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One-Pot Synthesis of C_2 Symmetric and Asymmetric N,N′,N′′-Substituted Guanidines from Aryl Isothiocyanates and Amines

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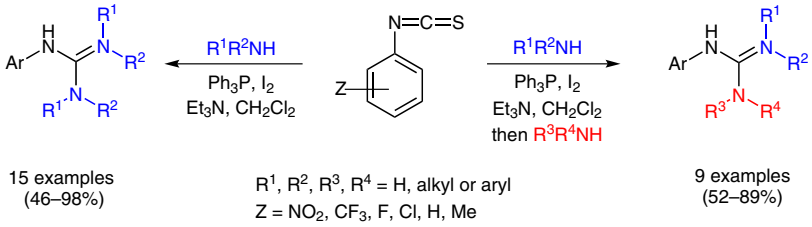

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Abstract Highly substituted guanidines were conveniently prepared through a one-pot reaction between aryl isothiocyanates and amines mediated by the Ph_3P–I_2/Et_3N system. The C_2-symmetric N,N′,N′′-substituted guanidines were readily accessed using a 1:2 molar ratio of an aryl isothiocyanate and an amine; while sequential addition of two different amines in equimolar ratios gave rise to asymmetric derivatives. Both primary and secondary amines were found to react preferentially with electron-deficient aryl isothiocyanates, rapidly providing guanidines in good yields under mild conditions.

Key words condensation, desulfurization, guanidine, isothiocyanate

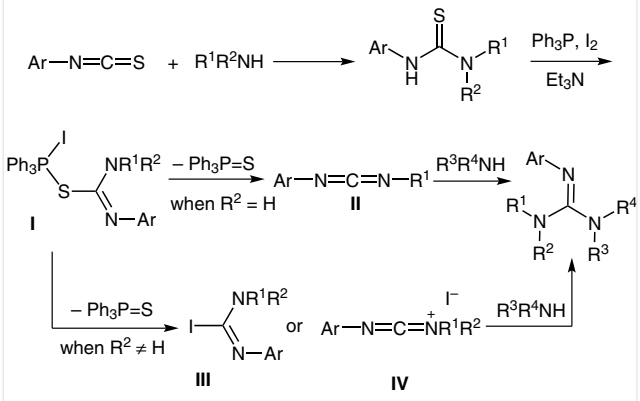
Substituted guanidines are an important class of compounds that exhibit widespread applications in the fields of medicinal chemistry, supramolecular chemistry, sensors, and catalysis.[1] In particular, *N,N′*-dialkyl guanidine derivatives have been widely used as ligands for the construction of a variety of organometallic catalysts.[2] As more complex structures are necessary to achieve desired properties, a new method that allows an easy access to highly substituted guanidines under mild conditions is of great interest.

The classical approaches to guanidines involve nucleophilic addition of an amine with electrophilic guanylating reagents.[3] Among the available methods, the reaction of an amine with carbodiimides commonly generated in a separate step via dehydrosulfurization of thioureas or dehydration of ureas provides a relatively simple route to a range of highly substituted guanidine derivatives.

In a continuation of our study into reactions promoted by the triphenylphosphine–iodine combination, we were interested in replacing the traditional promoters used for the guanylation of thioureas with this Ph_3P–I_2 system. Although similar reagent combinations using Ph_3P with additives such as carbon tetrachloride,[4] carbon tetrabromide,[5] diethyl azodicarboxylate,[6] or bromine[7] have previously been reported for the preparation of carbodiimides from N,N′-disubstituted ureas or thioureas; to the best of our knowledge, only one study has performed a stepwise guanylation of amines with resin-bound thioureas using Ph_3P–hexachloroethane as a dehydrosulfurizing agent.

In this study, we aimed to use an aryl isothiocyanate as a precursor since it would allow easy access to both C_2-symmetric and asymmetric N,N′,N′′-substituted guanidines through controlling the nature and amount of the amine counterparts. Additionally, numerous isothiocyanate derivatives are commercially available or can be readily prepared from amines or aldoxime precursors.[8]

It was envisaged that a thiourea generated *in situ* from the reaction of an aryl isothiocyanate with an amine would react with the preformed triphenylphosphine–diiodide in the presence of base leading to the formation of pentacoordinate phosphorous species **I**. Based on the reported literature,[4b,9] the corresponding carbodiimide **II** should be readi-



