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A Novel One-Pot Synthesis of Symmetrically Substituted Ureas

Xingxing Wu[1], Qingfen Niu[1], Tianduo Li[1]

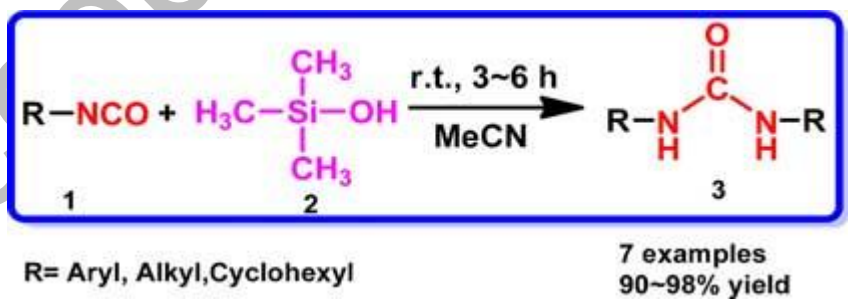
[1]Shandong Provincial Key Laboratory of Fine Chemicals, Qilu University of Technology, Jinan, People's Republic of China

Correspondence Authors E-mails:
Qingfen Niu: qf_niu1216@qlu.edu.cn
Tianduo Li: litianduo@163.com

Abstract

We demonstrated a novel, facile, high-yield and efficient one-pot approach for the synthesis of symmetrically disubstituted ureas from isocyanates in the presence of trimethylsilanol. This novel protocol boasts use of inexpensive reagents, operational simplicity, excellent yields of products, environment-friendly conditions and easy workup. To the best of our knowledge, this is the first example of synthesis of symmetrically disubstituted ureas from isocyanates in the presence of trimethylsilanol in one pot.

Graphical Abstract



KEYWORDS: One-pot synthesis; High-yield; Urea; Isocyanate; Trimethylsilanol

INTRODUCTION

By the virtue of their numerous important applications, the synthesis and uses of substituted ureas have attracted special attention in the recent years. Disubstituted ureas played an important role in industrial field[1,2] as dyes for cellulose fibers, antioxidants in gasoline, resin precursors and in organic synthesis as starting materials (especially for the production of carbamates, isocyanates, polymers and surfactants) and intermediates[3–5] (especially for the production of cosmetics, pharmaceuticals and agrochemicals), particularly in the medical field as tranquilizing, anticonvulsant, antidiabetic agents as well as inhibitors of HIV-1 protease. Owing to their increasing application of these compounds, a great variety of procedures have been used to investigate their synthesis[6,7].

A large number of experimental investigations have been made to search for an efficient and practical method to synthesize various urea-based compounds. The traditional procedures are available in the literature for the synthesis of substituted ureas (**Scheme 1**). They can be collected and classified into three groups: (i) The reaction of primary amines mainly with phosgene or triphosgene (BTC)[8]; (ii) Reaction of primary and secondary amines with isocyanates, prepared mainly from phosgene during organic

synthesis[9–10]. However, the phosgene has corrosive nature and its preparation usually generates excessive toxicological and environmental wastes; (iii) The reaction of primary amines with carbonyl derivatives (including dicyclohexylcarbodiimide, carbonyldiimidazole, carbonates and trichloroacetyl chlorides), carbon dioxide, carbon monoxide as well as oxygen[11–14]. The carboxylation of amines to ureas usually requires harsh conditions such as high pressure, high temperatures and even microwave irradiation conditions or metal catalysts[15].

However, the effectiveness of existing synthetic methods above suffer from some disadvantages[15] such as the use of metal-mediated catalysis, hazardous and expensive reagents, higher pressure or temperatures conditions, longer reaction times, low yields, incompatibility with functionalized substrates, multi-step synthesis as well as difficult workup, which not only reduce process efficiency but also pose serious environment problems.

