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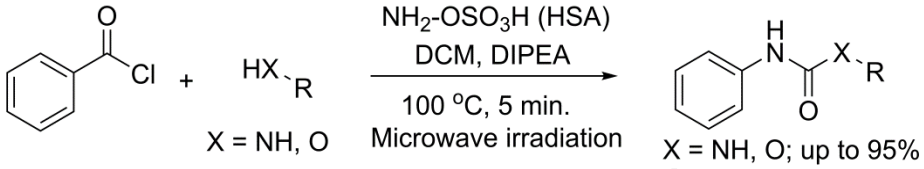

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An efficient one-pot synthesis of *N*,*N'*-disubstituted phenylureas and *N*-aryl carbamates using hydroxylamine-*O*-sulfonic acid

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ABSTRACT

We have developed an efficient one-pot method for the microwave-assisted synthesis of ureas and carbamates *via* a proposed Lossen rearrangement. Herein we report the first examples of the direct conversion of benzoyl chlorides into *N,N'*-disubstituted ureas and *N*-aryl carbamates using hydroxylamine-*O*-sulfonic acid as reagent. Using our general method, we have produced 11 examples of *N,N'*-disubstituted phenylureas in yields up to 95% using various substituted anilines, and primary and secondary amines. Additionally, we were able to generate a series of *N*-aryl carbamates in moderate yields using primary, secondary and tertiary alcohols.

1. Introduction

Ureas[1] (R-NHCONH-R') are a general class of heteroatomic compounds that have been shown to possess biological activity and serve as templates for numerous medicinal chemistry programs.[2] Historically, barbital (diethylmalonyl urea) was discovered in the early 1900's and was first used as the original commercially available barbiturate (sleep aid/hypnotic).[3] In the following century, urea functional groups have played an integral part in serving as a backbone motif for many drug discovery efforts. In fact, entire classes of therapeutic agents exist that possess ureas as a key functionality of the drug pharmacophore.[4] For instance, sulfonylureas are used to treat diabetes[5,6] and nitrosoureas serve as DNA alkylating agents for the treatment of cancer.[7,8] Several other urea-containing therapeutics also exist, such as the acylampicillins[9] (antibiotics), zileuton[10] (asthma), boceprevir[11] (HCV protease inhibitor) and sorafenib[12], regorafenib[13] (urea kinase inhibitors[14]), just to name a few.[15-18] As a result, ureas are a privileged motif in the field of medicinal chemistry and new methods for the synthesis of these biologically important functional groups are required to give efficient access to new drug candidates for medicinal chemistry programs. New methods for the synthesis of structurally similar carbamates (R-OCONH-R') are equally important to provide diversity, and biosimilar functional groups to ureas, in drug discovery programs.

Several methods currently exist for the synthesis of ureas, however, these protocols possess limitations as they rely on the use of potentially explosive reagents or require multiple synthetic steps and have primarily been synthesized *via* the *in situ* generation of acyl azides,[19] followed by a Curtius rearrangement,[20,21] Figure 1 A. Unfortunately, due to the use of highly toxic, and potentially explosive azidation reagents, these reactions pose a safety hazard and are difficult to perform on large scale, however some useful flow chemistry examples exist.[22] The use of transition metal catalyzed reactions for the synthesis of ureas has also been explored (Pd/C, XPhos, CO),[23] however, these reactions also require the use of potentially explosive aliphatic and aromatic azides. A Lossen rearrangement[21,24,25] is a general method for the generation of ureas and involves the conversion of hydroxamic acids into an isocyanate, followed by reaction with an amine, Figure 1 B. Unfortunately, these reactions require several synthetic and purification steps (generation of hydroxamic acid from commercially available carboxylic acids), and tend to have long reaction times.[26,27] Similarly, using small modifications of the above reactions and substituting an alcohol for the amine, many of these methods have also been used to generate analogous carbamates. As part of a general research program dedicated to the development of new synthetic methods, we set out to develop a method for the synthesis of ureas and carbamates that was safer (azide-free) and greener (fewer synthetic steps and metal-free conditions) than existing methods. We envisioned a microwave-

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assisted method that utilized hydroxylamine-*O*-sulfonic acid (HSA) as the key reagent that would enable the conversion of commercially available active acids into ureas (or carbamates), following addition of the corresponding amine (or alcohol, respectively), Figure 1 C. Previously, the McCubbin group had reported the use of HSA for the conversions of phenylboronic acids into the corresponding anilines.[28] As part of a collaboration, our group extended this work to include a method for the sonication and microwave-assisted primary amination of potassium aryltrifluoroborates and arylboronic acids.[29] We proposed that the use of HSA, following condensation with an acyl chloride, would generate an *O*-sulfonylhydroxamic acid intermediate that would undergo a Lossen rearrangement and form a reactive isocyanate *in situ*. Quenching this reactive intermediate with an amine/alcohol would result in unsymmetrical *N*,*N'*-disubstituted ureas or carbamates as a one-pot process. Overall, this proposed method would avoid the use of toxic and potentially explosive reagents, while also allowing for the development of a rapid and efficient one-pot process *via* microwave-assisted organic synthesis (MAOS).[30,31] To the best of our knowledge, a method has not appeared in the literature that outlines the directly conversion of benzoyl chlorides into *N*,*N'*-disubstituted ureas or carbamates using a hydroxylamine-*O*-sulfonic acid reagent, Figure 1 C, and the corresponding amine/alcohol. Typically, these types of conversions rely on the use of azidation reagents[32-34] or the generation of an activated leaving group using alternate reagents, such as *N*-acylbenzotriazoles,[35] ethyl 2-cyano-2-(4-nitrophenyl sulfonyloxyimino)acetate,[36] 1-propane phosphonic acid cyclic anhydride[37] or Heck reaction conditions[38]. Herein we are the first to report on the development of a general method for the synthesis of *N*,*N'*-disubstituted phenylureas and carbamates using hydroxylamine-*O*-sulfonic acid from benzoyl chloride (**1**) and various amines/alcohols, under microwave conditions.

