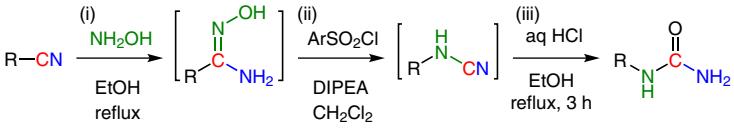
Synlett C.-H. Wang et al. Letter

# One-Pot Synthesis of N-Monosubstituted Ureas from Nitriles via Tiemann Rearrangement

**Chien-Hong Wang**
**Tsung-Han Hsieh**
**Chia-Chi Lin**
**Wen-Hsiung Yeh**
**Chih-An Lin**
**Tun-Cheng Chien***

Department of Chemistry, National Taiwan Normal University, No.88, Sec.4, Ting-Zhou Road, Taipei 11677, Taiwan
tcchien@ntnu.edu.tw



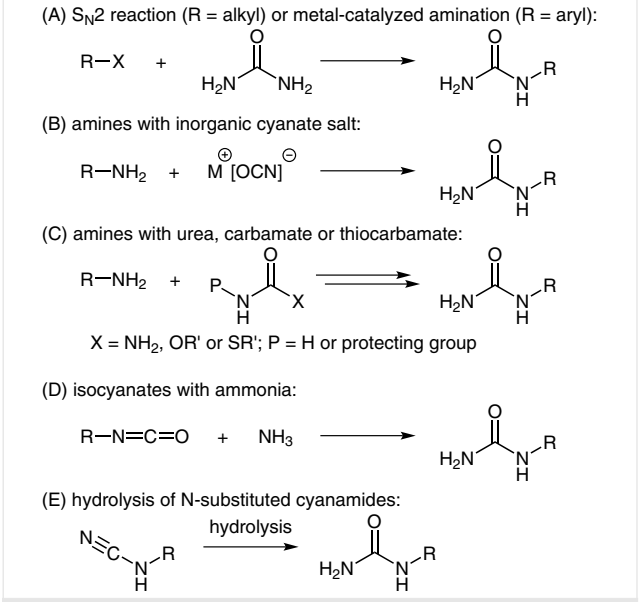

Received: 19.04.2015
Accepted after revision: 26.05.2015
Published online: 20.07.2015
DOI: 10.1055/s-0034-1381007; Art ID: st-2015-u0285-l

**Abstract** Amidoximes, obtained from the reaction of nitriles with hydroxylamine, underwent Tiemann rearrangement in the presence of benzenesulfonyl chlorides (TsCl or *o*-NsCl) to form the N-substituted cyanamides. Subsequently, acidic hydrolysis of the cyanamides afforded the corresponding N-monosubstituted ureas. The synthesis of N-monosubstituted ureas from nitriles was accomplished by three steps in one pot, which provides a direct access to versatile N-monosubstituted urea derivatives from a wide variety of nitriles.

**Key words** urea, cyanamide, amidoxime, hydrolysis, Tiemann rearrangement

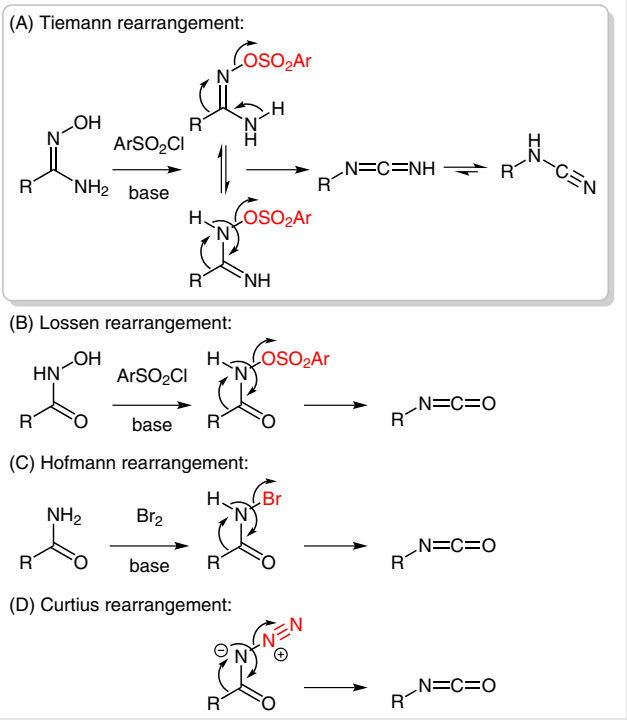
Urea is among the most stable nitrogen-containing functionalities which widely exists in natural substances,[1] biological metabolites,[2] synthetic reagents or catalysts,[3,4] pharmaceutical or agricultural ingredients,[5–7] and functional macromolecules.[8] Owing to its broad application prospect, various synthetic approaches for multisubstituted ureas have been developed and utilized for laboratorial and industrial preparation.