As a consequence, the introduction of new methods and/or further work on technical improvements to overcome these limitations is still an important experimental challenge. Therefore, from the point of the growing importance of symmetrically substituted ureas, the development of a simple, efficient and environmentally benign method for their synthesis is highly desirable. To the best of our knowledge, there are no literature reports available for the synthesis of symmetrically disubstituted ureas by using trimethylsilanol.

Herein, we have presented our new strategy, a novel, facile, high-yield and efficient one-pot synthesis of symmetrically disubstituted ureas from corresponding isocyanates in the presence of trimethylsilanol under mild conditions.

RESULTS AND DISCUSSION

The desired products disubstituted ureas **3** were obtained with isocyanates **1** (1.0 equiv) in CH_3CN at room temperature for 3-6 hours in the presence of Me_3SiOH (1.0 equiv) as shown in **Scheme 2**. The experimental results were summarized in **Table 1**. From the results in **Table 1**, it is concluded that all of the expected substituted ureas (**3a-g**) were obtained in excellent yields (90–98%). To our delight, unsubstituted aryl isocyanates were well reacted with trimethylsilanol under the optimized conditions (entries 2 and 5). To our satisfaction, the reaction can tolerate aryl substituents of different electronic effects at the meta or para positions, affording excellent yields (entries 3, 4, 6). However, certain functional group such as NO_2 group with strong electron-withdrawing nature was not tolerated in the protocol (entry 8). In order to further extend the substrate scope of the protocol, aliphatic substrates such as isocyanatocyclohexane and 1-isocyanato-2-methylbenzene with steric hindrance were tested. It is noteworthy that this reaction protocol can be successfully carried out by using aliphatic substrates to afford the corresponding products in excellent yields (up to 92%) after 6 h (entries 1 and 7). Therefore, this metal-free synthetic method could potentially be a mild and convenient

method of accessing such aryl, alkyl, and cyclohexyl structures. Products **3a-f** are known compounds[16–18] and were confirmed by the comparison of their spectral data with literature. Among these products, the product **3g** is as a new compound and fully characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS measurements.

In order to study the mechanism of these reactions, the proposed reaction mechanism of disubstituted ureas **3** is suggested in **Scheme 3**. The first step is nucleophilic attack of oxygen atom of Me_3SiOH upon the carbon atom of the carbonyl group of **1** to give rise to intermediate **A**. Next, nucleophilic attack of the Me_3SiOH oxygen atom on the carbon atom of the carbonyl group of **A** leads to the formation of intermediate **B**. Then the reductive elimination of intermediate **B** delivers compound **C** to furnish intermediate **D**. Finally, the end-product of disubstituted urea **3** is produced from **1** via nucleophilic attack of nitrogen atom of R-NH_2 upon the carbon atom of the carbonyl group of **1**.

CONCLUSIONS

In summary, we have successfully developed a one-pot, facile, high-yield and efficient approach for the synthesis of symmetrically disubstituted ureas from corresponding isocyanates including aryl, alkyl, and cyclohexyl substrates in the presence of trimethylsilanol. This novel method offers several advantages such as use of inexpensive

reagents, excellent yields of products, environment-friendly conditions, and simple experimental and work-up procedures. We expect that the metal-free synthetic approach would be highly practical and safe for the synthesis of symmetrically disubstituted ureas in the field of organic and medicinal chemistry.

EXPERIMENTAL

General

Unless otherwise stated, all solvents and reagents were of analytical grade from commercial suppliers, and were used without further purification. Infrared measurements with the KBr pellet technique were performed within the 4000–400 cm^{-1} region on a Bruker ALPHA FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance Ⅱ 400 using TMS as an internal standard operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR in DMSO-d_6, respectively. High resolution mass spectra (HRMS) were obtained from Agilent 6510 Accurate-Mass Q-TOF LC/MS system.