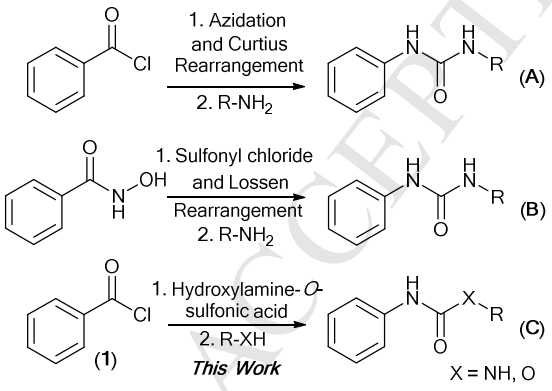
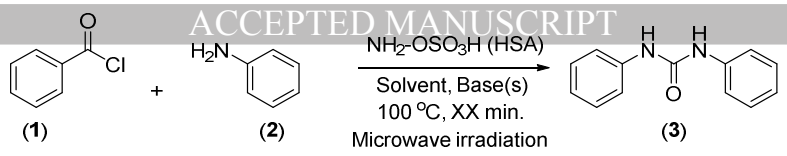


Fig 1. General methods for the synthesis of ureas and carbamates

2. Results and discussion

Our initial efforts into the development of a general method for this type of transformation centered on the use of HSA in the presence of benzoyl chloride and an amine. Representative examples of a survey of different reaction conditions for the development of an optimized method can be found in Table 1. We started by using the standard conditions developed previously for the primary amination of phenylboronic acids,[29] without the addition of any aniline **2**. Interestingly, we were able to generate the desired product in 26% isolated yield (following purification by column chromatography, Table 1, entry **a**), *via* incubating the reaction using microwave (MW) irradiation for 15 minutes at 100 ^{o}C. Following closer inspection, the result of the first step of this reaction leads to the formation of a reactive isocyanate generated *in situ* (Lossen rearrangement), and this result should not be that surprising. The subsequent reaction of the isocyanate with aqueous NaOH would simultaneously generate aniline **2** *in situ*, following the loss of CO_2. The newly generated aniline would then be free to react with an equivalent of the isocyanate and generate the desired symmetrical product. Removing the NaOH from these reaction conditions resulted in no product being generated, Table 1, entry **b**, however, adding 1.0 eq. of aniline to the newly formed isocyanate gave the product in 16% yield (Table 1, entry **c**, no water or NaOH). Recombining aqueous NaOH with an equivalent of aniline and HSA/DIPEA/benzoyl chloride in acetonitrile, Table 1, entry **d**, resulted in a moderate yield of 43%. Under these conditions, both a decrease and increase in the amount of DIPEA resulted in poorer yields, Table 1, entry **e** and **f**, respectively. Interestingly, removing aqueous NaOH from these last reaction conditions resulted in a doubling of the isolated yield, 50% versus 25% (entry **g** vs. **f**) while an additional increase of the amount of DIPEA to 6.0 eq. did not result in an appreciable increase in yield. In the next stage of surveying reaction conditions, various equivalents of benzoyl chloride and HSA were explored (entries **i** and **j**), along with various solvents, such as DCM and THF, concentrations and various temperatures and MW irradiation times, (not shown in totality in Table 1). Finally, the best reaction conditions were found to be, for the highest overall general yields, 1.25 eq. benzoyl chloride **1**, 1.0 eq., of aniline **2**, 1.5 eq. of HSA, in anhydrous DCM, at 100 ^{o}C for 5 minutes under microwave irradiation, entry **k**. These reaction conditions were used in all subsequent reactions as a general method for the synthesis of *N*,*N'*-disubstituted phenylureas and *N*-aryl carbamates.

The overall yields for the synthesis of different ureas *via* the condensation of HSA with benzoyl chloride under microwave conditions, followed by the reaction of the resultant isocyanate with various amines can be found in Table 2. Applying the general optimized reaction conditions to the synthesis of 1,3-diphenylurea using aniline as amine resulted in a 94% isolated yield following traditional column chromatography. In a practical sense, the reaction was performed by adding 1.5 eq. of HSA (a solid) to an oven dried microwave vial, followed by anhydrous DCM under argon with a rubber stopper. 4.0 eq. of DIPEA was added dropwise to the vial, and the HSA was stirred until dissolved (2-3 minutes). The benzoyl chloride was then added to the reaction *via* syringe and stirred for 2-3 minutes allowing for the formation of the *O*-sulfonyl hydroxamic acid. In the next stage of the one-pot sequence, 1.0 eq. of aniline was added to the vial *via* syringe, and the microwave vessel capped, and irradiated in the microwave to 100 ^{o}C for 5 minutes. Following the reaction, the crude reaction was placed in a larger round-bottom flask and pre-absorbed onto silica gel followed by immediate purification of the desired product by column chromatography, Table 2, entry **a**. For this particular reaction, the purified product appeared to contain an unidentified impurity and the purified product was triturated using cold chloroform and filtered through a PYREX 36060 fritted glass Buchner funnel (4-5.5 um, fine).

