

PAPER

 View Article Online
 View Journal | View Issue

 Cite this: *Green Chem.*, 2016, **18**, 6630

Solvent- and halide-free synthesis of pyridine-2-yl substituted ureas through facile C–H functionalization of pyridine *N*-oxides†

 Valentin A. Rassadin,^{*a} Dmitry P. Zimin,^a Gulnara Z. Raskil'dina,^{a,b} Alexander Yu. Ivanov,^c Vadim P. Boyarskiy,^a Semen S. Zlotskii^b and Vadim Yu. Kukushkin^{*a}

A novel solvent- and halide-free atom-economical 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 at any position of the pyridine ring (63–92%; 19 examples). In the cases of 3-substituted PyO, the C–H functionalization occurs regioselectively providing a route for facile generation of ureas bearing a 5-substituted pyridine-2-yl moiety.

 Received 12th September 2016,
 Accepted 5th October 2016

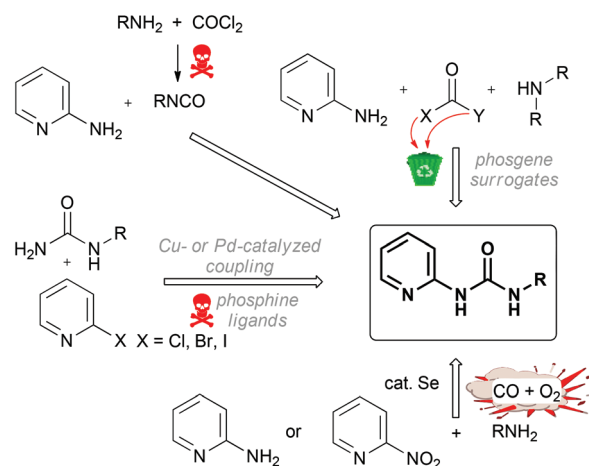
DOI: 10.1039/c6gc02556k

www.rsc.org/greenchem

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} antiviral,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 growth 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 a special laboratory set up to perform the reaction under high pressure. The most straightforward approach to ureas includes the reaction of amines with poisoning phosgene^{24,25} or hazardous isocyanates^{26–28} that leads – apart from the target products – to huge amounts of halide-containing wastes (Scheme 1).

It is clear that the employment of volatile and highly toxic phosgene is a serious drawback of this method, especially for large-scale industrial processes. Therefore several “phosgene surrogates”,²⁹ viz. trichloromethylchloroformate (diphos-



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

gene),³⁰ bis(trichloromethyl)carbonate (triphosgene),^{31,32} diethyl carbonate,³³ *S,S*-dimethyl dithiocarbonate,^{34,35} bis(4-nitrophenyl)carbonate,³⁶ carbonyldiimidazole,^{37,38} methanol,³⁹ and 1,1'-carbonylbisbenzotriazole,⁴⁰ have been applied for the preparation of ureas (Scheme 1). Although the listed surrogates are less dangerous than phosgene, these solvent-involving methods could not be considered as atom-economical as they lead to substantial amounts of waste and this contradicts with one of the cornerstones of green chemistry.⁴¹

Another halide-involving synthesis of bisaryl-substituted ureas is based on metal-catalyzed cross-coupling of aryl

^aInstitute of Chemistry, Saint Petersburg State University, Universitetskaya Nab. 7/9, 199034 Saint Petersburg, Russia. E-mail: v.rassadin@spbu.ru, v.kukushkin@spbu.ru

^bUfa State Petroleum Technological University, Kosmonavtov 1, Ufa, Bashkortostan, Russia

^cResearch Park SPbSU, Center for Magnetic Resonance, Saint Petersburg State University, Universitetskaya Nab. 7/9, 199034 Saint Petersburg, Russia

† Electronic supplementary information (ESI) available. CCDC 1473655–1473657. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6gc02556k

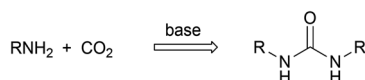


halides and unsubstituted urea. Despite good yields of the target ureas, the cross-coupling requires the employment of a toxic heavy metal (*i.e.* palladium) and occurs either in DME or in dioxane in the presence of toxic xanthene-based bidentate ligands (Scheme 1).^{42–44}

Yet another protocol employs Se-catalyzed oxidative carbonylation of amines with a mixture of CO and O₂ (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 O₂ should also be taken into account.⁴⁶ In another method, unsymmetrically substituted pyridyl ureas can be selectively obtained by Se- or SeO₂-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, the development of solvent- and halide-free sustainable reactions giving these species is a challenging task. It is not surprising that a few efforts have recently been carried out to find out green chemical processes for the synthesis of ureas and the obtained results have been published in this journal (Scheme 2).^{51–53} The suggested routes start from amine and CO₂ and they were conducted under extremely high pressure of CO₂ (25–55 atm) and, in some instances, performed in highly reprototoxic solvents such as *N*-methylpyrrolidinone;⁵⁴ ureas were isolated in low yields and the scope of the reaction includes only rather simple alkylamines such as butyl- or benzylamine. Although it is obvious that certain progress in the elaboration of green routes to ureas has already been reached, the developed approaches still need further improvement.

