeated recrystallization of a mixture of **5t** and **4t** from hexane/Et_2O. The structure of 3-(2-methoxypyridin-3-yl)-1,1-dimethylurea (**5t**) in the solid state has been additionally confirmed by single-crystal X-ray diffraction (Fig. 1) The bonds length values in the $C^{(2B)}$–$N^{(2B)}$–$C^{(7B)}$–($O^{(2B)}$)–$N^{(3B)}$ moiety of urea **5t** are typical for pyridine-3-yl substituted ureas and are in agreements with reported data.[85–88]

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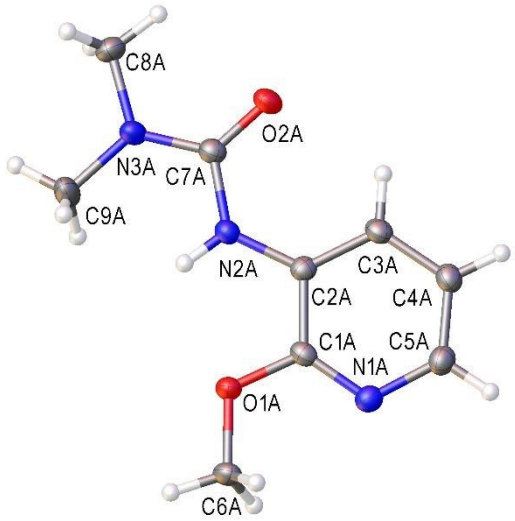

Fig. 1. View of molecular structure of **5t** (CCDC: 1473655). Thermal ellipsoids are drawn at the 50% probability level. Only one of two crystallographically independent molecules is presented. Selected bond lengths (Å): $N^{(2B)}$–$C^{(2B)}$ 1.403(2); $N^{(2B)}$–$C^{(7B)}$ 1.385(2); $O^{(2B)}$–$C^{(7B)}$ 1.226(2); $N^{(3B)}$–$C^{(7B)}$ 1.361(2).

Such unusual results obtained for 2-methoxypyridine *N*-oxide (**1t**) forced us to pay more attention to the structures of ureas obtained from pyridine *N*-oxide bearing either OMe group or, especially, halogen atom in the second position, which can react similar to *N*-oxide **1t**. In the case of 3-(4-methoxypyridin-2-yl)-1,1-dimethylurea (**4k**), the structure was confirmed by NOESY NMR. We observed two cross-peaks due to NOE between the protons of the methoxy group and two protons (H-3 and H-5) of the pyridine ring. For bromo- and chlorosubstituted ureas (**4o** and **4p**) the structures were additionally confirmed by single-crystal X-ray diffraction (Fig. 2).

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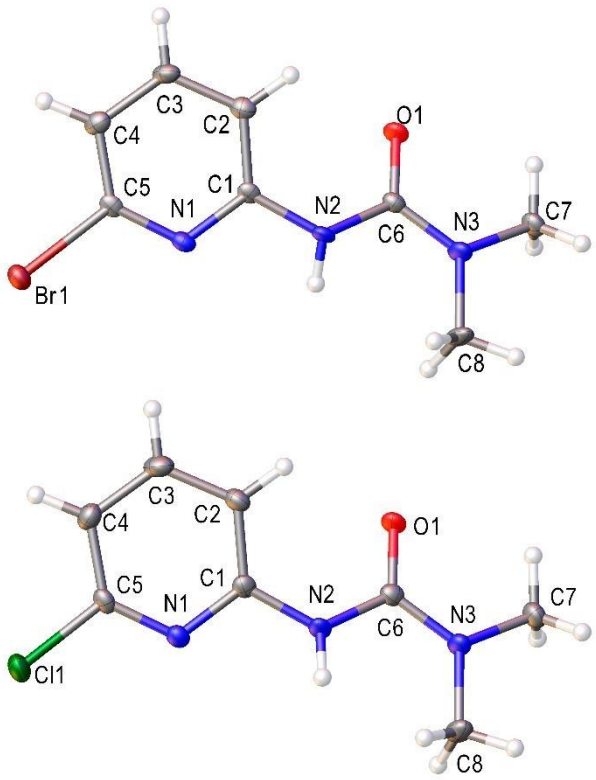

Fig. 2. View of molecular structure of **4o** (CCDC: 1473656) and **4p** (CCDC: 1473657). Thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths (Å): $N^{(2)}$–$C^{(1)}$ 1.400(4); $N^{(2)}$–$C^{(6)}$ 1.401(5); $O^{(1)}$–$C^{(6)}$ 1.233(4); $N^{(3)}$–$C^{(6)}$ 1.350(5) for **4o**; $N^{(2)}$–$C^{(1)}$ 1.396(2); $N^{(2)}$–$C^{(6)}$ 1.396(2); $O^{(1)}$–$C^{(6)}$ 1.235(2); $N^{(3)}$–$C^{(6)}$ 1.349(2) for **4p**.

For both ureas **4o** and **4p** bonds length values in the $C^{(1)}$–$N^{(2)}$–$C^{(6)}$–$O^{(1)}$–$N^{(3)}$ moiety are usual for pyridine-2-yl substituted ureas and correspond to reported data.[85,89–91] All these results indicate that 2-methoxypyridine *N*-oxide (**1t**) reacts differently to all others studied pyridine *N*-oxides and, in our opinion, the detailed investigation of a plausible mechanism goes beyond the scope of this work. We are going to provide a full account report (including both experimental and theoretical studies) on the mechanism of the observed transformation and corresponding works are underway in our group.

Conclusions

We have developed solvent- and halide-free green synthesis of pyridine-2-yl substituted ureas that is based on facile C–H functionalization of various pyridine *N*-oxides with a wide range of dialkylcyanamides. The observed C–H functionalization of PyO is suitable for the good-to-high yielding synthesis of a broad spectrum of pyridine-2-yl substituted ureas featuring either electron donating, or electron withdrawing groups in any position at the pyridine ring. Labile functional groups

such as halogen atoms, cyano or methoxycarbonyl groups survive the reaction conditions and obtained ureas could be used for the synthesis of more complex structures.

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Experimental Section

Experimental procedures and analytical data of all compounds (^{1}H and ^{13}C{H} NMR, IR, HRESIMS), copy of the ^{1}H, ^{13}C{H}, and 2D NMR spectra and also X-ray data are available in the Supporting Information.

Acknowledgements

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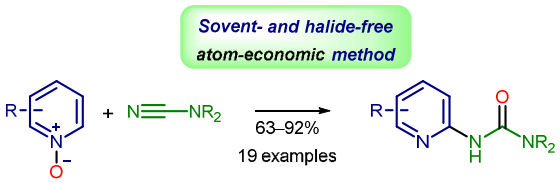

A solvent- and halide-free atom-economic synthesis of practically useful pyridine-2-yl substituted ureas utilizes pyridine *N*-oxides and dialkylcyanamides.