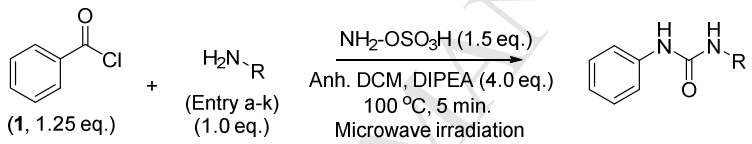


Scheme 1. Optimization reaction conditions for the synthesis of ureas

Table 1. Optimization reactions for the synthesis of 1,3-diphenylurea (**3**) using benzoyl chloride(**1**), aniline(**2**) and HSA (Scheme 1)

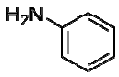
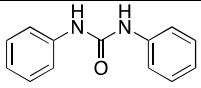
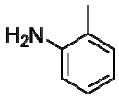
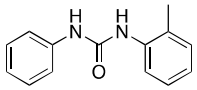
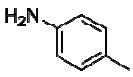
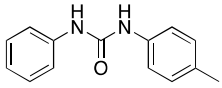
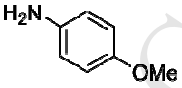
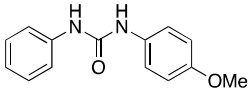
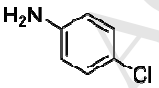
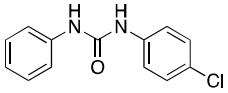
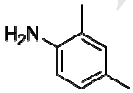
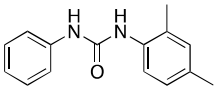
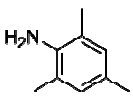
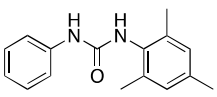
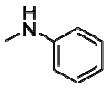
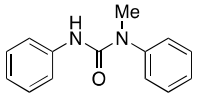
Entry	**1a**, **1b**, HSA (eq.)	Solvent	Base (eq.)	Base	MW (min.)	Yield %[a]
a	1.0, 0, 1.0	MeCN/H_2O	DIPEA (2.0)	NaOH	15	26
b	1.0, 0, 1.0	MeCN/H_2O	DIPEA (2.0)	--	15	--
c	1.0, 1.0, 1.0	MeCN	DIPEA (2.0)	--	15	16
d	1.0, 1.0, 1.0	MeCN/H_2O	DIPEA (2.0)	NaOH	15	43
e	1.0, 1.0, 1.0	MeCN/H_2O	DIPEA (1.0)	NaOH	15	7
f	1.0, 1.0, 1.0	MeCN/H_2O	DIPEA (4.0)	NaOH	15	25
g	1.0, 1.0, 1.0	MeCN	DIPEA (4.0)	--	15	50
h	1.0, 1.0, 1.0	MeCN	DIPEA (6.0)	--	15	53
i	1.2, 1.0, 1.0	MeCN	DIPEA (4.0)	--	5	54
j	1.2, 1.0, 1.2	MeCN	DIPEA (4.0)	--	5	46
k	1.25, 1.0, 1.5	DCM	DIPEA (4.0)	--	5	94[a](80)[b]

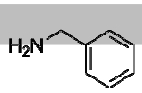
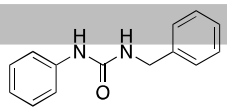
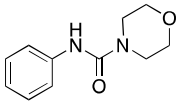
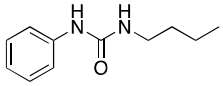
[a]Isolated yield following column chromatography (cc). [b]Isolated yield following trituration of cc purified product.



Scheme 2. General reaction conditions for the synthesis of *N,N'*-disubstituted ureas

Table 2. Synthesis of *N,N'*-disubstituted phenylureas using benzoyl chloride (**1**) and HSA (Scheme 2)

Entry	Amine	Product Name (**Compound #**)	Product Structure	Yield %[a]
a		1,3-Diphenylurea (**3**)		80[b]
b		*N*-(2-Methylphenyl)-*N'*-phenylurea (**4**)		80[b]
c		*N*-(4-Methylphenyl)-*N'*-phenylurea (**5**)		71[b]
d		*N*-(4-Methoxyphenyl)-*N'*-phenylurea (**6**)		68[b]
e		*N*-(4-Chlorophenyl)-*N'*-phenylurea (**7**)		52[b]
f		*N*-(2,4-Dimethylphenyl)-*N'*-phenylurea (**8**)		78
g		*N*-(2,4,6-Trimethylphenyl)-*N'*-phenylurea (**9**)		69
h		*N*-Methyl-*N,N'*-diphenylurea (**10**)		66

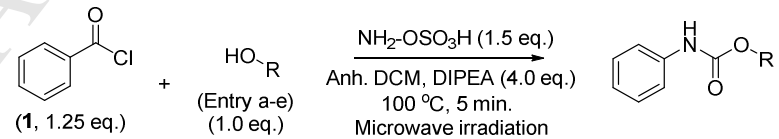
i		*N*-Benzyl-*N'*-phenylurea (**11**)		93
j		*N*-Phenyl-4-morpholinecarboxamide (**12**)		78
k		*N*-(Phenyl)-*N'*-butylurea (**13**)		95

[a]Isolated yield following column chromatography (cc). [b]Isolated yield following trituration of cc purified product.

