Iron-Catalyzed Reaction of Urea with Alcohols and Amines: A Safe Alternative for the Synthesis of Primary Carbamates

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A general study of the iron-catalyzed reaction of urea with nucleophiles is here presented. The carbamoylation of alcohols allows for the synthesis of N-unsubstituted (primary) carbamates, including present drugs (Felbamate and Meprobamate), without the necessity to apply phosgene and related derivatives. Using amines as nucleophiles gave rise to the respective mono- and disubstituted ureas via selective transamidation reaction. These atom-economical transformations provide a direct and selective access to valuable compounds from cheap and readily available urea using a simple Lewis-acidic iron(II) catalyst.
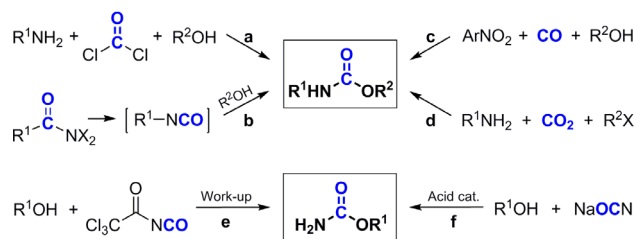
Introduction

Development of efficient and low-cost methodologies is becoming more and more relevant for the synthesis of fine chemicals and advanced building blocks.[1] Whereas traditional organic synthesis focused mainly on high-yield procedures, modern protocols demand improvements in terms of sustainability, waste prevention, and toxicity.[2] Obviously, greener methodologies should replace hazardous reagents by more eco-friendly resources. In addition, it is highly desired to improve the step-economy and increase the atom efficiency of a given transformation, thus minimizing the amount of residues.

Advantageously, compared to stoichiometric reactions, catalysis offers a tool for controlling the reactivity and selectivity of the substrates.[3] In recent years, iron-based catalysts are of particular interest owing to their low toxicity and high abundance. For example, a variety of iron salts are easily available at low prices, being effectively applied to the development of several catalytic processes.[4] In this regard, we herein propose to study the iron-catalyzed reaction of urea with common nucleophiles. Initially, we focused on the synthesis of primary carbamates from simple alcohols and urea, two cheap and non-toxic substrates. The resulting products represent an important class of compounds showing various interesting properties. Notably, they are applied on large scale in industry as ingredients of agrochemicals (i.e., herbicides, fungicides, and pesticides),[5] pharmaceuticals,[6] as well as precursors in polymer synthesis (polyurethanes and peptides).[7] Furthermore, such compounds are present in biologically active natural products and have recently gained importance in the field of drug design.[8] Moreov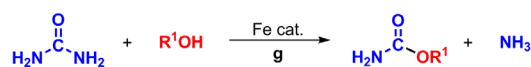er, this moiety plays an important role in many useful transformations. For example, carbamates are frequently used in organic synthesis as protecting groups for amines owing to high stability towards acids, bases, and hydrogenation.[9]

Among numerous conventional processes for the synthesis of carbamates,[10] the most widely applied involves the use of highly corrosive and toxic phosgene or its derivatives (Scheme 1a).[11] Alternative catalytic protocols have been subsequently developed, such as rearrangement reactions through isocyanate intermediates (Hoffmann, Curtius, Lossen),[12] reductive carbonylation of nitroaromatics,[13] or carboxylation of amines with CO_2 in presence of electrophilic agents or alcohols (Scheme 1b–d).[14] However, all these strategies cannot be easily applied to the synthesis of N-unsubstituted (primary) carbamates. In this case, traditional methods are focused on the reaction of alcohols with organic isocyanates or cyanate salts (Scheme 1e–f).[15] Such procedures present drawbacks, such as the preparation of carbamoylation agents from toxic precursors or the requirement of specific acidic catalysts. In this context, a benign alternative for the synthesis of primary carba-

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Scheme 1. Conventional procedures for the synthesis of N-substituted and primary carbamates. Iron-catalyzed reaction of urea with alcohols.

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mates would be the catalytic reaction of urea with alcohols (Scheme 1g). Limited precedents of this transformation have been published using polyphosphoric acid-, PbO-, BF$_3$- or Pd-catalyzed methodologies, although they are exclusively applied to the preparation of methyl carbamate and N-protected derivatives.[16] For the first time, we describe a general iron-catalyzed substitution reaction of urea with hydroxy- and amino-based nucleophiles for the synthesis of a variety of primary carbamates and unsymmetrical ureas.