N-Monosubstituted ureas are of our particular interest from the synthetic perspective. N-Monosubstituted ureas have been extensively used as organocatalsts, neighboring directing groups,[9] and, more importantly, N–C–N building blocks for the synthesis of heterocycles, more complicated ureas, and other $CN_2$ or $CN_3$ functionalities.[10] Nevertheless, only a limited number of synthetic strategies for N-monosubstituted ureas have been practically employed in the literature. The direct alkylation or arylation of urea is a straightforward approach. But O-alkylation cannot be completely excluded, and multialkylation or diarylation are often obtained due to the competing reactions of the monosubstituted ureas (Scheme 1,A).[11–14] The most common approach to N-monosubstituted ureas is the addition reaction of primary amines with inorganic cyanate salts under aqueous acidic condition (Scheme 1,B).[15] Similar approaches involve a nucleophilic addition of primary amines to ureas, carbamates or thiocarbamates, and extra steps for the removal of protecting groups may be required (Scheme 1,C).[16] Other methods include addition of ammonia or ammonia equivalents to organic isocyanates and hydrolysis of N-substituted cyanamides (Scheme 1,D and E).[5,6,17,18] The methods depicted in Scheme 1 (B–E) are mutually complementary since they are all originated from the corresponding primary amines with multistep manipulations.




**Scheme 1** Literature procedures for the preparation of N-monosubstituted ureas

In 1891, F. Tiemann reported that *N*-phenylurea was obtained from the arylsulfonylation of benzamidoxime, which is known as the Tiemann rearrangement.[19,20] The unusual formation of *N*-phenylurea dated back to the late 19th century has attracted our attention. However, a thorough survey of literature revealed that the arylsulfonylation of amidoximes could lead to diverse reaction outcomes with indefinite scopes, which substantially limited the synthetic application of Tiemann rearrangement.[19–23] The rearrangement reaction remains lack of practicality for over one century until few breakthroughs were recently disclosed.[21,22,24] Our previous investigation established that the reaction of amidoximes with TsCl or *o*-NsCl under anhydrous conditions afforded exclusively the N-substituted cyanamides in very good yields.[24] The proposed mechanism is sketched in Scheme 2 (A). The reaction starts with the O-arylsulfonylation of amidoximes to form the *O*-arylsulfonyl amidoxime intermediates. Subsequently, the N–O bond cleavage occurs with concomitantly R group migration over the C–N bond to furnish the N-substituted cyanamides. It is noteworthy that the rearrangement step is mechanistically similar to several well-known rearrangement reactions, including Lossen rearrangement, Hofmann rearrangement, and Curtius rearrangement (Scheme 2,B–D).