The product was then collected once again and provided for an 80% isolated yield of 1,3-diphenylurea. For subsequent reactions, some of the products required trituration due the presence of an impurity following column chromatography (entries **a-e**) while others did not, (entries **f-k**). The yields are reported following trituration, and/or alone following the initial column chromatography stage. The NMR of the products can be found in the supplemental section and the associated purity (as inferred by the spectra) is representative of the yield following column chromatography, or trituration if required.

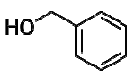
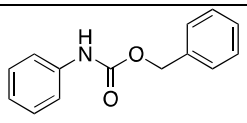
Table 2 summarizes the observed yields for the synthesis of *N,N'*-disubstituted phenylureas following addition of various amines. In comparison to aniline (80%), the substituted anilines gave similar or slightly diminished final isolated yields for electron donating substituents *ortho*-methyl (80%), *para*-methyl (71%), *para*-methoxy (68%), (for entries **b**, **c** and **d**, respectively). For the aniline containing an electron-withdrawing substituent, *para*-chloro, the yield was found to be the lowest overall at 52% following trituration. The use of 2,4-dimethyl- and 2,4,6-trimethylaniline was also explored under the general reaction conditions and found to give 78% and 69% yield, respectively (entries **f** and **g)**. The lower yield of the *ortho*-disubstituted aniline (entry **g**) is most likely a result of the reduced nucleophilicity of the aniline caused by steric hindrance and is not unexpected. Similarly, use of the secondary amine, *N*-methylaniline, also gave a similar yield of 66%. In the next entry (**i**), an amine that would be expected to serve as a stronger nucleophile (benzylamine) gave an excellent yield of 93%, while butylamine was found to give the highest overall yield of 95%. Morpholine, a secondary amine, was found to give a slightly diminished yield of 78%. Overall, from these 11 examples, it can be rationalized that the steric and electronic nature of the nucleophile from the corresponding amine would play a role in the overall yield of the reactions. The final stage of the reaction is a result of the nucleophilic addition of the amine, with the HSA/benzoyl chloride derived isocyanate, which would have an effect on the final yield. However, this step would normally be expected to occur relatively quickly.

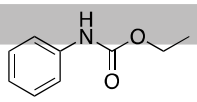
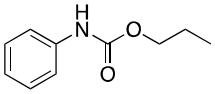
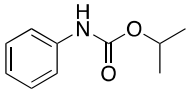
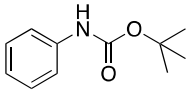
As with many other publications that seek to develop a new method for the synthesis of ureas, changing the nucleophile to an alcohol results in the generation of the corresponding carbamate, generally under similar reaction conditions originally developed for the generation of the ureas. To examine the synthetic utility of our general reaction method, we explored the same reaction conditions using various alcohols to trap the *in situ* generated isocyanate. Located in Table 3, are the results of this interrogation. For entry **a**, benzyl alcohol was found to give a moderate isolated yield of 45%, under the same conditions as previously reported for the ureas, (Table 3, entry **a** versus Table 2, entry **i**). Ethanol and propanol were also used under our general reaction conditions, and gave comparable yields of 48% and 49%, Table 3, entries **b** and **c**. Use of a secondary alcohol (isopropanol, entry **d**) also gave a similarly moderate yield of 48%. The very sterically hindered *tert*-butanol was found to give a lower yield of 27%, most likely due to the reduced nucleophilicity of the alcohol (Table 3, entry **e**). It is proposed that the reduced yields for the generation of the carbamates, in comparison to the ureas, is potentially a result of the presence of water in the alcohol reagents. For the chosen alcohols, an aliquot was taken from a reagent bottle that had been sitting on the self for an extend period of time, (rather than new anhydrous alcohols). There is a potential that these alcohols may contain a slightly elevated amount of water, in comparison to the anilines, resulting in reduced yields. In some of the cases, benzoic acid was observed as a by-product of the reaction, most likely a result of water quenching any unreacted benzoyl chloride. Alternately, if these reactions were conducted using anhydrous alcohols, it would be expected that the product may be generated in higher overall yields. However, due to the convenience of using easily obtainable benzoyl chlorides, HSA and readily available alcohols off-the-shelf, the representative reaction outlined in scheme **3** serves as an example of a useful one-pot synthetic method for the generation of carbamates, although occurring in moderate yields.



Scheme 3. General reaction conditions for the synthesis of *N*-aryl carbamates

Table 3. Synthesis of *N*-aryl carbamates using benzoyl chloride (**1**) and HSA (Scheme 3)

Entry	Alcohol	Product Name (**Compound #**)	Product Structure	Yield %[a]
a		Benzyl *N*-phenylcarbamate (**14**)		45

b		Ethyl *N*-phenylcarbamate (**15**)		48
c		Propyl *N*-phenylcarbamate (**16**)		49
d		Isopropyl *N*-Phenylcarbamate (**17**)		48
e		*tert*-Butyl *N*-Phenylcarbamate (**18**)		27

[a]Isolated yield following column chromatography (cc).