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, 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 a high yielding green approach to pyridine-2-yl substituted ureas. We now report on solvent- and halide-free atom-economical synthesis of *N,N*-dialkyl-*N'*-pyridine-2-yl ureas based on C–H functionalization between pyridine *N*-oxides and dialkylcyanamides.



Scheme 2 Attempted green synthesis of ureas.

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 Me₂CN proceeds under acid catalysis. This result indicates that the first step of the studied reaction is most likely the 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 an unknown reaction and only alkyltrilium 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 Me₂CN (**2a**). Initially the reaction was performed in neat dimethylcyanamide (**2a**) (10 equiv.) in the presence of 1.0 equiv. of methane sulfonic acid, MeSO₃H (**3**), at 60 °C for 3 h. Although we achieved full conversion of pyridine *N*-oxide (**1a**) (Table 1, entry 1) and the isolated yield of urea **4a** was 93% (NMR based conversion is 100%), this approach does not meet the requirements of green chemistry as it far from being atom-economical.

In the next step the 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 MeSO₃H. 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, a small amount of the yet unidentified by-product (10 and 5% for entries 5 and 6, respectively) was detected in the reaction mixture.

Table 1 Optimization of the reaction conditions^a

| Entry | Molar ratio of reagents | | Conditions (conversion, ^b %) | |
|-------|-------------------------|-----------------------------------|---|------------------|
| | 2a | Acid | | |
| 1 | 10 | MeSO ₃ H | 1.0 | 60 °C, 3 h (100) |
| 2 | 1.0 | MeSO ₃ H | 1.0 | 60 °C, 3 h (85) |
| 3 | 1.5 | MeSO ₃ H | 1.0 | 60 °C, 3 h (98) |
| 4 | 2.0 | MeSO ₃ H | 1.0 | 60 °C, 3 h (98) |
| 5 | 1.5 | MeSO ₃ H | 0.1 | 60 °C, 3 h (46) |
| 6 | 1.5 | MeSO ₃ H | 0.1 | 60 °C, 8 h (74) |
| 7 | 1.5 | H ₃ PO ₄ | 0.1 | 60 °C, 3 h (7) |
| 8 | 1.5 | CF ₃ SO ₃ H | 0.1 | 60 °C, 3 h (92) |
| 9 | 1.5 | MeSO ₃ H | 1.0 | 40 °C, 3 h (56) |
| 10 | 1.5 | MeSO ₃ H | 1.0 | 60 °C, 1 h (78) |
| 11 | 1.5 | MeSO ₃ H | 1.0 | 60 °C, 2 h (98) |

^a For more information related to optimization of the reaction conditions see the ESI. ^b Conversion of the PyO was estimated by ¹H NMR.



We assumed that changing of the acid would have an effect on the reaction rate and probably would decrease 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 the employment of the stronger $\text{CF}_3\text{SO}_3\text{H}$ gave a better result. Conversion of **1a** was 92% after 3 h and the 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 the employment of a catalytic amount of either methane sulfonic or trifluoromethane sulfonic acid led to the formation of a small amount of the by-product and required a longer reaction time. The formed pyridinium salt can be easily transformed into the corresponding free base by treatment with potassium carbonate and thus the formed $\text{CF}_3\text{SO}_3\text{K}$ can be utilized in the 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 to 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).