Results and Discussion

Initially, we studied the reaction of urea (1) with 1-undecanol (2a) as a model system. To our delight, the treatment of 0.5 mmol of 1 with 3 equivalents of 2a in the presence of 4 mol% of FeBr$_2$ in tert-amyl alcohol at 150°C for 18 h provided undecyl carbamate (3a) selectively in a good 76% yield (Table 1, entry 1).[17] Despite the excess of alcohol used, the nucleophilic substitution on urea only takes place once, so the formation of the corresponding acyclic carbonate is completely avoided.[18]

Next, we optimized this reaction owing to the high selectivity observed. Performing the experiment in toluene gave a slightly better 81% yield, whereas the use of 1,4-dioxane afforded 3a in 92% yield (Table 1, entries 2 and 3). Different iron salts showed good reactivity, although we selected FeBr$_2$ as optimal pre-catalyst (Table 1, entries 4–8). Then, we varied the ratio urea/alcohol since only monosubstitution was detected. In this way, the reaction of urea with 1.5 equivalents of 2a allowed the synthesis of the desired product in a similar 89%
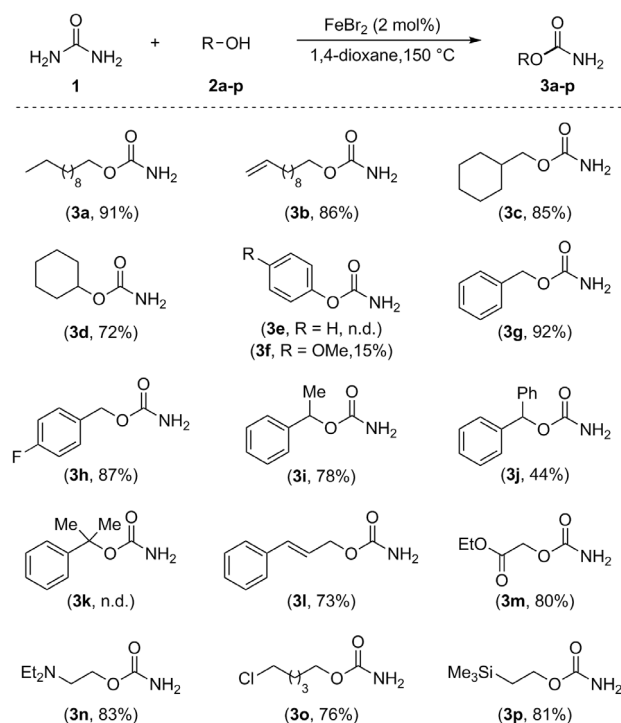
yield, while a different ratio implied a decrease of the effectivity (Table 1, entries 9–11). For further optimization we analyzed the effect of the catalyst loading and temperature. The reaction in the presence of 0.01 mmol of FeBr$_2$ provided the undecyl carbamate (3a) in an excellent 92% yield, but the use of higher catalyst loading did not yield a better result (Table 1, entries 12 and 13). Regarding the temperature, a considerable decrease of the reactivity was observed when the reaction was performed at 140°C, whereas the experiment at 130°C resulted in the same product in a moderate 48% yield (Table 1, entries 14 and 15). Finally, the reaction time could be reduced to 6 h, obtaining the desired product in 91% yield (Table 1, entry 16). Notably, the experiment in absence of catalyst proceeded slower providing 3a in much lower yield (45%).

Following, we extended the scope of this reaction by studying the reactivity of different alcohols under the previously developed best conditions [urea (0.5 mmol), alcohol (0.75 mmol), and FeBr$_2$ (0.01 mmol) in 1,4-dioxane at 150°C for 6 h]. As shown in Scheme 2, the reaction with alkyl alcohols 2b and 2c gave the corresponding N-unsubstituted carbamates in good 86 and 85% yield, respectively. Analogously, the treatment of urea with the more demanding secondary substrate 2d provided the desired cyclohexyl derivative 3d, in this case in a slightly lower 72% yield. On the other hand, the same experiment with phenol (2e) as nucleophile showed no conversion, whereas the use of a more electron-rich derivative, such as the 4-hydroxyanisol (2f), afforded the carbamate 3f in a low isolated yield (15%). Apparently, phenol is not nucleophilic enough

Table 1. Screening of reaction conditions for the iron-catalyzed synthesis of undecyl carbamate (3a) from urea (1) and 1-undecanol (2a).[a]

Entry	Catalyst	Solvent	T [°C]	Yield[b] [%]
1	FeBr$_2$	t-amyl alc.	150	76
2	FeBr$_2$	toluene	150	81
3	FeBr$_2$	1,4-dioxane	150	92
4	FeCl$_2$	1,4-dioxane	150	86
5	Fe(OAc)$_2$	1,4-dioxane	150	85
6	FeO	1,4-dioxane	150	90
7	FeBr$_3$	1,4-dioxane	150	89
8	Fe$_2$O$_3$	1,4-dioxane	150	87
9[c]	FeBr$_2$	1,4-dioxane	150	89
10[d]	FeBr$_2$	1,4-dioxane	150	89
11[e]	FeBr$_2$	1,4-dioxane	150	75
12[d,f]	FeBr$_2$	1,4-dioxane	150	92
13[d,g]	FeBr$_2$	1,4-dioxane	150	86
14[d,f]	FeBr$_2$	1,4-dioxane	140	75
15[d,f]	FeBr$_2$	1,4-dioxane	130	48
16[d,f,h]	FeBr$_2$	1,4-dioxane	150	91

[a] Unless otherwise specified, all reactions were carried out with catalyst (0.02 mmol), urea (1, 0.5 mmol), and 1-undecenol (2a, 1.5 mmol) in a solvent (1 mL) at the indicated temperature for 18 h. [b] Isolated yields. [c] 2a (1.0 mmol). [d] 2a (0.75 mmol) [e] 2a (0.6 mmol). [f] Catalyst (0.01 mmol). [g] Catalyst (0.03 mmol). [h] Reaction time: 6 h.