Scheme 1 Proposed mechanism for the Ph_3P–I_2-mediated guanylation of amines

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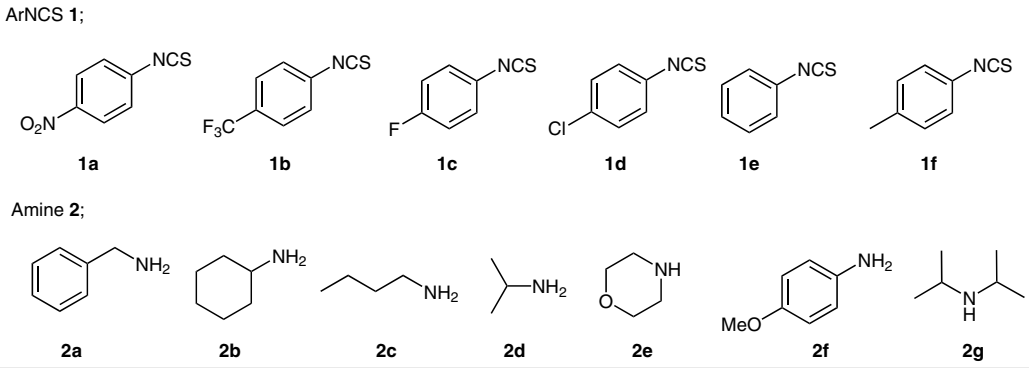
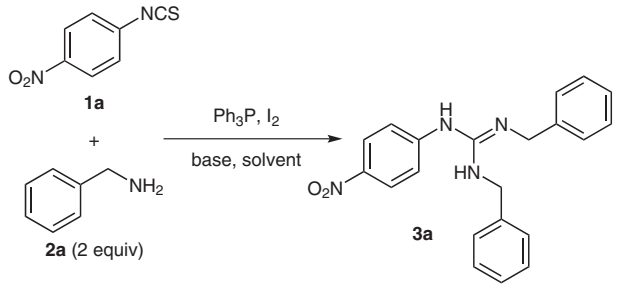


Figure 1 Structures of aryl isothiocyanates and amines used in the guanylation reaction

ly generated when R^2 = H, while carbimidoyl iodide **III** or the equivalent carbodiimide salt **IV** could be the key intermediate formed when $R^2 \neq H$.[10] In either case, thermodynamically favorable triphenylphosphine sulfide is released as a key driving force for the reaction. Subsequent reaction of the formed intermediates with an amine then furnishes the guanidine in one-pot (Scheme 1).

In our preliminary investigation, commercially available 4-nitrophenyl isothiocyanate (**1a**, 1 equiv) was reacted with benzylamine (**2a**, 2 equiv) using Ph_3P (1.2 equiv) and iodine (1.2 equiv) in dichloromethane at room temperature. It was found that, in the presence of triethylamine (5 equiv), the corresponding guanidine **3a** was obtained in 90% yield within 10 minutes (Table 1, entry 1). It is noted that excess base was used for deprotonation of the two protons of the *in situ* generated thiourea as well as keeping the reaction under basic conditions to enhance the reaction rate. Changing the base to diisopropylethylamine led to low product yield (Table 1, entry 2); while other weak organic and inorganic bases gave no conversion (Table 1, entries 3–5), possibly due to their inability to abstract weakly acidic protons attached to the nitrogen atoms of thiourea. A similar result was also obtained in the absence of the base (Table 1, entry 6). Switching the reaction medium from dichloromethane to other solvents also decreased the product yield, probably resulting from solubility problems of the reactants as well as instability of the formed carbodiimide intermediate.

Table 1 Optimization of Reaction Conditions[a]



Entry	Base	Solvent	Yield (%)
1	Et_3N	CH_2Cl_2	90
2	*i*-Pr_2NEt	CH_2Cl_2	71
3	pyridine	CH_2Cl_2	0
4	imidazole	CH_2Cl_2	0
5	K_2CO_3	CH_2Cl_2	0
6	none	CH_2Cl_2	0
7	Et_3N	toluene	55
8	Et_3N	THF	78

[a] Reaction conditions: 4-nitrophenyl isothiocyanate (**1a**, 0.28 mmol), benzylamine (**2a**, 0.56 mmol), Ph_3P (0.33 mmol), I_2 (0.33 mmol), and base (1.4 mmol), solvent (2 mL), 0 °C to r.t. for 15 min.