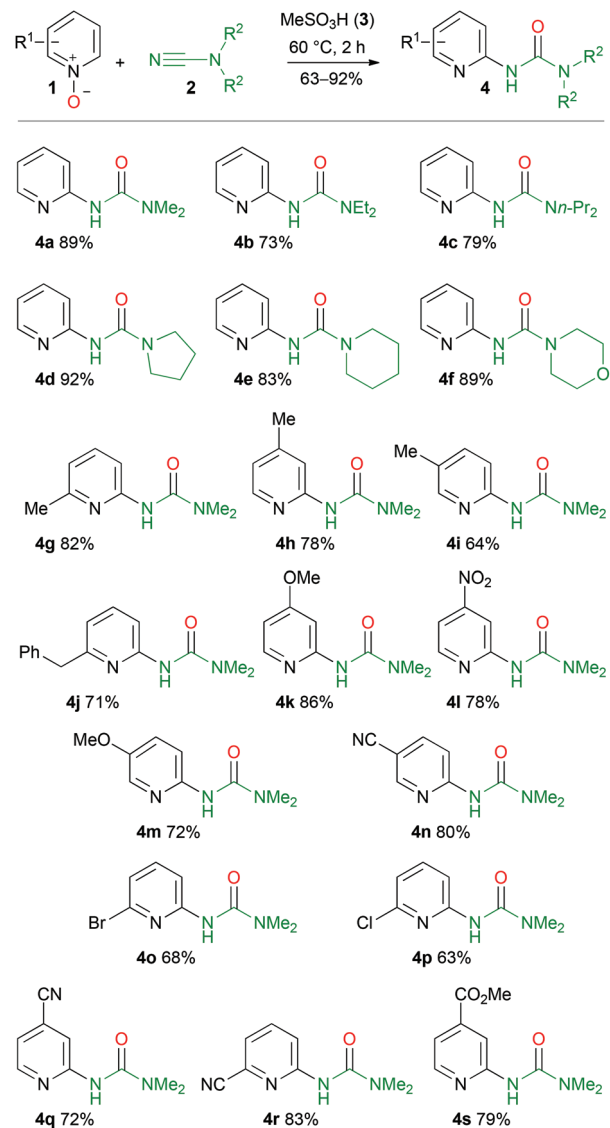
To demonstrate the possibility of the scale up synthesis of target urea **4a**, we carried out the reaction starting from 1.90 g of **1a** and the isolated yield of **4a** was 3.04 g (92%). We succeeded in recycling 550 mg (78% of excess Me_2NCN) of **2a** from the reaction mixture.

To summarize the optimization of the reaction conditions, we found that the employment of 1.5 equiv. of cyanamide and 1.0 equiv. of methane sulfonic acid leads to the best synthetic results. It is noteworthy that the excess of 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).

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 a conventional protocol.⁵⁹ Alternatively, green oxidation of *N*-heteroaromatic amines based on a 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–f** were obtained in 73–92% yields (Scheme 3). Even for 4-morpholine-carbonitrile, urea **4f** was isolated in 89% yield. To check the effect of substitution on the pyridine rings and to demonstrate the stability of a wide range of functional groups under the reaction conditions, several *N*-oxides were tested. Firstly, we



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

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-PhCH₂ **1j**), and strong electron withdrawing (4-NO₂ **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 comparatively slower and full conversion of **1m** was achieved only after stirring 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 even the traces of the isomeric 2,3-disubstituted pyridine urea in the reaction mixture by ^1H NMR. 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.

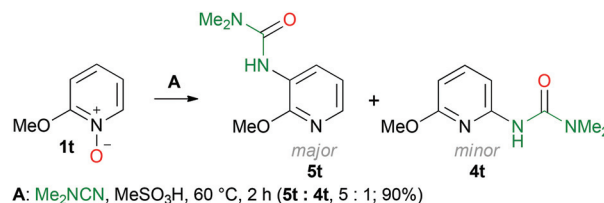
The halogen substituted pyridine *N*-oxides (2-Br **1o**, 2-Cl **1p**) gave appropriate ureas **4o** and **4p** in 68 and 63% yields, respectively. Pyridine *N*-oxides featuring cyano (3-NC **1n**, 4-NC **1q**, 2-NC **1r**) and methoxycarbonyl (4-MeO₂C **1s**) groups efficiently undergo the reaction and in all cases the corresponding ureas were isolated in 63–83% yields. It is noteworthy that obtained ureas **4n–s** are potentially suitable for further modifications. Thus, the halogen atom in the pyridine ring of **4o** and **4p** could be substituted with various nucleophiles through $\text{S}_{\text{N}}\text{Ar}$ ^{69–74} or metal-catalyzed reactions,^{75–82} whereas the methoxycarbonyl group in **4s** could be converted to amides and esters, reduced to alcohols or aldehydes as well as undergo the Barton decarboxylation.⁸³

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

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

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

An 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 the desired urea **4t**. The ^1H and ^{13}C as well as ^1H – ^{13}C HMBC and ^1H – ^{13}C HSQC spectra clearly indicate that both isomers feature the same fragments, but the position of the substituents on the pyridine ring needs to be specified; the ^1H – ^{15}N HSQC and ^1H – ^{15}N HMBC NMR experiments allowed the identification of both products (Scheme 5). A mixture of ureas **5t** and **4t** (molar ratio 5 : 1) was formed in 90% overall yield.