Scheme 2. Iron-catalyzed synthesis of carbamates (3) from urea (1) and alcohols (2). [a] Reactions performed with FeBr$_2$ (0.01 mmol), urea (1, 0.5 mmol), and alcohol (2a–p, 0.75 mmol) in 1,4-dioxane (1 mL) at 150°C for 6 h. [b] Isolated yields. n.d.: not detected.

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to perform efficiently the substitution reaction on the iron-activated urea, a factor that can be modulated by the introduction of electron-donor groups. Benzyl derivatives provided the desired products in excellent yields, allowing even the introduction of electron-withdrawing groups without lack of effectiveness (3g–h, 92 and 87% yield, respectively). Gratifyingly, the reaction of urea with the more sterically hindered 1-phenylethanol (2i) gave place to the product 3i in a bit lower 78% yield. However, the introduction of a second phenyl group at the nucleophile led to a drastic decrease of the conversion, and the reaction with diphenylmethanol (2j) only afforded the corresponding primary carbamate in 44% isolated yield. Relatedly, the product expected from the reaction of urea with the tertiary alcohol 2k was not detected.

Alternatively, this transformation takes place with allyl alcohols. Thus, cinnamyl alcohol (2l) gave rise to allyl carbamate 3l in a good yield (73%). Then, we tested alcohols presenting heteroatoms in their structure. In this way, ethyl glycolate (2m) was effectively converted into the desired product 3m in 80% yield. Besides to the ester group, this reaction also tolerates functional groups, such as tertiary amines, halides, or silanes. Hence, the iron-catalyzed treatment of urea with alcohols 2n–p afforded the respective carbamates in good yields and selectivities (3n–p, 76-83%). Unfortunately, corresponding thiols showed no conversion under the same reaction conditions. In general, all these reactions showed to be highly selective towards the synthesis of primary carbamates producing only one equivalent of ammonia as stoichiometric residue. This selectivity and the possibility of using differently substituted alcohols provide an added value to this methodology.

To increase the versatility of this protocol, we tested different electrophiles in the iron-catalyzed reaction with 1-undecenol (2a). Initially, we proposed the use of N-monosubstituted ureas to study the potential formation of N-substituted carbamates. Unfortunately, the reaction of 2a (0.75 mmol) with N-tert-butylurea (4a, 0.5 mmol) under FeBr$_2$ catalysis (0.01 mmol) in 1,4-dioxane at 150°C, led to a mixture of products. The corresponding N-tert-butylcarbamate 7a was obtained in 49% yield, whereas the formation of the corresponding product 3a was observed in 40% yield (Table 2, entry 1). The use of benzylurea (4b) afforded a similar result (Table 2, entry 2). However, when phenlyurea (4c) was used as electrophile, the N-phenyl substituted carbamate 7c was obtained in a good yield (80%; Table 2, entry 3). Here, 3a was isolated in only 15% yield, which demonstrates the lower reactivity of aniline to act as leaving group. At that point, we investigated the synthesis of thiocarbamates, but the reaction of 1-undecenol (2a) with thiourea (5) showed no conversion (Table 2, entry 4). Apparently, in this case the iron(II) bromide is unable to activate the electrophile by coordination to the sulfur atom, disfavoring the nucleophilic substitution. On the other hand, the iron-catalyzed transcarbamoylation reaction using different substituted carbamates (6a–c) works well.[19] As shown in Table 2 (entries 5–7), this latter transformation provided the primary carbamate 3a in excellent yields using either O-methyl, -benzyl, and -phenyl carbamates. In this case a competitive substitution reaction between the starting alcohol and the leaving group can take
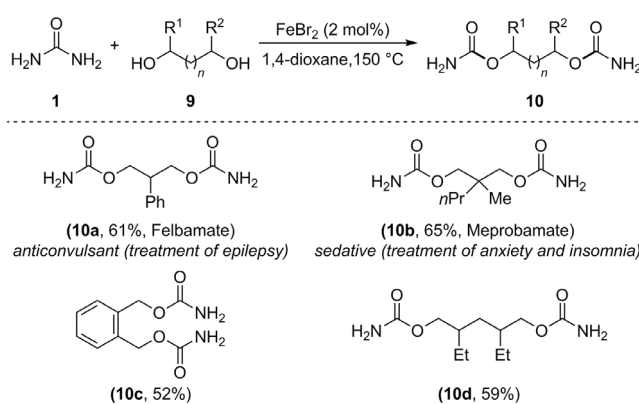
Table 2. Iron-catalyzed reaction of 1-undecenol (2a) with different substituted ureas and carbamates (4–6).[a]

Entry	Electrophile structure	R	label	Product structure	label	yield[b] [%]
1	RHN–(C=O)–NH$_2$	tBu	4a		7a	49[c]
2		Bn	4b	(NHR carbamate)	7b	31[d]
3		Ph	4c		7c	80[e]
4	H$_2$N–(C=S)–NH$_2$	–	5	(NH$_2$ thiocarbamate)	8	n.d.[f]
5	RO–(C=O)–NH$_2$	Me	6a		3a	84
6		Bn	6b	(NH$_2$ carbamate)	3a	83
7		Ph	6c		3a	97

[a] Unless otherwise specified, all reactions were carried out with FeBr$_2$ (0.01 mmol), urea or carbamate (4–6, 0.5 mmol), and 1-undecenol (2a, 0.75 mmol) in 1,4-dioxane (1 mL) at 150°C for 6 h. [b] Isolated yields. [c] 3a was isolated in 40% yield. [d] 3a was isolated in 27% yield. [e] 3a was isolated in 15% yield. [f] n.d.: not detected.

place, but 1-undecenol was shown to be more reactive in all examples. Since aromatic alcohols are not active in this transformation as discussed above, the use of phenyl carbamate (6c) afforded 3a in quantitative yield.