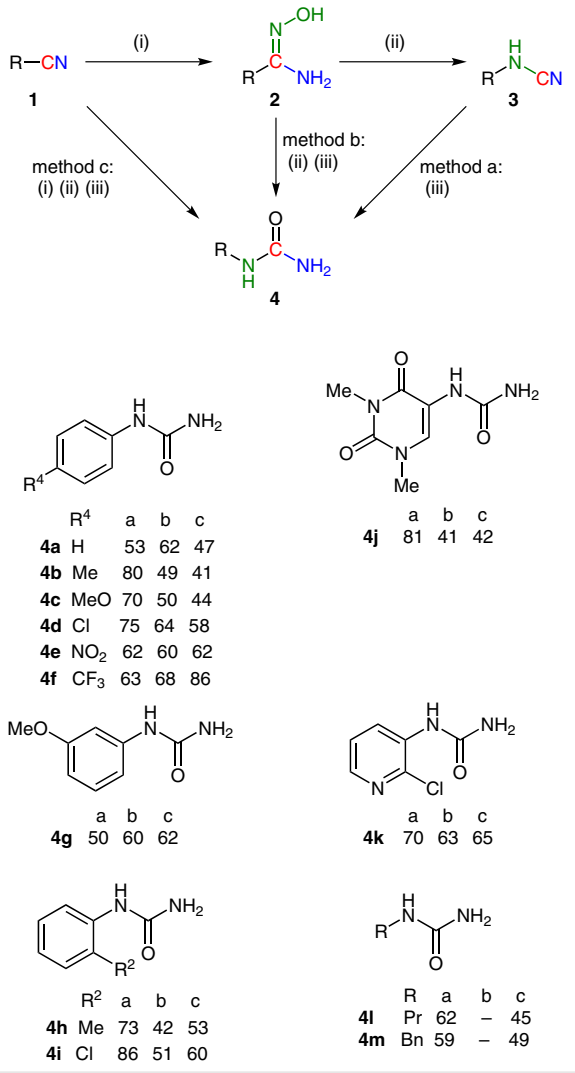

**Scheme 2** Proposed mechanism for: (A) Tiemann rearrangement; (B) Lossen rearrangement; (C) Hofmann rearrangement; (D) Curtius rearrangement

The rearrangement reaction features a broad substrate scope and provides a viable synthesis of N-substituted cyanamide derivatives from corresponding nitriles. We rationalized that the formation of *N*-phenylurea from benzamidoxime originally observed by F. Tiemann was a consequence from the hydrolysis of the *N*-phenylcyanamide.[19,20,23] Thus, we embarked on the investigation to evaluate whether the Tiemann rearrangement followed by a consecutive acidic hydrolysis would be a general and feasible approach for the preparation of various types of N-monosubstituted urea derivatives.

A perusal of literature suggested that the hydrolysis of N-substituted cyanamides to ureas can be achieved under the catalysis of either Brønsted or Lewis acids.[18] We envisioned that the byproducts from Tiemann rearrangement are arylsulfonic acid and hydrogen chloride. In order to keep two consecutive reactions in consistent conditions, a simple diluted hydrochloric acid condition was chosen to examine the hydrolysis reaction of N-substituted cyanamides,[6] which would later allow the development of the one-pot reaction sequence. Therefore, a series of N-substituted cyanamide derivatives **3**, prepared from the nitriles **1** via Tiemann rearrangement,[24] were subjected to the acidic hydrolysis in aqueous ethanolic HCl solution. The results showed that *N*-aryl, *N*-heteroaryl-, and *N*-alkyl cyanamides **3** could all be hydrolyzed to the corresponding N-monosubstituted ureas **4** in good yields (method a in Scheme 3).[25,26]

We estimated that the byproducts, arylsulfonic acid and hydrogen chloride, from Tiemann rearrangement should be adjuvant to the acidic hydrolysis of cyanamides to ureas. Since there is no need to isolate the N-substituted cyanamides **3**, a one-pot process from amidoximes to ureas would be viable. We demonstrated that the amidoximes **2** were subjected to the Tiemann rearrangement conditions followed by a successive acidic hydrolysis to give the corresponding N-monosubstituted ureas **4** presumably in the same yields (method b in Scheme 3). Moreover, the reaction of nitriles **1** with hydroxylamine could afford the amidoximes **2** in fairly good yields, which allowed the one-pot reaction sequence to be further extended. Thus, the preparation of the N-monosubstituted ureas **4** can be accomplished by sequential reactions from nitriles **1** in one-pot, starting from the conversion of nitriles to amidoximes followed by the Tiemann rearrangement and immediate acidic hydrolysis, to give comparable yields (method c in Scheme 3).

In summary, our investigation has provided a facile and practical synthesis of N-monosubstituted ureas directly from nitriles via Tiemann rearrangement. The methodology features a broad substrate scope to achieve a wide variety of *N*-aryl, *N*-heteroacryl, and *N*-alkyl ureas. Although the hydrolysis of individual N-substituted cyanamides remains to be further optimized, we anticipated that alternative methods from the literature can also be adopted.[6,18] The feasibili-




**Scheme 3** One-pot synthesis of N-monosubstituted ureas **4** from nitriles **1** [percentage yield (%)]. *Reagents and conditions*: (i) $NH_2OH$, EtOH, reflux; (ii) $ArSO_2Cl$, DIPEA, $CH_2Cl_2$; (iii) aq HCl–EtOH, reflux.

ty of the reaction sequence was validated and characterized step-by-step, and the one-pot protocol has been established, which made the historical discovery of F. Tiemann become a practical approach for the synthesis of N-monosubstituted urea derivatives.