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

The cross-peaks corresponding to the 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 were observed in the ^1H – ^{15}N HMBC spectra of the major isomer. In the case of the minor isomer, we observed the cross-peaks corresponding to the coupling of the pyridine nitrogen and the H-3 and H-5 protons of the pyridine ring (for more details see the ESI†). Moreover, for the major isomer, the signal of the H-5 proton (6.84 ppm) appears as a 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 the well-known fact that for pyridines the value of the H-2/H-3 coupling constant is smaller than that of H-3/H-4 (for pyridine: $^3J_{\text{H-2/H-3}} = 4.88$ Hz and $^3J_{\text{H-3/H-4}} = 7.67$ 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 times. We isolated pure urea **5t** (328 mg, 42%) by the repeated recrystallization of a mixture of **5t** and **4t** from hexane/Et₂O. 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 bond length values in the $\text{C}^{(2\text{B})}$ – $\text{N}^{(2\text{B})}$ – $\text{C}^{(7\text{B})}$ – $(\text{O}^{(2\text{B})})$ – $\text{N}^{(3\text{B})}$ moiety of urea **5t** are typical for pyridine-3-yl

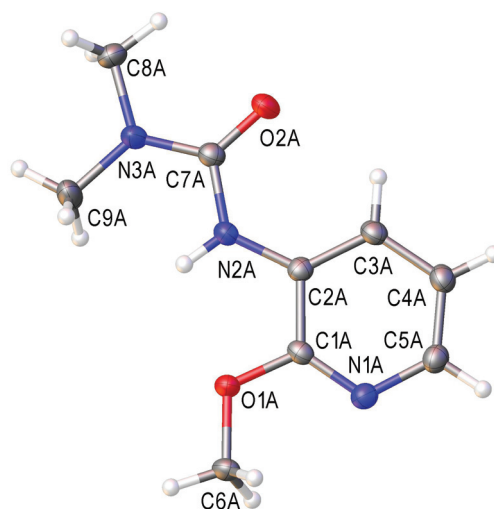
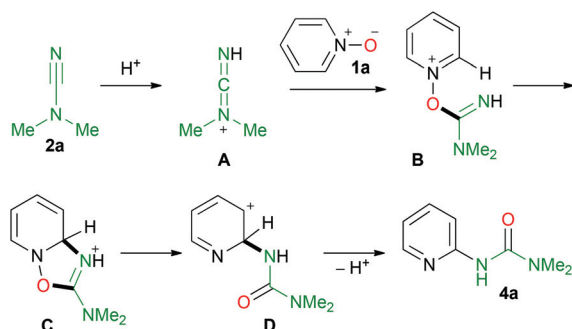


Fig. 1 View of the molecular structure of **5t** (CCDC 1473655). Thermal ellipsoids are drawn at the 50% probability level. Only one of the two crystallographically independent molecules is presented. Selected bond lengths (Å): $\text{N}^{(2\text{B})}$ – $\text{C}^{(2\text{B})}$ 1.403(2); $\text{N}^{(2\text{B})}$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



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



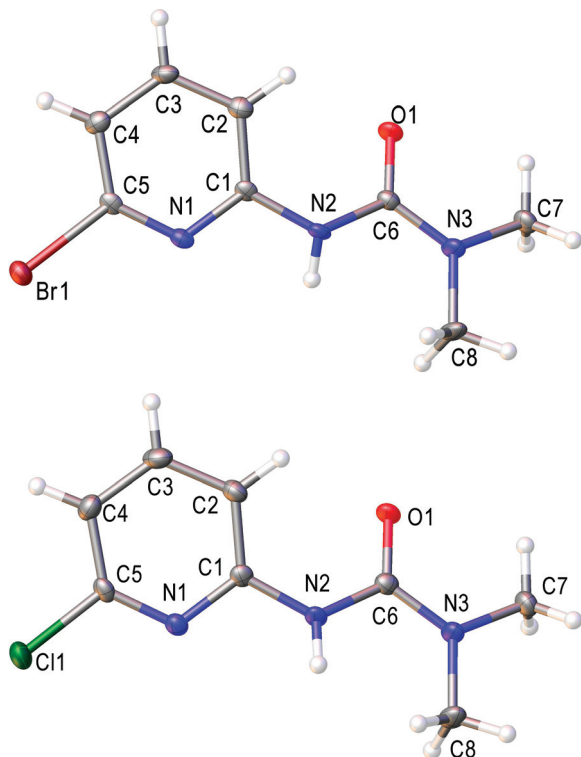


Fig. 2 View of the molecular structure of **4o** (CCDC 1473656) and **4p** (CCDC 1473657). Thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths (Å): N⁽²⁾–C⁽¹⁾ 1.400(4); N⁽²⁾–C⁽⁶⁾ 1.401(5); O⁽¹⁾–C⁽⁶⁾ 1.233(4); N⁽³⁾–C⁽⁶⁾ 1.350(5) for **4o**; N⁽²⁾–C⁽¹⁾ 1.396(2); O⁽¹⁾–C⁽⁶⁾ 1.235(2);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

substituted ureas and are in agreement with the reported data.^{85–88}

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 the OMe group or, especially, the halogen atom at the second position, which can react similarly 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 the 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).