For practical applications the use of diols as nucleophiles on our process is highly interesting, since the resulting bifunctional products are valuable building blocks for polymers/oligomers (Scheme 3). Notably, these substrates might promote also an intramolecular reaction to afford the cyclic carbonate. In fact, the reaction of urea (1, 0.5 mmol) with 2-phenyl-1,3-propanediol (9a, 0.75 mmol) under FeBr$_2$ catalysis (0.01 mmol) gave a mixture of the respective mono- and dicarbamates. Owing to the biological relevance of 10a, an anticonvulsant drug used for the treatment of epilepsy (Felbamate),[20] we optimized this reaction to favor its synthesis. In this way, the use of 2.0 mmol of urea and 0.5 mmol of 9a in the presence of
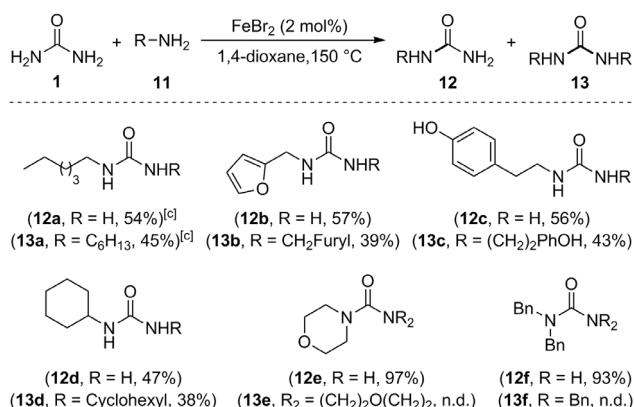

(10a, 61%, Felbamate)
anticonvulsant (treatment of epilepsy)

(10b, 65%, Meprobamate)
sedative (treatment of anxiety and insomnia)

(10c, 52%)

(10d, 59%)

Scheme 3. Iron-catalyzed reaction of urea (1) with diols (9). [a] Reactions performed with FeBr$_2$ (0.02 mmol), urea (1, 2.0 mmol), and diol (9a–d, 0.5 mmol) in 1,4-dioxane (1 mL) at 150°C for 6 h. [b] Isolated yields.

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0.02 mmol of iron(II) bromide afforded **10a** in 61% yield, together with 22% of the monocarbamate as a side product. Interestingly, the related 6-membered cyclic carbonate was not detected. An increase of the catalyst loading, temperature, and reaction times, as well as higher amounts of urea, did not yield better efficiency. Analogously, Meprobamate (**10b**),[21] was synthesized following the same procedure. This product is a sedative used for the treatment of anxiety and insomnia. It was prepared from urea and the corresponding 1,3-diol **9b** in 65% yield (Scheme 3). Classical methodologies for the synthesis of such bioactive compounds generally involve a two-step sequence starting from the same diols. In this case, the formation of a sensitive and toxic chloroformate is followed by treatment with ammonia. Advantageously, here their synthesis is accomplished in one step using an eco-friendly iron-catalyzed methodology from cheap urea as the carbamoylation agent. We applied this methodology to different-sized diols. Thus, substrates **9c** and **9d** were converted into the respective primary biscarbamates in moderate yields (**10c–d**, 52 and 59%, respectively; Scheme 3).

Finally, we were interested to use amines as nucleophiles instead of alcohols (Scheme 4). Obviously, the corresponding iron-catalyzed transamidation reaction would allow accessing different substituted ureas,[22] structures with several applications in organic chemistry, in a straightforward and convenient manner. With this aim, we analyzed the reaction of urea (**1**, 0.5 mmol) with hexylamine (**11a**, 0.75 mmol) under the previously optimized conditions. In this case, the monosubstituted urea **12a** was isolated in 47% yield (0.23 mmol), whereas the double substitution was also favored affording 70% yield of the 1,3-dihexylurea (**13a**, 0.26 mmol of a maximum of 0.375 mmol).
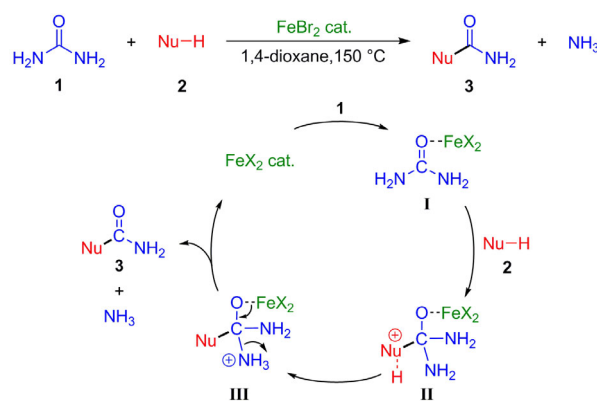
To improve the selective formation of unsymmetrically substituted ureas, we decreased the concentration of the amine substrate and performed an experiment using a 1:1 ratio urea/amine obtaining **12a** in 54% yield and **13a** in 45% yield (Scheme 4). Similarly, furfurylamine **11b** afforded the mono-