## Acknowledgment

This work was supported by Research Grants 103-2113-M-003-007- and 102-2113-M-003-004- from Ministry of Science and Technology, Taiwan.

## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1381007.

## References and Notes

(1) (a) Han, S.; Siegel, D. S.; Morrison, K. C.; Hergenrother, P. J.; Movassaghi, M. *J. Org. Chem.* **2013**, *78*, 11970. (b) Reyes, J. C. P.; Romo, D. *Angew. Chem. Int. Ed.* **2012**, *51*, 6870. (c) Rogers, E. W.; Molinski, T. F. *J. Org. Chem.* **2009**, *74*, 7660. (d) Knott, K. E.; Auschill, S.; Jaeger, A.; Knoelker, H.-J. *Chem. Commun.* **2009**, 1467. (e) Rogers, E. W.; Dalisay, D. S.; Molinski, T. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 8086. (f) Jacquot, D. E. N.; Zoellinger, M.; Lindel, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 2295. (g) Hanessian, S.; Huang, G.; Chenel, C.; Machaalani, R.; Loiseleur, O. *J. Org. Chem.* **2005**, *70*, 6721.

(2) McKay, M. J.; Nguyen, H. M. *Carbohydr. Res.* **2014**, *385*, 18.

(3) (a) Heravi, M.; Asadi, S.; Lashkariani, B. *Mol. Diversity* **2013**, *17*, 389. (b) El Gihani, M. T.; Heaney, H. *Synthesis* **1998**, 357.

(4) (a) Hernández-Rodríguez, M.; Avila-Ortiz, C. G.; del Campo, J. M.; Hernández-Romero, D.; Rosales-Hoz, M. J.; Juaristi, E. *Aust. J. Chem.* **2008**, *61*, 364. (b) Connon, S. J. *Chem. Commun.* **2008**, 2499. (c) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418.

(5) Belfrage, A. K.; Gising, J.; Svensson, F.; Åkerblom, E.; Sköld, C.; Sandström, A. *Eur. J. Org. Chem.* **2015**, 978.

(6) Gong, H.; Yang, M.; Xiao, Z.; Doweyko, A. M.; Cunningham, M.; Wang, J.; Habte, S.; Holloway, D.; Burke, C.; Shuster, D.; Gao, L.; Carman, J.; Somerville, J. E.; Nadler, S. G.; Salter-Cid, L.; Barrish, J. C.; Weinstein, D. S. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3268.

(7) (a) Lin, W.-H.; Hsu, J. T. A.; Hsieh, S.-Y.; Chen, C.-T.; Song, J.-S.; Yen, S.-C.; Hsu, T.; Lu, C.-T.; Chen, C.-H.; Chou, L.-H.; Yang, Y.-N.; Chiu, C.-H.; Chen, C.-P.; Tseng, Y.-J.; Yen, K.-J.; Yeh, C.-F.; Chao, Y.-S.; Yeh, T.-K.; Jiaang, W.-T. *Bioorg. Med. Chem.* **2013**, *21*, 2856. (b) Li, H.-F.; Lu, T.; Zhu, T.; Jiang, Y.-J.; Rao, S.-S.; Hu, L.-Y.; Xin, B.-T.; Chen, Y.-D. *Eur. J. Med. Chem.* **2009**, *44*, 1240. (c) Michaux, C.; Dogné, J.-M.; Rolin, S.; Masereel, B.; Wouters, J.; Durant, F. *Eur. J. Med. Chem.* **2003**, *38*, 703.

(8) Tuerp, D.; Bruchmann, B. *Macromol. Rapid Commun.* **2015**, *36*, 138.

(9) (a) Wang, L.; Liu, S.; Li, Z.; Yu, Y. *Org. Lett.* **2011**, *13*, 6137. (b) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem. Int. Ed.* **2009**, *48*, 1830.

(10) (a) Abdigali, A. B.; Aleksandr, Y. Y.; Sergei, N. V. *Russ. Chem. Rev.* **1998**, *67*, 295. (b) Vishnyakova, T. P.; Golubeva, I. A.; Glebova, E. V. *Russ. Chem. Rev.* **1985**, *54*, 249. (c) Kutepov, D. F. *Russ. Chem. Rev.* **1962**, *31*, 633.