For both ureas **4o** and **4p** bond length values in the C⁽¹⁾–N⁽²⁾–C⁽⁶⁾–O⁽¹⁾–N⁽³⁾ moiety are typical for pyridine-2-yl substituted ureas and correspond to the reported data.^{85,89–91} All these results indicate that 2-methoxypyridine *N*-oxide (**1t**) reacts differently with all other 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 the corresponding research work is underway in our group.

Conclusions

We have developed solvent- and halide-free green synthesis of pyridine-2-yl substituted ureas that is based on the facile C–H functionalization of various pyridine *N*-oxides with a wide range of dialkylcyanamides. The observed C–H functionalization of the pyridine moiety 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 at any position of 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.

Experimental section

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

Acknowledgements

V. A. R. gratefully acknowledges support from the Scientific Council of the President of the Russian Federation (Grant MK-3228.2015.3) and he also thanks Saint Petersburg State University for postdoctoral grant (12.50.1190.2014). G. Z. R. expresses her gratitude towards the Russian Foundation for Basic Research for sabbatical grant (15-33-50913 mol_nr). Structural studies of the obtained compounds were supported by Saint Petersburg State University (research grant 12.37.214.2016). All physicochemical measurements were performed at the Center for Magnetic Resonance, the Center for Chemical Analysis and Material Research, the Center for X-ray Diffraction Methods, and the Educational Center of Chemistry (all belong to Saint Petersburg State University).

Notes and references

- 1 I. Gallou, *Org. Prep. Proced. Int.*, 2007, **39**, 355–383.
- 2 K. Matsuda, *Med. Res. Rev.*, 1994, **14**, 271–305.
- 3 G. D. Francisco, Z. Li, J. D. Albright, N. H. Eudy, A. H. Katz, P. J. Petersen, P. Labthavikul, G. Singh, Y. Yang, B. A. Rasmussen, Y.-I. Lin and T. S. Mansour, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 235–238.
- 4 K. Pandurangan, J. A. Kitchen, S. Blasco, F. Paradisi and T. Gunnlaugsson, *Chem. Commun.*, 2014, **50**, 10819–10822.
- 5 Y. Zhang, M. Anderson, J. L. Weisman, M. Lu, C. J. Choy, V. A. Boyd, J. Price, M. Sigal, J. Clark, M. Connelly, F. Zhu, W. A. Guiguemde, C. Jeffries, L. Yang, A. Lemoff, A. P. Liou, T. R. Webb, J. L. Derisi and R. K. Guy, *ACS Med. Chem. Lett.*, 2010, **1**, 460–465.