The proposed mechanism for this reaction is relatively straight-forward. As eluded to earlier, we envisioned that the condensation of HSA with benzoyl chloride, under base catalyzed conditions (DIPEA), would generate an *O*-sulfonyl hydroxamic acid derivative that is poised to perform an intramolecular rearrangement. In the next step, it is possible that the hydroxamic acid derivative is converted to its conjugate base by abstraction of a hydrogen atom by base (from nitrogen, not shown), followed by a spontaneous rearrangement to form an isocyanate intermediate. However, it is clear that a Lossen rearrangement is the most likely process that instills a nitrogen atom in between the aromatic group and the carbonyl carbon, leading to the generation of an isocyanate. In the next step of the one-pot reaction, nucleophilic addition of the amine or alcohol leads to the production of the urea (Table 2) or carbamate (Table 3), respectively.

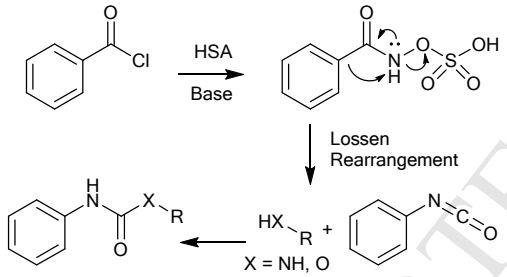


Fig. 2 Proposed mechanism *via* Lossen rearrangement

3. Conclusion

Overall, we have developed a synthetically useful one-pot method for the generation of ureas and carbamates that uses readily commercially available reagents, that is performed under safer (azide-free) and greener conditions (fewer total synthetic/purification steps and metal-free) than alternate methods. In total we were able to develop a general method for the synthesis of *N*,*N*'-disubstituted phenylureas, 11 entries, Table 1, with excellent yields up to 95% using microwave irradiation and very short reaction times (5 minutes). Overall, we used a number of different amines, from sterically hindered anilines, to primary and secondary amines to generate products in yields from 52% to 90+%. When applied to the generation of carbamates, this method also produced the corresponding *N*-aryl carbamates in moderate yields. Correspondingly, we would expect that the general conditions reported here are well suited to serve as a general method for the generation of ureas or carbamates using HSA/acyl chlorides and various nucleophiles (amines/alcohols). Currently, we are modifying these general reaction condition to convert carboxylic acids (instead of benzoyl chlorides) into the corresponding ureas and carbamates using hydroxylamine-*O*-sulfonic acid as the key reagent.

4. Experimental section

4.1. General information

All glass microwave vessels were oven dried overnight before use. Microwave reactions were performed using the CEM Discover® SP Microwave Synthesizer. All chemicals and solvents were purchased from commercial sources and used without further purification. Anhydrous DCM and acetonitrile were purchased from VWR as DriSolv® solvents in septum sealed bottles and used without further purification. Purification of products were performed by flash chromatography using the Combiflash® Rf+ system, with Redi*Sep*® 12g normal phase disposable columns and crude material pre-absorbed onto silica gel (40-60µ, 60A Redi*Sep*® Silica gel) and purified *via* the solid load method. Analytical thin layer chromatography was performed on Merck TLC plates (Silica Gel 60 F_{254} Aluminum sheets). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 400 MHz machine with chemical shifts reported in parts per million ($(CD_3)_2SO$ = 2.50 ppm), coupling constants (*J*) in Hertz (Hz), and multiplicity as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, tt = triplet of triplets, q = quartet, m = multiplet, bs = broad singlet.

4.2. General procedure for the synthesis of *N*,*N*'-disubstituted phenylureas (Table 2)

To an oven dried 10 mL or 35 mL microwave vial capped with a rubber septum and placed under argon, 0.2545 g hydroxylamine-*O*-sulfonic acid (HSA) (1.5 eq., 2.25 mmol) was added followed by 5 mL of anhydrous DCM with stirring. 1.05 mL diisopropylethyl amine (DIPEA) (4.0 eq., 6 mmol) was added slowly *via* syringe to the mixture to allow HSA to dissolve, and the reaction stirred for approx. 2-3 minutes. Benzoyl chloride (1.25 eq., 1.88 mmol) was then added dropwise *via* syringe to the solution and the reaction stirred for approx. 2-3 minutes, until the reaction appeared to have subsided. Aniline or amine (1.0 eq., 1.5 mmol) was then added *via* syringe and the vial was removed from under argon and capped with a microwave cap. The reaction vessel was then placed in the microwave reactor where it was irradiated at 100 °C for 5 minutes. Once complete, the reaction mixture was transferred to a 100 mL RB flask and pre-absorbed onto silica gel where it was purified *via* flash chromatography in a gradient of 0 → 100% EtOAc/Hexanes to yield the target product.

Some isolated aryl ureas appeared to contain unidentified contaminants as seen in the ^{1}H-NMR as well as the presence of colour within the product. Therefore, certain aryl ureas that required further purification were vacuum filtered through a 15

mL PYREX 36060 fritted glass Buchner funnel (4-5.5 μm, fine) and triturated with small amounts of cold chloroform after flash chromatography, provided they were insoluble, in order to yield pure product. The purity of the final triturated products can be verified by examining the NMR located in the supplemental for compounds **3** through **7**.