substituted compound in comparable yield (57%). Interestingly, using 4-hydroxyphenethylamine (**11c**) containing both amino and hydroxyl groups this iron-catalyzed nucleophilic substitution selectively leads to 1- and 1,3-disubstituted ureas **12c** and **13c** in 56 and 43% yields, respectively. Cyclohexylamine **11d** performed analogously. To our delight, transformations with secondary amines, such as morpholine (**11e**) and dibenzylamine (**11f**), provided the corresponding unsymmetrical ureas **12e–f** in excellent yields (97 and 93%, respectively). Here, the second nucleophilic substitution is completely avoided under the used reaction conditions.

As depicted in Scheme 5, we propose the following mechanism for the iron-catalyzed reaction of urea with nucleophiles. Urea (**1**) is initially activated by O-coordination to the iron cata-

Scheme 5. Proposed mechanism for the iron-catalyzed reaction of urea with nucleophiles.

lyst, which acts as Lewis acid. Subsequently, the nucleophile **2**, probably also activated by hydrogen bonding, attacks the carbonyl carbon of intermediate I giving place to species II. Migration of a proton from nucleophile to an amino group affords intermediate III, which after dissociation of the iron catalyst and elimination of ammonia gives rise to the final product **3**.

Conclusions

We have developed a general methodology for iron-catalyzed reactions of urea with common nucleophiles. This straightforward nucleophilic substitution allows for the synthesis of primary carbamates and substituted ureas from simple alcohols and amines, respectively. In addition, the use of diols gives rise to double carbamoylations which makes bioactive compounds such as Felbamate and Meprobamate easily accessible. Applying a safe, inexpensive and less toxic iron(II) salts as catalyst, a high degree of selectivity is observed avoiding the formation of side products such as acyclic carbonates, oligo- or polymers. With the aim of enhancing this methodology, other valuable Lewis acids and microwave heating might be helpful for future applications.

Scheme 4. Iron-catalyzed reaction of urea (**1**) with amines (**11**). [a] Reactions performed with FeBr$_2$ (0.01 mmol), urea (**1**, 0.5 mmol), and amines (**11a–f**, 0.5 mmol) in 1,4-dioxane (1 mL) at 150 °C for 6 h. [b] Isolated yields. [c] Reaction performed with 0.75 mmol of **11a** gave 47% yield of **12a** and 70% yield of **13a**. n.d.: not detected.

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Experimental Section

General information. Unless otherwise is stated, all reactions were conducted under an argon atmosphere with exclusion of moisture from reagents and glassware using standard techniques for manipulation air sensitive compounds. Reaction temperatures refer to external bath temperatures. TLC was effected on silica gel 60 F_{254} (layer thickness 0.2 mm) and components were located by observation under UV light and/or by treating the plates with a phosphomolybdic acid, or *p*-anisaldehyde reagent followed by heating. Column chromatography was performed on silica gel (230–400 mesh) using 30% ethyl acetate/heptane or 10% methanol/dichloromethane as eluent. NMR spectra were performed in a Bruker Avance 400 spectrometer using the residual solvent signal as internal standard [chloroform: 7.26 ppm (^{1}H), 77.0 ppm (^{13}C)]. All measurements were carried out at room temperature unless otherwise stated, and DEPT was used to assign carbon types. Mass spectra were in general recorded on a MAT 95XP or a HP 5973N mass selective detector. Gas chromatography was performed on a HP 6890N chromatograph with a HP5 column. Unless otherwise statement, commercial reagents were used as received without purification.

General procedure for the iron-catalyzed reaction of urea with alcohols. In a glass pressure tube (25 mL) under an Ar atmosphere, $FeBr_2$ (2.2 mg, 0.01 mmol), urea (30.1 mg, 0.5 mmol) and alcohol (0.75 mmol) were dissolved in 1,4-dioxane (1 mL). Next the pressure tube was closed and the resulting mixture was stirred at 150 °C in an oil bath for 6 h. After cooling down to room temperature, the crude was directly purified by flash chromatography on silica gel to afford, after concentration and high-vacuum drying, the corresponding products in the reported yields.

Acknowledgements

[1] a) A. D. Patel, K. Meesters, H. den Uil, E. de Jong, K. Blok, M. K. Patel, *Energy Environ. Sci.* **2012**, *5*, 8430–8444; b) C. Jiménez-González, C. S. Ponder, Q. B. Broxterman, J. B. Manley, *Org. Process Res. Dev.* **2011**, *15*, 912–917; c) R. Ballini, *Eco-Friendly Synthesis of Fine Chemicals*, Royal Society of Chemistry, Oxford, **2009**; d) C. A. M. Afonso, J. G. Crespo, *Green Separation Processes: Fundamentals and Applications*, Wiley-VCH, Weinheim, Germany, **2005**; e) M. Eissen, J. O. Metzger, E. Schmidt, U. Schneidewind, *Angew. Chem. Int. Ed.* **2002**, *41*, 414–436; *Angew. Chem.* **2002**, *114*, 402–425.