To evaluate the scope and limitations of the Ph_3P–I_2 system, a series of C_2-symmetrical substituted guanidines was synthesized using various aryl isothiocyanates and amines (Figure 1) under the optimized reaction conditions.[11] As shown in Table 2, the yields and reaction times were varied depending on the nucleophilicity of the amine nucleophiles and electronic nature of aryl isothiocyanates. For electron-deficient isothiocyanates, the substrate containing the NO_2 group reacted readily with both primary and secondary alkylamines to provide the products in high yields (Table 2, entries 1–5). The reaction with an aromatic amine containing the electron-donating OMe group (**2f**) also proceeded without difficulty (Table 2, entry 6). However, the reaction did not proceed with the weakly nucleophilic 4-nitroaniline (data not shown). Addition of DMAP (10 mol%) also did not lead to the product. Nevertheless, we noticed that the formed thiourea was not soluble in the reaction media. Thus, this could be the reason for lack of conversion. Hence, no further reaction with this amine was attempted.

Other aryl isothiocyanates containing electron-withdrawing groups such as F, Cl, CF_3 were also found to react smoothly with aliphatic amines to give high yields of the products; although long reaction times were required, especially with the more hindered isopropylamine (Table 2, entries 7–13).

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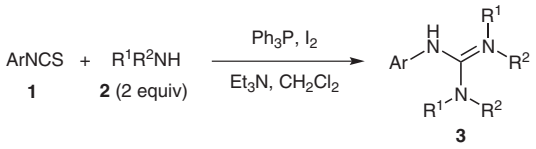
Table 2 One-Pot Synthesis of C_2-Symmetric N,N′,N′′-Trisubstituted Guanidines[a]



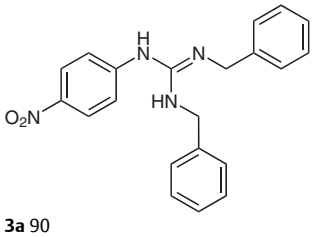
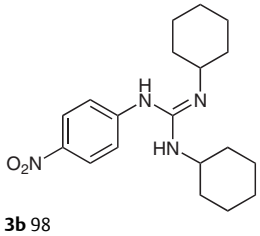
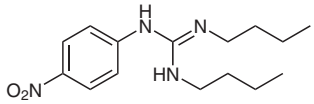
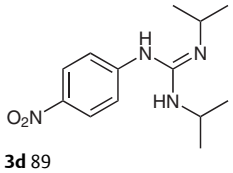
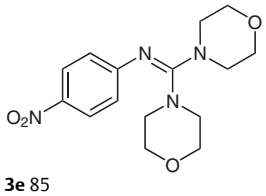
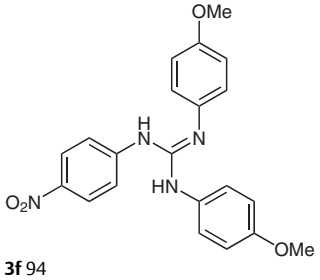
Entry	1	2	Time (min)	Yield (%)
1	**1a**	**2a**	15	 **3a** 90
2	**1a**	**2b**	15	 **3b** 98
3	**1a**	**2c**	20	 **3c** 96
4	**1a**	**2d**	15	 **3d** 89
5	**1a**	**2e**	15	 **3e** 85
6	**1a**	**2f**	30	 **3f** 94

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Table 2 (continued)

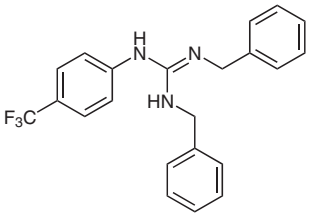
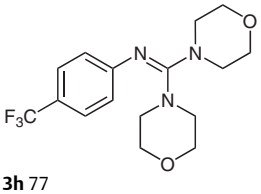
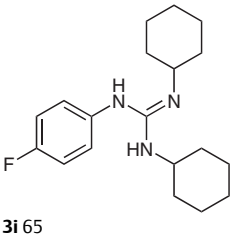
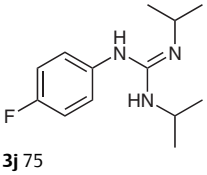
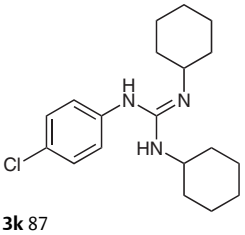
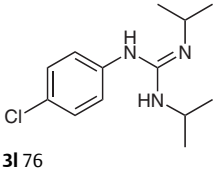
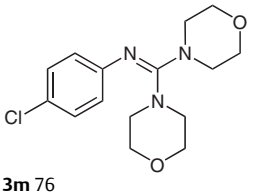
Entry	1	2	Time (min)	Yield (%)
7	**1b**	**2a**	45	 **3g** 80
8	**1b**	**2e**	30	 **3h** 77
9	**1c**	**2b**	60	 **3i** 65
10	**1c**	**2d**	75	 **3j** 75
11	**1d**	**2b**	60	 **3k** 87
12	**1d**	**2d**	45	 **3l** 76
13	**1d**	**2e**	75	 **3m** 76