(11) (a) Sharma, R.; Samadhiya, P.; Srivastava, S. D.; Srivastava, S. K. *Helv. Chim. Acta* **2012**, *95*, 514. (b) Samadhiya, P.; Sharma, R.; Srivastava, S. K.; Srivastava, S. D. *Chin. J. Chem.* **2011**, *29*, 1745. (c) Hackl, K. A.; Falk, H. *Monatsh. Chem.* **1992**, *123*, 599.

(12) Curtis, N. *Aust. J. Chem.* **1988**, *41*, 585.

(13) Breitler, S.; Oldenhuis, N. J.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2011**, *13*, 3262.

(14) (a) Nandakumar, M. V. *Tetrahedron Lett.* **2004**, *45*, 1989. (b) Sergeev, A. G.; Artamkina, G. A.; Beletskaya, I. P. *Tetrahedron Lett.* **2003**, *44*, 4719. (c) Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. *Russ. J. Org. Chem.* **2002**, *38*, 538. (d) Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. *Tetrahedron Lett.* **2001**, *42*, 4381.

(15) (a) Dalby, A.; Mo, X.; Stoa, R.; Wroblewski, N.; Zhang, Z.; Hagen, T. J. *Tetrahedron Lett.* **2013**, *54*, 2737. (b) De Luca, L.; Porcheddu, A.; Giacomelli, G.; Murgia, I. *Synlett* **2010**, 2439. (c) El-Deeb, I. M.; Bayoumi, S. M.; El-Sherbeny, M. A.; Abdel-Aziz, A. A. M. *Eur. J. Med. Chem.* **2010**, *45*, 2516. (d) Harriman, G. C.; Brewer, M.;

Bennett, R.; Kuhn, C.; Bazin, M.; Larosa, G.; Skerker, P.; Cochran, N.; Gallant, D.; Baxter, D.; Picarella, D.; Jaffee, B.; Luly, J. R.; Briskin, M. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2509.

(16) (a) Nasrollahzadeh, M.; Azarian, A.; Ehsani, A.; Sajadi, S. M.; Babaei, F. *Mater. Res. Bull.* **2014**, *55*, 168. (b) Mohy El Dine, T.; Chapron, S.; Duclos, M.-C.; Duguet, N.; Popowycz, F.; Lemaire, M. *Eur. J. Org. Chem.* **2013**, 5445. (c) Manidhar, D. M.; Uma Maheswara Rao, K.; Sures Reddy, C.; Syamasunder, C.; Adeppa, K.; Misra, K. *Res. Chem. Intermed.* **2012**, *38*, 2479. (d) Atkinson, B. N.; Chhatwal, A. R.; Lomax, H. V.; Walton, J. W.; Williams, J. M. J. *Chem. Commun.* **2012**, *48*, 11626. (e) Verardo, G.; Bombardella, E.; Venneri, C. D.; Strazzolini, P. *Eur. J. Org. Chem.* **2009**, 6239. (f) Diss, M. L.; Kennan, A. J. *Biopolymers* **2007**, *86*, 276. (g) Liu, Q.; Luedtke, N. W.; Tor, Y. *Tetrahedron Lett.* **2001**, *42*, 1445. (h) Seyferth, D.; Dow, A. W.; Menzel, H.; Flood, T. C. *J. Am. Chem. Soc.* **1968**, *90*, 1080.

(17) (a) Ludek, O. R.; Marquez, V. E. *J. Org. Chem.* **2012**, *77*, 815. (b) Browne, D.; O'Brien, M.; Koos, P.; Cranwell, P. B.; Polyzos, A.; Ley, S. V. *Synlett* **2012**, *23*, 1402. (c) Boiocchi, M.; Fabbrizzi, L.; Garolfi, M.; Licchelli, M.; Mosca, L.; Zanini, C. *Chem. Eur. J.* **2009**, *15*, 11288. (d) Reisman, S. E.; Ready, J. M.; Weiss, M. M.; Hasuoka, A.; Hirata, M.; Tamaki, K.; Ovaska, T. V.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 2087. (e) Tao, B.; Timberlake, J. W. *Synthesis* **2000**, 1449. (f) Kobayashi, T.; Seki, T.; Ichimura, K. *Chem. Commun.* **2000**, 1193.