- 6 S. Jiang, S. T. Prigge, L. Wei, Y. Gao, T. H. Hudson, L. Gerena, J. B. Dame and D. E. Kyle, *Antimicrob. Agents Chemother.*, 2001, **45**, 2577–2584.
- 7 E. Comer, B. Munoz, J. A. Beaudoin, S. T. Le Quement, C. Scherer, J. Duvall, N. Kato, M. Maetani and B. E. Braibant, *WO* 2015002755, 2015; *Chem. Abstr.*, 2015, 34782.
- 8 T. Hu, X. Han, B. Kou, H. Shen, S. Yan and Z. Zhang, *WO* 2016113273, 2016; *Chem. Abstr.*, 2016, 1192981.
- 9 A. Bader, J. Zhao and A. Guerrero, *WO* 2016081773, 2016; *Chem. Abstr.*, 2016, 851904.
- 10 M. E. Pacold, K. R. Brimacombe, S. H. Chan, J. M. Rohde, C. A. Lewis, L. J. Y. M. Swier, R. Possemato, W. W. Chen, L. B. Sullivan, B. P. Fiske, S. Cho, E. Freinkman, K. Birsoy, M. Abu-Remaih, Y. D. Shaul, C. M. Liu, M. Zhou, M. J. Koh, H. Chung, S. M. Davidson, A. Luengo, A. Q. Wang, X. Xu, A. Yasgar, L. Liu, G. Rai, K. D. Westover, M. G. Vander Heiden, M. Shen, N. S. Gray, M. B. Boxer and D. M. Sabatini, *Nat. Chem. Biol.*, 2016, **12**, 452–458.
- 11 Y. Nakazawa, S. Kawano, J. Matsui, Y. Funahashi, O. Tohyama, H. Muto, T. Nakagawa and T. Matsushima, *Cancer Sci.*, 2015, **106**, 201–207.
- 12 J. Lim, E. H. Kelley, J. L. Methot, H. Zhou, A. Petrocchi, H. Chen, S. E. Hill, M. C. Hinton, A. Hruza, J. O. Jung, J. K. F. Maclean, M. Mansueto, G. N. Naumov, U. Philipp, S. Raut, P. Spacciopoli, D. Sun and P. Siliphaivanh, *J. Med. Chem.*, 2016, **59**, 6501–6511.
- 13 L.-Y. Ma, B. Wang, L.-P. Pang, M. Zhang, S.-Q. Wang, Y.-C. Zheng, K.-P. Shao, D.-Q. Xue and H.-M. Liu, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 1124–1128.
- 14 M. O. Anderson, H. Yu, C. Penaranda, B. A. Maddux, I. D. Goldfine, J. F. Youngren and R. K. Guy, *J. Comb. Chem.*, 2006, **8**, 784–790.
- 15 Y. Yin, K. Zheng, N. Eid, S. Howard, J.-H. Jeong, F. Yi, J. Guo, C. M. Park, M. Bibian, W. Wu, P. Hernandez, H. Park, Y. Wu, J.-L. Luo, P. V. LoGrasso and Y. Feng, *J. Med. Chem.*, 2015, **58**, 1846–1861.
- 16 S. Göring, D. Bensinger, E. C. Naumann and B. Schmidt, *ChemMedChem*, 2015, **10**, 511–522.
- 17 Y. Oguro, N. Miyamoto, K. Okada, T. Takagi, H. Iwata, Y. Awazu, H. Miki, A. Hori, K. Kamiyama and S. Imamura, *Bioorg. Med. Chem.*, 2010, **18**, 7260–7273.
- 18 R. Boulahjar, A. Ouach, S. Bourg, P. Bonnet, O. Lozach, L. Meijer, C. Guguen-Guillouzo, R. Le Guevel, S. Lazar, M. Akssira, Y. Troin, G. Guillaumet and S. Routier, *Eur. J. Med. Chem.*, 2015, **101**, 274–287.
- 19 Y. Dai, K. Hartandi, Z. Ji, A. A. Ahmed, D. H. Albert, J. L. Bauch, J. J. Bouska, P. F. Bousquet, G. A. Cunha, K. B. Glaser, C. M. Harris, D. Hickman, J. Guo, J. Li, P. A. Marcotte, K. C. Marsh, M. D. Moskey, R. L. Martin, A. M. Olson, D. J. Osterling, L. J. Pease, N. B. Soni, K. D. Stewart, V. S. Stoll, P. Tapang, D. R. Reuter, S. K. Davidsen and M. R. Michaelides, *J. Med. Chem.*, 2007, **50**, 1584–1597.