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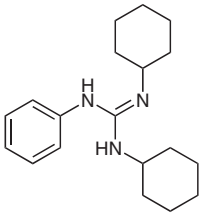
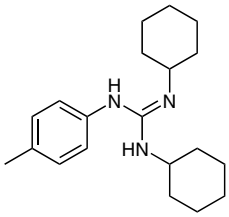
Table 2 (continued)

Entry	1	2	Time (min)	Yield (%)
14	**1e**	**2b**	3 h	 **3n** 68
15	**1f**	**2b**	3 h	 **3o** 46

[a] Reaction conditions: aryl isothiocyanate (0.28 mmol), amine (0.56 mmol), Ph_3P (0.33 mmol), I_2 (0.33 mmol) and Et_3N (1.4 mmol), CH_2Cl_2 (2 mL), 0 °C to r.t.

Using phenyl isothiocyanate **1e** and the electron-rich system **1f**, reaction with cyclohexylamine was sluggish and gave low conversions (Table 2, entries 14 and 15). Evidently, the electron-donating substituent on the aromatic ring of the aryl isothiocyanate causes the intermediates to be more electron-rich and, as a result, nucleophilic attack by an amine is less favorable.

It should be noted that N,N′-dialkylsubstituted guanidines are often synthesized from the reaction of amines with 1,3-dialkylcarbodiimides through metal-catalyzed reactions.[12] The methods generally require expensive catalysts, harsh reaction conditions, and/or long reaction times. Our protocol provides an alternative route to these types of guanidines using inexpensive reagents under mild conditions.

In the synthesis of asymmetrically N,N′,N″-substituted guanidines, the above guanylation procedure was repeated, with the modification that two different amines were added sequentially in the one-pot procedure.[11] Addition of the first amine to an aryl isothiocyanate at 1:1 molar ratio provided a substituted thiourea. After treatment with the Ph_3P–I_2 combination in the presence of triethylamine, the second amine (1 equiv) was added to the mixture, that was allowed to stir until the reaction was complete (15–60 min).

As shown in Table 3, isolation of the formed thiourea prior to guanylation with the second amine was unnecessary since the reaction of the electron-deficient 4-nitrophenyl isothiocyanate with various amines proceeded smoothly to give the respective guanidines in high yields even with the steric hindered diisopropylamine (**2g**, Table 3, entries 1–7). Again, the reaction was less effective with electron-rich isothiocyanate substrates leading to the guanidine products in moderate yields with some carbodiimide remaining. It is important to note that when *N*-cyclohexyl-*N*-phenylcarbodiimide or *N*-cyclohexyl-*N*-(*p*-tolyl)carbodiimide were prepared in a separate step before treatment with morpholine, no guanylation reaction was observed after 16 hours. This observation suggested that, instead of the well-known carbodiimide, other highly reactive intermediate(s) such as carboimidoyl iodide could be involved in the Ph_3P–I_2 mediated guanylation reaction with the *in situ* generated N,N′-disubstituted thioureas.

In summary, we have reported a convenient one-pot procedure for the synthesis of both symmetrically and asymmetrically substituted guanidines directly from aryl isothiocyanates and amines. With the Ph_3P–I_2/Et_3N system, electron-withdrawing substituents on the isothiocyanates accelerate the reaction; whereas less reactive electron-rich derivatives require longer times for reaction completion. Both primary and secondary amines could be guanylated in satisfactory yields under mild conditions. An investigation into the mechanism underlying the guanylation process is ongoing and will be reported shortly.

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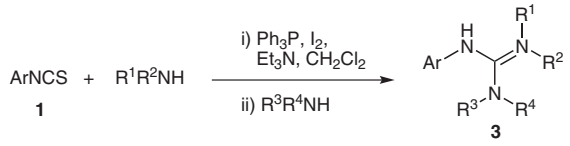
Table 3 One-Pot Synthesis of Asymmetric N,N′,N′′-Trisubstituted Guanidines[a]