*4.2.1. 1,3-Diphenylurea (**3**)*

The title compound was prepared following the general procedure using benzoyl chloride (0.22 mL, 2.25 mmol) and aniline (0.14 mL, 1.5 mmol). After flash chromatography, 306 mg (94% yield) of solid was isolated. Following trituration with cold chloroform, 260 mg (80% yield) of the title compound was obtained as an off-white solid and had similar spectroscopic data to that reported in the literature.[34] R_f : 0.41 (50% EtOAc/Hexanes). **^{1}H-NMR** (400 MHz, DMSO-d^6): δ 8.66 (s, 2H), 7.45 (d, *J* = 7.9, 4H), 7.27 (t, *J* = 7.8, 4H), 6.96 (t, *J* = 7.3, 2H). **^{13}C-NMR** (101 MHz, DMSO-d^6): δ 152.5, 139.7, 128.8, 121.8, 118.2.

*4.2.2. N-(2-Methylphenyl)-N'-phenylurea (**4**)*

The title compound was prepared following the general procedure using benzoyl chloride (0.22 mL, 2.25 mmol) and *o*-toluidine (0.16 mL, 1.5 mmol). After flash chromatography, 339 mg (98% yield) of solid was isolated. Following trituration with cold chloroform, 274 mg (80% yield) of the title compound was obtained as an off-white solid and had similar spectroscopic data to that reported in the literature.[39] R_f: 0.42 (50% EtOAc/Hexanes). **^{1}H-NMR** (400 MHz, DMSO-d^6): δ 9.03 (s, 1H), 7.93 (s, 1H), 7.85 (d, *J* = 7.9, 1H), 7.47 (d, *J* = 7.6, 2H), 7.28 (t, *J* = 7.9, 2H), 7.18-7.12 (m, 2H), 6.98-6.92 (m, 2H), 2.24 (s, 3H). **^{13}C-NMR** (101 MHz, DMSO-d^6): δ 152.7, 139.9, 137.4, 130.2, 128.8, 127.5, 126.2, 122.7, 121.7, 121.0, 118.0, 17.9

*4.2.3. N-(4-Methylphenyl)-N'-phenylurea (**5**)*

The title compound was prepared following the general procedure using benzoyl chloride (0.22 mL, 2.25 mmol) and p-toluidine (161 mg, 1.5 mmol). After flash chromatography, 310 mg (91% yield) of solid was isolated. Following trituration with cold chloroform, 241 mg (71% yield) of the title compound was obtained as an off-white solid and had similar spectroscopic data to that reported in the literature.[40,41] R_f: 0.42 (50% EtOAc/Hexanes).**^{1}H-NMR** (400 MHz, DMSO-d^6): δ 8.62 (s, 1H), 8.56 (s, 1H), 7.44 (d, *J* = 7.9, 2H), 7.33 (d, *J* = 8.4, 2H), 7.26 (t, *J* = 7.9, 2H), 7.08 (d, *J* = 8.3, 2H), 6.95 (t, *J* = 7.3, 1H), 2.24 (s, 3H). **^{13}C-NMR** (101 MHz, DMSO-d^6): δ 152.6, 139.8, 137.1, 130.6, 129.2, 128.8, 121.7, 118.3, 118.1, 20.3.

*4.2.4. N-(4-Methoxyphenyl)-N'-phenylurea (**6**)*

The title compound was prepared following the general procedure using benzoyl chloride (0.22 mL, 2.25 mmol) and 4-methoxyaniline (185 mg, 1.5 mmol). After flash chromatography, 301 mg (81% yield) of solid was isolated. Following trituration with cold chloroform, 252 mg (68% yield) of the title compound was obtained as a pale purple solid and had similar spectroscopic data to that reported in the literature.[40] R_f: 0.30 (50% EtOAc/Hexanes). **^{1}H-NMR** (400 MHz, DMSO-d^6): δ 8.57 (s, 1H), 8.46 (s, 1H), 7.43 (dd, *J* = 7.5, 1.1, 2H), 7.35 (d, *J* = 9.0, 2H), 7.26 (t, *J* = 7.9, 2H), 6.94 (tt, *J* =7.4, 1.1, 1H), 6.86 (d, *J* = 9.0, 2H), 3.71 (s, 3H). **^{13}C-NMR** (101 MHz, DMSO-d^6): δ 154.4, 152.7, 139.9, 132.7, 128.7, 121.6, 120.0, 118.1, 114.0, 55.2.

*4.2.5. N-(4-Chlorophenyl)-N'-phenylurea (**7**)*

The title compound was prepared following the general procedure using benzoyl chloride (0.22 mL, 2.25 mmol) and 4-chloroaniline (0.191 g, 1.5 mmol). After flash chromatography, 248 mg (67% yield) of off-white solid was isolated. Following trituration with cold chloroform, 193 mg (52% yield) of the title compound was obtained as an off-white solid and had similar spectroscopic data to that reported in the literature.[42] R_f: 0.34 (50% EtOAc/Hexanes). **^{1}H-NMR** (400 MHz, DMSO-d^6): δ 8.86 (s, 1H), 8.75 (s, 1H), 7.51- 7.44 (m, 4H), 7.33- 7.25 (m, 4H), 6.97 (t, *J* = 7.3, 1H). **^{13}C-NMR** (101 MHz, DMSO-d^6): δ 152.5, 139.6, 138.8, 128.8, 128.6, 125.3, 122.0, 119.7, 118.3.