(18) (a) Nasrollahzadeh, M.; Enayati, M.; Khalaj, M. *RSC Adv.* **2014**, *4*, 26264. (b) Nasrollahzadeh, M. *RSC Adv.* **2014**, *4*, 29089. (c) Sajadi, S. M.; Maham, M. *J. Chem. Res.* **2013**, 623. (d) Kim, S. H.; Park, B. R.; Kim, J. N. *Bull. Korean Chem. Soc.* **2011**, *32*, 716. (e) Xiao, Z. L.; Yang, M. G.; Tebben, A. J.; Galella, M. A.; Weinstein, D. S. *Tetrahedron Lett.* **2010**, *51*, 5843. (f) Iio, K.; Ichikawa, E. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2009.

(19) (a) Tiemann, F. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 4162. (b) Pinnow, J. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 4167.

(20) Partridge, M. W.; Turner, H. A. *J. Pharm. Pharmacol.* **1953**, *5*, 103.

(21) (a) Bakunov, S. A.; Rukavishnikov, A. V.; Tkachev, A. V. *Synthesis* **2000**, 1148. (b) Bakunov, S. A.; Rukavishnikov, A. V.; Tkachev, A. V. *Synthesis* **1994**, 935.

(22) Ulrich, H.; Tucker, B.; Richter, R. *J. Org. Chem.* **1978**, *43*, 1544.

(23) (a) Richter, R.; Tucker, B.; Ulrich, H. *J. Org. Chem.* **1983**, *48*, 1694. (b) Damrauer, R.; Soucy, D.; Winkler, P.; Eby, S. *J. Org. Chem.* **1980**, *45*, 1315. (c) Dondoni, A.; Barbaro, G.; Battaglia, A. *J. Org. Chem.* **1977**, *42*, 3372. (d) Garapon, J.; Sillion, B.; Bonnier, J. M. *Tetrahedron Lett.* **1970**, *11*, 4905. (e) Boyer, J. H.; Frints, P. J. A. *J. Org. Chem.* **1970**, *35*, 2449.

(24) Lin, C.-C.; Hsieh, T.-H.; Liao, P.-Y.; Liao, Z.-Y.; Chang, C.-W.; Shih, Y.-C.; Yeh, W.-H.; Chien, T.-C. *Org. Lett.* **2014**, *16*, 892.

(25) **General Procedure for the One-Pot Synthesis of N-Monosubstituted Urea 4 from Nitrile 1 (Scheme 3)**

To the solution of nitrile **1** in EtOH (0.1 M) was added 50 wt% aq hydroxylamine solution (1.2 equiv). The mixture was stirred at reflux temperature for 1.5 h. After cooling to r.t., the reaction mixture was concentrated under reduced pressure. The crude amidoxime product **2** was dissolved in $CH_2Cl_2$ (0.1 M), and $ArSO_2Cl$ (TsCl or *o*-NsCl, 1.05 equiv) and DIPEA (1.05 equiv) were added at 0 °C. The mixture was stirred under nitrogen atmosphere at r.t. for 3 h or at reflux temperature for 1 h.[24] The mixture was concentrated under reduced pressure. The crude cyanamide product **3** was dissolved in the mixture of 1 N aq HCl solution and EtOH (0.1 M, 1 N HCl–EtOH = 1:4, v/v). The mixture was stirred at reflux temperature for 3 h under nitrogen. After cooling to r.t. the reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography.

(26) **Analytical Data of Compounds 4e–k**

***N*-(4-Nitrophenyl)urea (4e)**

Mp 213–215 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.29 (s, 1 H, NH), 8.11 (d, 2 H, *J* = 9.2 Hz), 7.62 (d, 2 H, *J* = 9.2 Hz), 6.20 (s, 2 H, $NH_2$). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 155.4, 147.3, 140.5, 125.1 (CH), 117.0 (CH). MS (EI, 20 eV): *m/z* = 108 (56), 138 (100), 181 (40) [M$^+$]. ESI-MS: *m/z* = 167 (100), 182 (73) [M + 1]. HRMS (EI): *m/z* calcd for $C_7H_7N_3O_3$: 181.0487; found: 181.0486.