[2] a) R. A. Sheldon, *Chem. Soc. Rev.* **2012**, *41*, 1437–1451; b) K. Sanderson, *Nature* **2011**, *469*, 18–20; c) P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301–312; d) M. Gupta, S. Paul, R. Gupta, *Curr. Sci.* **2010**, *99*, 1341–1360; e) C.-J. Li, B. M. Trost, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 13197–13202; f) P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, **1998**.

[3] a) I. Delidovich, R. Palkovits, *Green Chem.* **2016**, *18*, 590–593; b) R. A. Sheldon, I. W. C. E. Arends, U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, Germany, **2007**; c) P. T. Anastas, M. M. Kirchhoff,

T. C. Williamson, *Appl. Catal. A* **2001**, *221*, 3–13; d) R. A. Sheldon, *J. Chem. Technol. Biotechnol.* **1997**, *68*, 381–388.

[4] a) I. Bauer, H.-J. Knölker, *Chem. Rev.* **2015**, *115*, 3170–3387; b) *Topics in Organometallic Chemistry-Iron Catalysis: Fundamentals and Applications* (Ed.: B. Plietker), Springer, Berlin, **2011**; c) L.-X. Liu, *Curr. Org. Chem.* **2010**, *14*, 1099–1126; d) *Iron Catalysis in Organic Chemistry* (Ed.: B. Plietker), Wiley-VCH, Weinheim, Germany, **2008**; e) S. Enthaler, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2008**, *47*, 3317–3321; *Angew. Chem.* **2008**, *120*, 3363–3367.

[5] a) K. Ganske, C. Wiegand, U.-C. Hipler, T. Heize, *Macromol. Biosci.* **2015**, DOI: 10.1002/mabi.201500324; b) *The Pesticide Manual 16th Edition* (Ed.: C. MacBean), BCPC Publications, Hampshire, UK, **2012**; c) T. Goto, Y. Ito, S. Yamada, H. Matsumoto, H. Ok, H. Nagase, *Anal. Chim. Acta* **2006**, *555*, 225–232; d) J. Ma, N. Lu, W. Qin, R. Xu, Y. Wang, X. Chen, *Eco-toxicol. Environ. Saf.* **2006**, *63*, 268–274; e) H. Buschhaus, *Fungicides, Carbamates. Encyclopedia of Agrochemicals*; Wiley, Weinheim, Germany, **2003**.

[6] a) J. C. Verheijen, K. A. Wiig, S. Du, S. L. Connors, A. N. Martin, J. P. Ferreira, V. I. Slepnev, U. Kochendörfer, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3243–3246; b) S. M. Rahmathullah, R. R. Tidwell, S. K. Jones, J. E. Hall, D. W. Boykin, *Eur. J. Med. Chem.* **2008**, *43*, 174–177; c) S. Ray, S. R. Pathak, D. Chaturvedi, *Drugs Future* **2005**, *30*, 161–180; d) B. Testa, J. M. Mayer, *Hydrolysis in Drug and Prodrug Metabolism-Chemistry, Biochemistry and Enzymology*, Wiley-VCH, Weinheim, Germany, **2003**.

[7] a) R. H. Heyn, I. Jacobs, R. H. Carr, *Adv. Inorg. Chem.* **2014**, *66*, 83–115; b) O. Kreye, H. Mutlu, M. A. R. Meier, *Green Chem.* **2013**, *15*, 1431–1455; c) B. Husár, R. Liska, *Chem. Soc. Rev.* **2012**, *41*, 2395–2405; d) S. Neffgen, J. Kusan, T. Fey, H. Keul, H. Höcker, *Macromol. Chem. Phys.* **2000**, *201*, 2108–2114; e) D. Feldman, A. Barbalata, *Synthetic Polymers, Technology, Properties, Applications*, Chapman and Hall, London, **1996**, pp. 273.

[8] a) D. Chaturvedi, *Role of Organic Carbamates in Anticancer Drug Design, in Chemistry and Pharmacology of Naturally Ocurring Bioactive Compounds, 1st ed.* (Ed.: G. Brahmachari), Taylor&Francis Group, Boca Raton, **2013**; b) A. K. Ghosh, M. Brindisi, *J. Med. Chem.* **2015**, *58*, 2895–2940; c) K. Miller, B. Neilan, D. M. Y. Sze, *Recent Pat. Anti-Cancer Drug Discovery* **2008**, *3*, 14–19; d) S. J. Shaw, *Mini-Rev. Med. Chem.* **2008**, *8*, 276–284; e) S. Ray, D. Chaturvedi, *Drugs Future* **2004**, *29*, 343–358.

[9] a) A. Isidro-Llobet, M. Álvarez, F. Albericio, *Chem. Rev.* **2009**, *109*, 2455–2504; b) T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis, 4th ed.*, Wiley, New York, **2007**; c) P. J. Kocienski, *Protective Groups, 3rd ed.*, Thieme, Stuttgart, **2003**.