*4.2.6. N-(2,4-Dimethylphenyl)-N'-phenylurea (**8**)*

The title compound was prepared following the general procedure using benzoyl chloride (0.22 mL, 2.25 mmol) and 2,4-dimethylaniline (0.19 mL, 1.5 mmol). After flash chromatography, 286 mg (78% yield) of the title compound was obtained as a beige solid and had similar spectroscopic data to that reported in the literature.[43] R_f: 0.42 (50% EtOAc/Hexanes). **^{1}H-NMR** (400 MHz, DMSO-d^6): δ 8.94 (s, 1H), 7.85 (s, 1H), 7.66 (d, *J* = 8.2, 1H), 7.45 (d, *J* = 8.0, 2H), 7.27 (t, *J* = 7.7, 2H), 6.98- 6.93 (m, 3H), 2.22 (s, 3H), 2.20 (s, 3H). **^{13}C-NMR** (101 MHz, DMSO-d^6): δ 152.8, 140.0, 134.8, 131.7, 130.7, 128.8, 127.8, 126.6, 121.6, 121.5, 117.9, 20.4, 17.8.

*4.2.7. N-(2,4,6-Trimethylphenyl)-N'-phenylurea (**9**)*

The title compound was prepared following the general procedure using benzoyl chloride (0.22 mL, 2.25 mmol) and 2,4,6-trimethylaniline (0.14 mL, 1.5 mmol). After flash chromatography, 263 mg (69% yield) of the title compound was obtained as an off-white solid and had similar spectroscopic data to that reported in the literature.[34] R_f: 0.37 (50% EtOAc/Hexanes). **^{1}H-NMR** (400 MHz, DMSO-d^6): δ 8.68 (bs, 1H), 7.61 (s, 1H), 7.44 (d, *J* = 8.1, 2H), 7.24 (t, *J* = 7.8, 2H), 6.93-6.87 (m, 3H), 2.22 (s, 3H), 2.16 (s, 6H). **^{13}C-NMR** (101 MHz, DMSO-d^6): δ 153.3, 140.4, 135.3, 134.9, 132.7, 128.7, 128.3, 121.3, 117.8, 20.5, 18.2.

*4.2.8. N-Methyl-N,N'-diphenylurea (**10**)*

The title compound was prepared following the general procedure using benzoyl chloride (0.22 mL, 2.25 mmol) and *N*-methylaniline (0.16 mL, 1.5 mmol). After flash chromatography, 219 mg (66% yield) of the title compound was obtained as a white solid and had similar spectroscopic data to that reported in the literature.[44] R_f: 0.42 (50% EtOAc/Hexanes). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.45 (t, *J* = 7.6, 2H), 7.36- 7.28 (m, 5H), 7.21 (t, *J* = 7.9, 2H), 6.96 (t, *J* = 7.2, 1H), 6.33 (bs, 1H), 3.32 (s, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 154.1, 142.6, 138.7, 130.0, 128.5, 127.5, 127.1, 122.5, 118.9, 37.0.

*4.2.9. N-Benzyl-N'-phenylurea (**11**)*

The title compound was prepared following the general procedure using benzoyl chloride (0.22 mL, 2.25 mmol) and benzylamine (0.16 mL, 1.5 mmol). After flash chromatography, 308 mg (93% yield) of the title compound was obtained as a white solid and had similar spectroscopic data to that reported in the literature.[40] R_f: 0.36 (50% EtOAc/Hexanes). **^{1}H-NMR** (400 MHz, DMSO-d^6): δ 8.56 (s, 1H), 7.40 (d, *J* = 8.2, 2H), 7.35-7.29 (m, 4H), 7.25-7.20 (m, 3H), 6.89 (t, *J* = 7.4, 1H), 6.61 (t, *J* = 5.8, 1H), 4.30 (d, *J* = 6.0, 2H). **^{13}C-NMR** (101 MHz, DMSO-d^6): δ 155.3, 140.5, 140.4, 128.7, 128.3, 127.1, 117.7, 42.7.

*4.2.10. N-Phenyl-4-morpholinecarboxamide (**12**)*

The title compound was prepared following the general procedure using benzoyl chloride (0.22 mL, 2.25 mmol) and morpholine (0.13 mL, 1.5 mmol). After flash chromatography, 239 mg (78% yield) of the title compound was obtained as a white solid and had similar spectroscopic data to that reported in the literature.[45] R_f: 0.33 (100% EtOAc). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.35-7.32 (m, 2H), 7.30-7.25 (m, 2H), 7.04 (tt, *J* = 7.3, 1.3, 1H), 6.57 (bs, 1H), 3.69 (t, *J* = 4.9, 4H), 3.45 (t, *J* = 4.9,

4H). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 155.2, 138.7, 128.9, 123.3, 120.1, 66.4, 44.2.

*4.2.11. N-(Phenyl)-N'-butylurea (**13**)*

The title compound was prepared following the general procedure using benzoyl chloride (0.22 mL, 2.25 mmol) and 1-butylamine (0.15 mL, 1.5 mmol). After flash chromatography, 277 mg (95% yield) of the title compound was obtained as a white solid and had similar spectroscopic data to that reported in the literature.[40] R_f: 0.37 (50% EtOAc/Hexanes). **^{1}H-NMR** (400 MHz, DMSO-d^6): δ 8.37 (s, 1H), 7.37 (d, *J* = 8.2, 2H), 7.20 (t, *J* = 7.8, 2H), 6.86 (t, *J* = 7.2, 1H), 6.09 (t, *J* = 5.5, 1H), 3.06 (app. q, *J* = 6.4, 2H), 1.44-1.25 (m, 4H), 0.89 (t, *J* = 7.2, 3H). **^{13}C-NMR** (101 MHz, DMSO-d^6): δ 155.2, 140.6, 128.6, 120.9, 117.5, 38.7, 31.9, 19.5, 13.7.