***N*-(4-Trifluoromethylphenyl)urea (4f)**

Mp 144–145 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.95 (s, 1 H, NH), 7.60 (d, 2 H, *J* = 8.7 Hz), 7.54 (d, 2 H, *J* = 8.7 Hz), 6.04 (s, 2 H, $NH_2$). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 155.7, 144.3, 125.9 (q, *J* = 3.0 Hz, CH), 124.6 (q, *J* = 270.0 Hz, $CF_3$), 121.1 (q, *J* = 32.0 Hz), 117.4 (CH). MS (EI, 20 eV): *m/z* = 161 (100), 204 (41) [M$^+$]. ESI-MS: *m/z* = 205 (100) [M + 1]. HRMS (EI): *m/z* calcd for $C_8H_7F_3N_2O$: 204.0510; found: 204.0508.

***N*-(3-Methoxyphenyl)urea (4g)**

Mp 128–130 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.51 (s, 1 H, NH), 7.08–7.12 (m, 2 H), 6.87 (d, 1 H, *J* = 7.9 Hz), 6.47 (d, 1 H, *J* = 8.0 Hz), 5.81 (s, 2 H, $NH_2$), 3.69 (s, 3 H, $CH_3$). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 159.7, 156.0, 141.8, 129.4 (CH), 110.2 (CH), 106.5 (CH), 103.6 (CH), 54.9 (CH). ESI-MS: *m/z* = 167 [M + 1]. HRMS (EI): *m/z* calcd for $C_8H_{10}N_2O_2$: 166.0742; found: 166.0741.

***N*-(2-Methylphenyl)urea (4h)**

Mp 194–196 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 7.77 (d, 1 H, *J* = 8.0 Hz), 7.66 (s, 1 H, NH), 7.12–7.06 (m, 2 H), 6.87 (t, 1 H, *J* = 7.3), 6.00 (s, 2 H, $NH_2$), 2.18 (s, 3 H, $CH_3$). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 156.1, 138.2, 130.0 (CH), 127.0 (CH), 126.0, 123.0 (CH), 120.9 (CH), 17.9 ($CH_3$). MS (EI, 20 eV): *m/z* = 107 (100), 150 (62) [M$^+$]. HRMS (EI): *m/z* calcd for $C_8H_{10}N_2O$: 150.0793; found: 150.0792.

***N*-(2-Chlorophenyl)urea (4i)**

Mp 190–192 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.12 (dd, 1 H, *J* = 8.4, 1.3 Hz), 8.03 (s, 1 H, NH), 7.38 (dd, 1 H, *J* = 8.3, 0.9 Hz), 7.24–7.20 (m, 1 H), 6.96–6.92 (m, 1 H), 6.37 (s, 2 H, $NH_2$). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 155.6, 136.7, 129.0, 127.4, 122.5, 121.4, 121.1. MS (EI, 20 eV): *m/z* = 127 (100), 129 (30), 135 (40), 170 (18) [M$^+$], 172 (8) [M + 2]. HRMS (EI): *m/z* calcd for $C_7H_7ClN_2O$: 170.0247; found: 170.0246.

**1,3-Dimethyl-5-ureidouracil (4j)**

Mp 254–258 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.09 (s, 1 H, NH), 7.84 (s, 1 H), 6.26 (s, 2 H, $NH_2$), 3.29 (s, 3 H, $CH_3$), 3.20 (s, 3 H, $CH_3$). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 160.2, 156.5, 149.8, 128.5, 115.0, 70.2, 37.1, 28.4. MS (EI, 20 eV): *m/z* = 70 (42), 155 (100), 198 (10) [M$^+$]. HRMS (EI): *m/z* calcd for $C_7H_{10}N_4O_3$: 198.0753; found: 198.0760.

**2-Chloro-3-ureidopyridine (4k)**

Mp 210–212 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.50 (dd, 1 H, *J* = 8.2, 1.5 Hz), 8.19 (s, 1 H, NH), 7.96 (dd, 1 H, *J* = 4.5, 1.5 Hz), 7.32 (dd, 1 H, *J* = 8.2, 4.6 Hz), 6.52 (s, 2 H, $NH_2$). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 155.4, 141.5 (CH), 138.5, 133.9, 128.3 (CH), 123.3 (CH). ESI-MS: *m/z* = 155 (28), 172 (100) [M + 1]. HRMS (EI): *m/z* calcd for $C_6H_6ClN_3O$: 171.0199; found: 171.0201.