General Procedure For The Synthesis Of Symmetrically Substituted Urea 3

To a well-stirred, isocyanate (**1**, 1.0 mmol) was added in MeCN (10 mL, anhydrous), then trimethylsilanol (**2**, 1.0 mmol) was added in the reaction system. The reaction mixture

was stirred for 3–6 h at room temperature. After that, the solvent was removed to afford the corresponding symmetrically substituted urea product **3**.

1,3-Bis(2-(Tert-Butyldimethylsilyloxy)Ethyl)Urea (3g)

Yield 90%; Light yellow liquid; IR (KBr, cm^{-1}): ν = 3425 (NH), 2979, 2808, 2472, 2633 (C=O(NH)), 1459,1392, 1154, 1040, 803; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.93 (s, 2H), 3.5 (t, J = 6.0 Hz, 4H), 3.05 (t, J = 6.0 Hz, 4H), 0.85 (s, 18H), 0.01 (s, 12H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.914, 62.424, 41.749, 25.788, 17.845, -5.67; HRMS: *m/z* calculated 376.2673 $[M+H]^+$, found 377.3441 $[M+H]^+$.

The products **3a-f** are known compounds[16-18] and were characterized by comparing the IR, ^{1}H NMR, ^{13}C NMR and HRMS spectroscopic data with authentic samples reported in the literature. See supplementary data for the characterization of products **3a-f**.

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REFERENCES

[1] (a) Holmes, D. H.; Smith, E. M.; Nowick, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 7665–7669; (b) Nowick, J. S.; Mahrus, S.; Smith, E. M.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 1066–1072; (c) Nowick, J. S.; Holmes, D. L.; Mackin, G.; Noronha, G.; Shaka, A. J.; Smith, E. M. *J. Am. Chem. Soc.* **1996**, *118*, 2764–2765; (d) Nowick, J. S.; Smith, E. M.; Noronha, G. *J. Org. Chem*. **1995**, *60*, 7386–7387.

[2] (a) McKay, M. J.; Nguyen, H. M. *Carbohydr. Res.* **2014**, *385*, 18–44; (b) Wilson, M. E.; Nowick, J. S. *Tetrahedron Lett.* **1998**, *39*, 6613–6616; (c) Burgess, K.; Ibarzo, J.; Linthicum, D. S.; Russell, D. H.; Shin, H.; Shitangkoon, A.; Totani, R.; Zhang, A. J. *J. Am. Chem. Soc.* **1997**, *119*, 1556–1564; (d) Kruijtzer, J. A. W.; Lefeber; D. J.; Liskamp, R. M. J. *Tetrahedron Lett.* **1997**, *38*, 5335–5338; (e) Kim, J.-M.; Wilson, T. E.; Norman, T. C.; Schultz, P. G. *Tetrahedron Lett.* **1996**, *37*, 5309–5312; (f) Burgess, K.; Linthicum, D. S.; Shin, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 907–909.

[3] Belfrage, A. K.; Gising, J.; Svensson, F.; Åkerblom, E.; Sköld, C.; Sandström, A. *Eur. J. Org. Chem.* **2015**, 978–986.

[4] 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*, 3268–3273.

[5] Nasrollahzadeh, M.; Babaei, F.; Sajadi, S. M.; Ehsani, A. *Spectrochim. Acta Part A* **2014**, *132*, 423–429.

[6] (a) Heravi, M. M.; Asadi, S.; Lashkariani, B. M. *Mol. Diversity* **2013**, *17*, 389–407; (b) Getman, D. P.; Decrescenzo, G. A.; Heintz, R. M.; Reed, K. L.; Talley, J. J.; Bryant, M. L.; Clare, M.; Houseman, K. A.; Marr, J. J.; Mueller, R. A.; Vazquez, M. L.; Shieh, H. S.; Stallings, W. C.; Stegeman, R. A. *J. Med. Chem.* **1993**, *36*, 288–291.