[10] For reviews on synthesis of carbamates, see: a) D. Chaturvedi, *Tetrahedron* **2012**, *68*, 15–45; b) M. Carafa, E. Quarante, *Mini-Rev. Org. Chem.* **2009**, *6*, 168–183; c) D. Chaturvedi, N. Mishra, V. Mishra, *Curr. Org. Synth.* **2007**, *4*, 308–320.

[11] a) V. A. Vaillard, M. González, J. P. Perotti, R. J. Grau, S. E. Vaillard, *RSC Adv.* **2014**, *4*, 13012–13017; b) P. A. Duspara, M. S. Islam, A. J. Lough, R. A. Batey, *J. Org. Chem.* **2012**, *77*, 10362–10368; c) L. Cotarca, P. Delgu, A. Mardelli, V. Sunjuc, *Synthesis* **1996**, 553–576; d) B. R. Neustadt, *Tetrahedron Lett.* **1994**, *35*, 379–380; e) H. J. Twitchett, *Chem. Soc. Rev.* **1974**, *3*, 209–230.

[12] a) F. Hamon, G. Prie, F. Lecornue, S. Papot, *Tetrahedron Lett.* **2009**, *50*, 6800–6802; b) P. Dubé, N. F. F. Nathel, M. Vetelino, M. Couturier, C. L. Aboussafy, S. Pichete, M. L. Jorgensen, M. Hardink, *Org. Lett.* **2009**, *11*, 5622–5625; c) A. Palmieri, S. V. Ley, K. Hammond, A. Polyzos, I. R. Baxendale, *Tetrahedron Lett.* **2009**, *50*, 3287–3289; d) P. Gogoi, D. Konwar, *Tetrahedron Lett.* **2007**, *48*, 531–533; e) T. Nishikawa, D. Urabe, M. Tomita, T. Tsujimoto, T. Iwabuchi, M. Isobe, *Org. Lett.* **2006**, *8*, 3263–3265; f) H. Lebel, O. Leogane, *Org. Lett.* **2005**, *7*, 4107–4110; g) E. W. Wallis, J. F. Lane, *Org. React.* **1946**, *3*, 267–306; h) A. A. S. Smith, *Org. React.* **1946**, *3*, 337–449.

[13] a) S. T. Gadge, B. M. Bhanage, *RSC Adv.* **2014**, *4*, 10367–10389; b) F. Ragaini, C. Cognolato, M. Gasperini, S. Cenini, *Angew. Chem. Int. Ed.* **2003**, *42*, 2886–2889; *Angew. Chem.* **2003**, *115*, 2992–2995; c) F. Shi, Y. He, D. Li, Y. Ma, Q. Zhang, Y. Deng, *J. Mol. Catal. A* **2006**, *244*, 64–67; d) A. M. Tafesh, J. Weiguny, *Chem. Rev.* **1996**, *96*, 2035–2052; e) S. Cenini, C. Crotti, M. Pizzoti, F. Porta, *J. Org. Chem.* **1988**, *53*, 1243–1250.

[14] a) R. A. Watile, B. M. Bhanage, *RSC Adv.* **2014**, *4*, 23022–23026; b) M. Zhang, X. Zhao, S. Zheng, *Chem. Commun.* **2014**, *50*, 4455–4458; c) S. L. Peterson, S. M. Stucka, C. J. Dinsmore, *Org. Lett.* **2010**, *12*, 1340–1343; d) A. Ion, C. Van Doorslaer, V. Parvulescu, P. Jacobs, D. De Vos, *Green Chem.* **2008**, *10*, 111–116; e) D. Chaturvedi, S. Ray, *Curr. Org. Chem.*

2007, *11*, 987–998; f) C. B. Dell'Amico, F. Calderazzo, L. Labella, F. Marchetti, G. Pampaloni, *Chem. Rev.* **2003**, *103*, 3857–3898; g) R. N. Salvatore, F. Chu, A. S. Nagle, E. A. Kapxhiu, R. M. Cross, *Tetrahedron* **2002**, *58*, 3329–3347; h) M. Abla, J. C. Choi, T. Sakakura, *Chem. Commun.* **2001**, 2238–2239.

[15] a) A. R. Sardarian, I. D. Inaloo, *RSC Adv.* **2015**, *5*, 76626–76641; b) A. R. Modarresi-Alam, F. Khamooshi, M. Nasrollahzadeh, H. A. Amirazizi, *Tetrahedron* **2007**, *63*, 8723–8726; c) A. R. Modarresi-Alam, M. Nasrollahzadeh, F. Khamooshi, *ARKIVOC* **2007**, *XVI*, 238–245; d) A. R. Modarresi-Alam, M. Rostamizahed, P. Najafi, *Turk. J. Chem.* **2006**, *30*, 269–276; e) Y. Ichikawa, M. Osada, I. I. Ohtani, M. Isobe, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1449–1456; f) P. Kočovský, *Tetrahedron Lett.* **1986**, *27*, 5521–5524.