4.3. General procedure for the synthesis of *N*-aryl carbamates (Table 3)

To an oven dried 10 mL or 35 mL microwave vial capped with a rubber septum and placed under argon, 0.2545 g hydroxylamine-*O*-sulfonic acid (1.5 eq., 2.25 mmol) was added followed by 5 mL of anhydrous DCM with stirring. 1.05 mL DIPEA (4.0 eq., 6 mmol) was added slowly *via* syringe to the mixture to allow HSA to dissolve, and the reaction stirred for approx. 2-3 minutes. Benzoyl chloride (1.25 eq., 1.88 mmol) was then added dropwise *via* syringe to the solution and the reaction stirred for approx. 2-3 minutes, until the reaction appeared to have subsided. Alcohol (1.0 eq., 1.5 mmol) was then added *via* syringe and the vial was removed from under argon and capped with a microwave cap. The reaction vessel was then placed in the microwave reactor where it was irradiated at 100 ^oC for 15 minutes. Once complete, the reaction mixture was transferred to a 100 mL RB flask and pre-absorbed onto silica gel where it was purified *via* flash chromatography in a gradient of 0 → 20% EtOAc/ Hexanes to yield the target product.

*4.3.1. Benzyl-N-phenylcarbamate (**14**)*

The title compound was prepared following the general procedure using benzoyl chloride (0.22 mL, 2.25 mmol) and benzylalcohol (0.16 mL, 1.5 mmol). After flash chromatography, 157 mg (45% yield) of the title compound was obtained as a colorless crystalline solid and had similar spectroscopic data to that reported in the literature.[46] R_f: 0.43 (20% EtOAc/Hexanes). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.41- 7.29 (m, 9H), 7.08 (t, *J* = 7.3, 1H), 6.76 (bs, 1H), 5.21 (s, 2H). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 153.3, 137.7, 136.0, 129.0, 128.6, 128.3, 128.3, 123.5, 118.7, 67.0.

*4.3.2. Ethyl-N-phenylcarbamate (**15**)*

The title compound was prepared following the general procedure using benzoyl chloride (0.22 mL, 2.25 mmol) and ethanol (0.09 mL, 1.5 mmol). After flash chromatography, 123 mg (48% yield) of the title compound was obtained as a colorless crystalline solid and had similar spectroscopic data to that reported in the literature.[47] Rf: 0.37 (20% EtOAc/Hexanes). **1H-NMR** (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.9, 2H), 7.30 (t, *J* = 8.0, 2H), 7.08 (tt, *J* = 7.3, 1.2, 1H), 6.78 (bs, 1H), 4.23 (q, *J* = 7.1, 2H), 1.31 (t, *J* = 7.1, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 153.7, 137.9, 129.0, 123.3, 118.6, 61.1, 14.5.

*4.3.3. Propyl-N-phenylcarbamate (**16**)*

The title compound was prepared following the general procedure using benzoyl chloride (0.22 mL, 2.25 mmol) and 1-propranol (0.11 mL, 1.5 mmol). After flash chromatography, 130 mg (49% yield) of the title compound was obtained as a colorless crystalline solid and had similar spectroscopic data to that reported in the literature.[48] Rf: 0.44 (20% EtOAc/Hexanes). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.8, 2H), 7.30 (t, *J* = 8.0, 2H), 7.06 (tt, *J* = 7.3, 1.1, 1H), 6.83 (bs, 1H), 4.13 (t, *J* = 6.7, 2H), 1.74-1.66 (m, 2H), 0.98 (t, *J* = 7.4, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 153.8, 138.0, 128.9, 123.2, 118.6, 66.8, 22.2, 10.3.

*4.3.4. Isopropyl-N-phenylcarbamate (**17**)*

The title compound was prepared following the general procedure using benzoyl chloride (0.22 mL, 2.25 mmol) and 2-propranol (0.11 mL, 1.5 mmol). After flash chromatography, 123 mg (48% yield) of the title compound was obtained as a colorless crystalline solid and had similar spectroscopic data to that reported in the literature.[48] Rf: 0.47 (20% EtOAc/Hexanes). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7.9, 2H), 7.30 (t, *J* = 7.9, 2H), 7.05 (t, *J* = 7.3, 1H), 6.66 (bs, 1H), 5.03 (m, 1H), 1.30 (d, *J* = 6.2, 6H). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 153.2, 138.1, 129.0, 123.2, 118.5, 68.7, 22.0.

*4.3.5. tert-Butyl-N-phenylcarbamate (**18**)*

The title compound was prepared following the general procedure using benzoyl chloride (0.22 mL, 2.25 mmol) and *tert*-butanol (0.11 mL, 1.5 mmol). After flash chromatography, 83 mg (27% yield) of the title compound was obtained as a colorless crystalline solid and had similar spectroscopic data to that reported in the literature.[46] Rf: 0.51 (20% EtOAc/Hexanes). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.0, 2H), 7.31-7.26 (m, 2H), 7.03 (t, *J* = 7.3, 1H), 6.49 (bs, 1H), 1.52 (s, 9H). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 152.7, 138.3, 129.0, 123.0, 118.5, 80.5, 28.3.

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Supplementary data

Supplementary material related to this article can be found at [insert DOI url for website].

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