[7] (a) Artuso, E.; Degani, I.; Fochi, R.; Magistris, C. *Synthesis* **2007**, *22*, 3497–3506; (b) Hai, S. M. A.; Perveen, S.; Khana, R. A.; Khanb, K. M.; Afza, N. *Nat. Prod. Res*. **2003**, *17*, 351–362; (c) Ahamad, T.; Kumar, V.; Nishat, N. *J. Biomed. Mater. Res. Part A* **2009**, *88A*, 288–294; (d) Beraa, R. K.; Hartmanb, N. G.; Jayb, M. *Int. J. Radiat. Appli. Instrumen. Part A. Applied Radiation and Isotopes*. **1991**, *42*, 407–409.

[8] Ciro, M.; Alessandra, F.; Kazuki, S.; Valeria, L. P.; Amodio, L. B.; Luciana, M.; Antonello, M.; Ettore, N.; Sabrina, C.; Alessandra, T.; Gianluca, S. *J. Med. Chem.* **2015**, *58*, 2779–2798.

[9] (a) Valizadeh, H.; Dinparast, L. *Monatsh. Chem.* **2012**, *143*, 251–254; (b) Li, X.-Q.; Wang, W.-K.; Han, Y.-X.; Zhang, C. *Adv. Synth. Catal.* **2010**, *352*, 2588–2598.

[10] (a) Anderson, J. C.; Moreno, R. B. *Org. Biomol. Chem.* **2012**, *10*, 1334–1338; (b) Zhang, C.; Wang, W.-K.; He, T. *Synthesis* **2012**, *44*, 3006–3014.

[11] Wu, J. W.; Wu, Y. D.; Dai, J. J.; Xu, H. J. *Adv. Synth. Catal*. **2014**, *356*, 2429–2436.

[12] Kuwahara, Y.; Zhang, A.; Soma, H.; Tsuda, A. *Org. Lett.* **2012**, *14*, 3376–3379.

[13] Gadgea, S. T.; Kusumawatib, E. N.; Haradac, K.; Sasakic, T.; Nishio-Hamaned, D.; Bhanagea, B. M. *J. Mol. Catal. A Chem*. **2015**, *400*, 170–178.

[14] Didgikar, M. R.; Roy, D.; Gupte, S. P.; Joshi, S. S.; Chaudhari, R. V. *Ind. Eng. Chem. Res.* **2010**, *49*, 1027–1032.

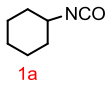
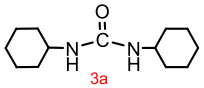
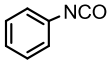
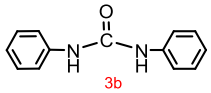
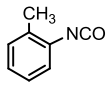
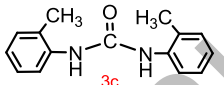
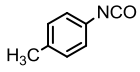
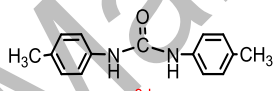
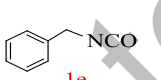
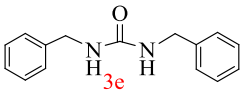
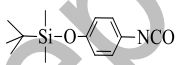
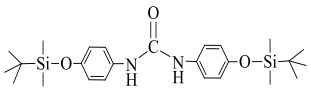
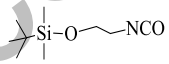
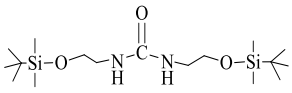
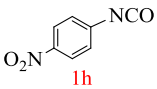
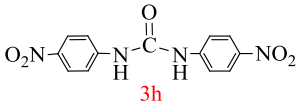
[15] (a) Valizadeh, H.; Dinparast, L. Monatsh. Chem. **2012**, *143*, 251–254; (b) Anderson, J. C.; Moreno, R. B. *Org. Biomol. Chem.* **2012**, *10*, 1334–1338; (c) Gadgea, S. T.; Kusumawatib, E. N.; Haradac, K.; Sasakic, T.; Nishio-Hamaned, D.; Bhanagea, B. M. *J. Mol. Catal. A: Chem*. **2015**, *400*, 170–178; (d) Li, P. F.; Cheng, G. L.; Zhang, H.; Xu, X. X.; Gao, J. Y.; Cui, X. L. *J. Org. Chem.* **2014**, *79*, 8156–8162.