[16] a) L. Dou, X. Zhao, H. An, G. Wang, Y. Wang, *Ind. Eng. Chem. Res.* **2013**, *52*, 4408–4413; b) F. Qin, Q. Li, J. Wang, Y. Feng, M. Kang, Y. Zhu, X. Wang, *Catal. Lett.* **2008**, *126*, 419–425; c) J. Sun, B. Yang, H. Lin, *Chem. Eng. Technol.* **2004**, *27*, 435–439; d) J. Wang, Q. Li, W. Dong, M. Kang, X. Wang, S. Peng, *Appl. Catal. A* **2004**, *261*, 191–197; e) N. V. Kaminskaia, N. M. Kostić, *Inorg. Chem.* **1998**, *37*, 4302–4312.

[17] Reaction conditions based on our previous work on the iron-catalyzed synthesis of five-membered cyclic carbonates from vicinal diols: M. Peña-López, H. Neumann, M. Beller, *Eur. J. Org. Chem.* **2016**, DOI: 10.1002/ejoc.201600476.

[18] For examples on acyclic carbonate synthesis from urea and alcohols, see: a) P. Wang, S. Liu, F. Zhou, B. Yang, A. S. Alshammari, Y. Deng, *RSC Adv.* **2015**, *5*, 19534–19540; b) Z. Hou, L. Luo, K. Liu, Y. Wang, L. Dai, *Chem. Eng. J.* **2014**, *236*, 415–418; c) X. Wu, M. Kang, Y. Yin, F. Wang, N. Zhao, F. Xiao, W. Wei, Y. Sun, *Appl. Catal. A* **2014**, *473*, 13–20; d) D. Wang, B. Yang, X. Zhai, L. Zhou, *Fuel Process. Technol.* **2007**, *88*, 807–812.

[19] For examples on transcarbamoylation between alcohols and carbamates, see: a) Y. Ichikawa, Y. Morishita, S. Kusaba, N. Sakiyama, Y. Matsuda, K. Nakano, H. Kotsuki, *Synlett* **2010**, 1815–1818; b) B. Jousseaume, C. Laporte, T. Toupance, J.-M. Bernard, *Tetrahedron Lett.* **2002**, *43*, 6305–6307.

[20] a) H.-R. Chang, C.-C. Kuo, *J. Med. Chem.* **2008**, *51*, 1534–1545; b) J. M. Rho, S. D. Donevan, M. A. Rogawski, *Ann. Neurol.* **1995**, *35*, 229–234; c) J. M. Rho, S. D. Donevan, M. A. Rogawski, *J. Pharmacol. Exp. Ther.* **1997**, *280*, 1383–1391; d) O. Devinsky, R. E. Faught, B. J. Wilder, A. M. Kanner, M. Kamin, L. D. Kramer, A. Rosenberg, *Epilepsy Res.* **1995**, *20*, 241–246; e) J. M. Rho, S. D. Donevan, M. A. Rogawski, *Ann. Neurol.* **1994**, *35*, 229–234; f) D. Walker, E. Babad, C. H. Tann, D. L. Kwok, K. A. Belski, L. Herczeg, *PCT Int. Appl.* WO94/06737A1, **1994**.

[21] a) L. A. Zawertailo, U. E. Busto, H. L. Kaplan, D. J. Greenblatt, E. M. Sellers, *J. Clin. Psychopharmacol.* **2003**, *23*, 269–280; b) C. Belzung, A. M. Le Guisquet, A. Agmo, *Pharmacol. Biochem. Behav.* **2000**, *65*, 465–474; c) R. E. Delong, J. W. Phillis, R. A. Barraco, *Eur. J. Pharmacol.* **1985**, *118*, 359–362; d) J. W. Phillis, R. E. Delong, *Eur. J. Pharmacol.* **1984**, *101*, 295–297; e) F. M. Berger, B. J. Ludwig, U.S. Patent 2724720A, **1955**; f) B. J. Ludwig, E. C. Piech, *J. Am. Chem. Soc.* **1951**, *73*, 5779–5781.

[22] For examples on transamidation of urea with amines, see: a) R. Zhang, L. Guo, J. Chen, H. Gan, B. Song, W. Zhu, L. Hua, Z. Hou, *ACS Sustainable Chem. Eng.* **2014**, *2*, 1147–1154; b) J.-W. Wu, Y.-D. Wu, J.-J. Dai, H.-J. Xu, *Adv. Synth. Catal.* **2014**, *356*, 2429–2436; c) M. Zhang, S. Imm, S. Bähn, L. Neubert, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2012**, *51*, 3905–3909; *Angew. Chem.* **2012**, *124*, 3971–3975.

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FULL PAPERS

RX = H$_2$N, RHN, RO
Nu−H = alcohol, diol, amine

30 examples
up to 97% yield

R^1 = Ph, R^2 = H, *Felbamate*
R^1 = nPr, R^2 = Me, *Meprobamate*

M. Peña-López, H. Neumann, M. Beller*

■■ – ■■

Iron-Catalyzed Reaction of Urea with Alcohols and Amines: A Safe Alternative for the Synthesis of Primary Carbamates

Iron-clad method: An iron-catalyzed reaction of urea with common nucleophiles is described. The synthesis of primary carbamates is accomplished by carbamoylation of alcohols, while a transamidation reaction with amines provides the respective substituted ureas. The use of readily available reagents and the application of a benign iron source make this atom-economical process a green and safe alternative for the synthesis of such valuable compounds.

These are not the final page numbers! ↗↗