- 20 Y. Oguro, N. Miyamoto, T. Takagi, K. Okada, Y. Awazu, H. Miki, A. Hori, K. Kamiyama and S. Imamura, *Bioorg. Med. Chem.*, 2010, **18**, 7150–7163.
- 21 W. A. Bolhofer, A. A. Deana, C. N. Habecker, J. M. Hoffman, N. P. Gould, A. M. Pietruszkiewicz, J. D. Prugh, M. Lou Torchiana, E. J. Cragoe and R. Hirschmann, *J. Med. Chem.*, 1983, **26**, 538–544.
- 22 X. Le Yin, L. Jiang, N. H. Song and H. Yang, *J. Agric. Food Chem.*, 2008, **56**, 4825–4831.
- 23 J. G. Kim, Y. Takami, T. Mizugami, K. Beppu, T. Fukuda and I. Kataoka, *Sci. Hortic.*, 2006, **110**, 219–222.
- 24 V. Papesch and E. F. Schroeder, *J. Org. Chem.*, 1951, **16**, 1879–1890.
- 25 U. Petersen, *Methoden der Org. Chemie, Houben-Weyl*, 1983, vol. E4, pp. 335–337.
- 26 E. A. German, J. E. Ross, P. C. Knipe, M. F. Don, S. Thompson and A. D. Hamilton, *Angew. Chem., Int. Ed.*, 2015, **54**, 2649–2652.
- 27 C. L. Cioffi, N. Dobri, E. E. Freeman, M. P. Conlon, P. Chen, D. G. Stafford, D. M. C. Schwarz, K. C. Golden, L. Zhu, D. B. Kitchen, K. D. Barnes, B. Racz, Q. Qin, E. Michelotti, C. L. Cywin, W. H. Martin, P. G. Pearson, G. Johnson and K. Petrukhin, *J. Med. Chem.*, 2014, **57**, 7731–7757.
- 28 G. S. Basarab, J. I. Manchester, S. Bist, P. A. Boriack-Sjodin, B. Dangel, R. Illingworth, B. A. Sherer, S. Sriram, M. Uria-Nickelsen and A. E. Eakin, *J. Med. Chem.*, 2013, **56**, 8712–8735.
- 29 F. Bigi, R. Maggi and G. Sartori, *Green Chem.*, 2000, **2**, 140–148.
- 30 K. Kurita, T. Matsumura and Y. Iwakura, *J. Org. Chem.*, 1976, **41**, 2070–2071.
- 31 H. Eckert and B. Forster, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 894–895.
- 32 L. Cotarca, P. Delogu, A. Nardelli and V. Šunjić, *Synthesis*, 1996, 553–576.
- 33 R. Ballini, D. Fiorini, R. Maggi, P. Righi, G. Sartori and R. Sartorio, *Green Chem.*, 2003, **5**, 396–398.
- 34 M. Leung, J.-L. Lai, K.-H. Lau, H. Yu and H.-J. Hsiao, *J. Org. Chem.*, 1996, **61**, 4175–4179.
- 35 E. Artuso, I. Degani, R. Fochi and C. Magistris, *Synthesis*, 2007, 3497–3506.
- 36 J. Izdebski and D. Pawlak, *Synthesis*, 1989, 423–425.
- 37 K. Otrubova, V. Srinivasan and D. L. Boger, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3807–3813.
- 38 R. A. Batey, V. Santhakumar, C. Yoshina-Ishii and S. D. Taylor, *Tetrahedron Lett.*, 1998, **39**, 6267–6270.
- 39 S. H. Kim and S. H. Hong, *Org. Lett.*, 2016, **18**, 212–215.
- 40 A. R. Katritzky, D. P. M. Pleyne and B. Yang, *J. Org. Chem.*, 1997, **62**, 4155–4158.
- 41 R. A. Sheldon, *Green Chem.*, 2016, **18**, 3180–3183.
- 42 G. A. Artamkina, A. G. Sergeev and I. P. Beletskaya, *Tetrahedron Lett.*, 2001, **42**, 4381–4384.
- 43 A. Abad, C. Agulló, A. C. Cuñat and C. Vilanova, *Synthesis*, 2005, 915–924.