[16] Pasha, M. A.; Reddy, M. B. M. *Synth. Commun*. **2009**, *39*, 2928–2934.

[17] Guan, Z.-H.; Lei, H.; Chen, M.; Ren, Z.-H.; Bai, Y.; Wang, Y.-Y. *Adv. Synth. Catal.* **2012**, *354*, 489–496.

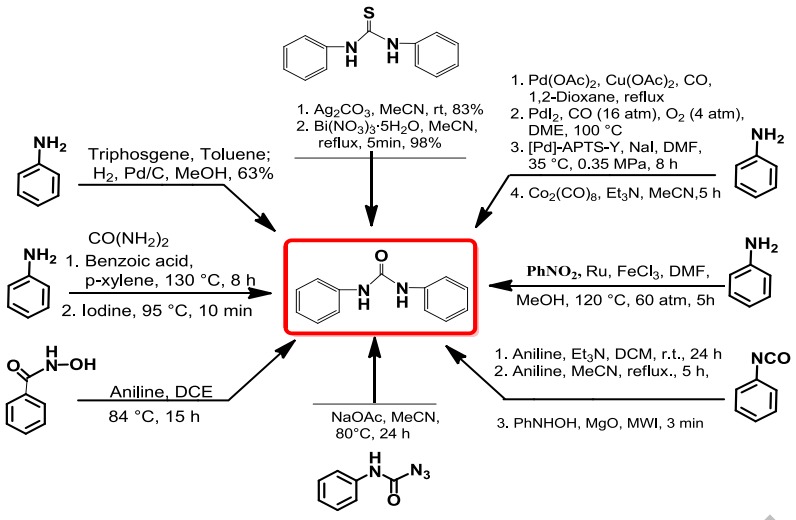
[18] Wu, X. X.; Niu, Q. F.; Li, T. D. *Sensor. Actuat. B Chem.* **2016**, *222*, 714–720.

Table 1. Synthesis of disubstituted ureas **3** using isocyanates and Me_3SiOH.[a]

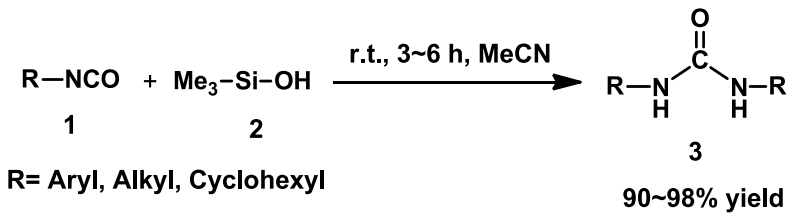
Entry	Substrate	Product	Yield (%)[d]
1[c]	 1a	 3a	92
2[b]	 1b	 3b	95
3[c]	 1c	 3c	91
4[b]	 1d	 3d	98
5[b]	 1e	 3e	94
6[c]	 1f	 3f	96
7[c]	 1g	 3g	90
8[e]	 1h	 3h	NR

[a]Reaction conditions: isocyanates (**1**, 1.0 equiv.) and trimethylsilanol (**2**, 1.0 equiv.) were reacted at room temperature; [b] 3 h; [c] 6 h; [d] isolated yields;[e] No reaction.

Scheme 1. The conventional procedures for synthesis of substituted ureas in literature.



Scheme 2. One-pot synthesis of substituted ureas **3** from isocyanates in the presence of trimethylsilanol.



Scheme 3 The proposed reaction mechanism of disubstituted ureas **3**.