- 44 B. J. Kotecki, D. P. Fernando, A. R. Haight and K. A. Lukin, *Org. Lett.*, 2009, **11**, 947–950.
- 45 X. Zhang, D. Li, X. Ma, Y. Wang and G. Zhang, *Synthesis*, 2013, 1357–1363.
- 46 D. J. Díaz, A. K. Darko and L. McElwee-White, *Eur. J. Org. Chem.*, 2007, 4453–4465.
- 47 S. Lu, *Tetrahedron Lett.*, 1999, **40**, 4845–4846.
- 48 J. Chen, G. Ling and S. Lu, *Tetrahedron*, 2003, **59**, 8251–8256.
- 49 J. Mei, Y. Yang, Y. Xue and S. Lu, *J. Mol. Catal. A: Chem.*, 2003, **191**, 135–139.
- 50 J. Chen and S. Lu, *Appl. Catal., A*, 2004, **261**, 199–203.
- 51 A. Ion, V. Parvulescu, P. Jacobs and D. De Vos, *Green Chem.*, 2007, **9**, 158–161.
- 52 C. Wu, H. Cheng, R. Liu, Q. Wang, Y. Hao, Y. Yu and F. Zhao, *Green Chem.*, 2010, **12**, 1811–1816.
- 53 T. Jiang, X. Ma, Y. Zhou, S. Liang, J. Zhang and B. Han, *Green Chem.*, 2008, **10**, 465–469.
- 54 J. Sherwood, H. L. Parker, K. Moonen, T. J. Farmer and A. J. Hunt, *Green Chem.*, 2016, **18**, 3990–3996.
- 55 V. A. Rassadin, V. P. Boyarskiy and V. Y. Kukushkin, *Org. Lett.*, 2015, **17**, 3502–3505.
- 56 M. G. Hitzler, C. C. Freyhardt and J. C. Jochims, *J. Prakt. Chem.*, 1996, **338**, 243–250.
- 57 S. N. Karad and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2014, **53**, 5444–5448.
- 58 B. Banowski and M. Claas, WO 2015055200, 2015; *Chem. Abstr.*, 2015, 691565.
- 59 A. R. Katritzky, J. A. T. Beard and N. A. Coats, *J. Chem. Soc.*, 1959, 3680–3683.
- 60 F. Yang, X. Zhang, F. Li, Z. Wang and L. Wang, *Green Chem.*, 2016, **18**, 3518–3521.
- 61 M.-H. Larraufie, G. Maestri, M. Malacria, C. Ollivier, L. Fensterbank and E. Lacôte, *Synthesis*, 2012, 1279–1292.
- 62 M.-H. Larraufie, C. Ollivier, L. Fensterbank, M. Malacria and E. Lacôte, *Angew. Chem., Int. Ed.*, 2010, **49**, 2178–2181.
- 63 N. A. Bokach and V. Y. Kukushkin, *Coord. Chem. Rev.*, 2013, **257**, 2293–2316.
- 64 D. D. Nekrasov, *Chem. Heterocycl. Compd.*, 2004, **40**, 1107–1123.
- 65 R. Crutchley, *Coord. Chem. Rev.*, 2001, **219–221**, 125–155.
- 66 A. S. Smirnov, E. S. Yandanova, N. A. Bokach, G. L. Starova, V. V. Gurzhiy, M. S. Avdontceva, A. A. Zolotarev and V. Y. Kukushkin, *New J. Chem.*, 2015, **39**, 9330–9344.
- 67 D. S. Bolotin, V. A. Rassadin, N. A. Bokach and V. Y. Kukushkin, *Inorg. Chim. Acta*, 2016, DOI: 10.1016/j.ica.2016.02.025.
- 68 M. Y. Demakova, D. S. Bolotin, N. A. Bokach, G. L. Starova and V. Y. Kukushkin, *Inorg. Chim. Acta*, 2015, **425**, 114–117.
- 69 T. Lister, R. H. Prager, M. Tsacónas and K. L. Wilkinson, *Aust. J. Chem.*, 2003, **56**, 913–916.
- 70 S. J. Connors and A. F. Hegarty, *Eur. J. Org. Chem.*, 2004, 3477–3483.
- 71 Q. Wang, H. Sun, H. Cao, M. Cheng and R. Huang, *J. Agric. Food Chem.*, 2003, **51**, 5030–5035.
- 72 J. E. Argüello, L. C. Schmidt and A. B. Peñéñory, *Org. Lett.*, 2003, **5**, 4133–4136.
- 73 F. Ghelfi, M. Pattarozzi, F. Roncaglia, A. Parsons, F. Felluga, U. Pagnoni, E. Valentin, A. Mucci and F. Bellesia, *Synthesis*, 2008, 3131–3141.
- 74 X. Jia, L. Yu, J. Liu, Q. Xu, M. Sickert, L. Chen and M. Lautens, *Green Chem.*, 2014, **16**, 3444–3449.
- 75 L. Nicolas, P. Angibaud, I. Stansfield, L. Meerpoel, S. Reymond and J. Cossy, *RSC Adv.*, 2013, **3**, 18787–18790.
- 76 S. M. Crawford, C. B. Lavery and M. Stradiotto, *Chem. – Eur. J.*, 2013, **19**, 16760–16771.
- 77 Q. Shen, S. Shekhar, J. P. Stambuli and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2005, **44**, 1371–1375.
- 78 C. Salomé, M. Schmitt and J.-J. Bourguignon, *Tetrahedron Lett.*, 2009, **50**, 3798–3800.
- 79 L. Alcaraz, C. Bennion, J. Morris, P. Meghani and S. M. Thom, *Org. Lett.*, 2004, **6**, 2705–2708.
- 80 X. Wang, A. Guram, M. Ronk, J. E. Milne, J. S. Tedrow and M. M. Faul, *Tetrahedron Lett.*, 2012, **53**, 7–10.
- 81 A. Reichelt, J. R. Falsey, R. M. Rzasa, O. R. Thiel, M. M. Achmatowicz, R. D. Larsen and D. Zhang, *Org. Lett.*, 2010, **12**, 792–795.
- 82 J. B. Arterburn, C. Corona, K. V. Rao, K. E. Carlson and J. A. Katzenellenbogen, *J. Org. Chem.*, 2003, **68**, 7063–7070.
- 83 D. H. R. Barton, D. Crich and W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 1983, 939–941.
- 84 V. M. S. Gil and A. J. L. Pinto, *Mol. Phys.*, 2006, **19**, 573–575.
- 85 P. Byrne, D. R. Turner, G. O. Lloyd, N. Clarke and J. W. Steed, *Cryst. Growth Des.*, 2008, **8**, 3335–3344.
- 86 K. Yamaguchi and K. Shudo, *J. Agric. Food Chem.*, 1991, **39**, 793–796.
- 87 L. S. Reddy, S. Basavoju, V. R. Vangala and A. Nangia, *Cryst. Growth Des.*, 2006, **6**, 161–173.
- 88 R. W. Troff, R. Hovorka, T. Weilandt, A. Lützen, M. Cetina, M. Nieger, D. Lentz, K. Rissanen and C. A. Schalley, *Dalton Trans.*, 2012, **41**, 8410–8420.
- 89 B. Ośmiałowski, K. Mroczńska, E. Kolehmainen, M. Kowalska, A. Valkonen, M. Pietrzak and K. Rissanen, *J. Org. Chem.*, 2013, **78**, 7582–7593.
- 90 V. Velikova, O. Angelova and K. Kossev, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1997, **53**, 1273–1275.
- 91 Y. Sun, Z. Zhang, X. Wang, X. Li, L. Weng and X. Zhou, *Organometallics*, 2009, **28**, 6320–6330.