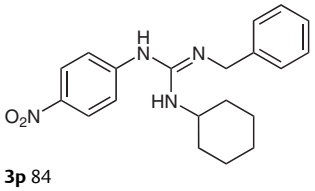
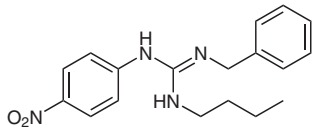
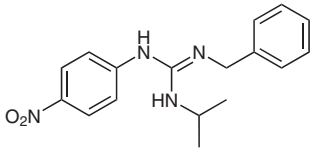
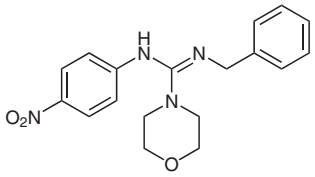
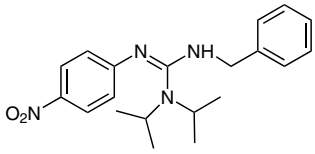
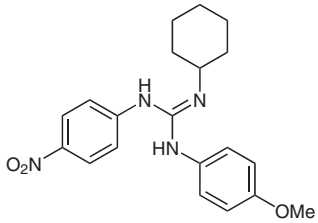
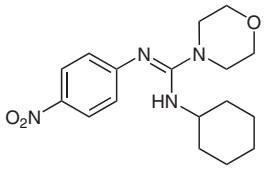
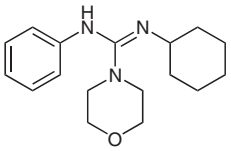
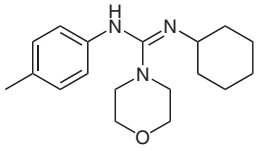
Entry	1	R^1R^2NH	R^3R^4NH	Yield (%)
1	**1a**	**2a**	**2b**	 **3p** 84
2	**1a**	**2a**	**2c**	 **3q** 89
3	**1a**	**2a**	**2d**	 **3r** 83
4	**1a**	**2a**	**2e**	 **3s** 85
5	**1a**	**2a**	**2g**	 **3t** 87
6	**1a**	**2b**	**2f**	 **3u** 79

Table 3 (continued)

Entry	1	R^1R^2NH	R^3R^4NH	Yield (%)
7	**1a**	**2e**	**2b**	 **3v** 85
8	**1e**	**2b**	**2e**	 **3w** 52
9	**1f**	**2b**	**2e**	 **3x** 55

[a] Reaction conditions: aryl isothiocyanate (0.28 mmol), R^1R^2NH (0.28 mmol), Ph_3P (0.33 mmol), I_2 (0.33 mmol), and Et_3N (1.4 mmol), CH_2Cl_2 (2 mL), 0 °C to r.t., then R^3R^4NH (0.28 mmol).

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561201.

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(11) **General Procedure**

Amine (0.56 mmol) and Et_3N (1.4 mmol) were added to a solution of aryl isothiocyanate (0.28 mmol) in CH_2Cl_2 (2 mL). After stirring at r.t. for 10 min, the mixture was cooled to 0 °C, then Ph_3P (0.33 mmol) and iodine (0.33 mmol) were added in one portion. The reaction mixture was stirred at r.t. until reaction completion as indicated by TLC. The reaction mixture was washed with H_2O, and the combined organic layers were dried over anhydrous Na_2SO_4 before filtering and concentrating *in vacuo*. The residue was purified by flash column chromatography to give the product. All products were identified by NMR spectroscopic and mass spectrometric analysis. In the synthesis of asymmetrically substituted guanidines, the amount of the first amine added to aryl isothiocyanate was reduced to 0.28 mmol, while the second amine (0.28 mmol) was added after treatment with Ph_3P–I_2 when the formed thiourea has completely disappeared (ca. 5–10 min).

***N*-(Dimorpholinomethylene)-4-nitroaniline (3e, Table 2 Entry 5)**

Yellow solid (0.0761 g, 85%); mp 158–159 °C; R_f = 0.38 (EtOAc). FTIR (neat): ν_{max} = 2965, 2854, 1547, 1321, 1265, 1111 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.0 Hz, 2 H), 6.76 (d, *J* = 8.0 Hz, 2 H), 3.66 (s, 8 H), 3.16 (s, 8 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0, 150.9, 141.4, 125.3, 121.4, 66.3, 49.2.

1,3-Dibenzyl-2-[4-(trifluoromethyl)phenyl]guanidine (3g, Table 2, Entry 7)

Colorless oil (0.0859 g, 80%). R_f = 0.36 (30% EtOAc–hexane). FTIR (neat): ν_{max} = 3426, 3289, 3031, 2922, 2871, 1632, 1596, 1323, 1164 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.4 Hz, 2 H), 7.35–7.26 (m, 6 H), 7.24–7.22 (m, 4 H), 7.01 (d, *J* = 8.4 Hz, 2 H), 4.36 (s, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3, 151.1, 138.4, 128.8, 128.6, 127.6, 127.2, 126.6 (q, *J* = 14.8 Hz), 123.5, 46.0.

1-Benzyl-3-cyclohexyl-2-(4-nitrophenyl)guanidine (3p, Table 3, Entry 1)

Yellow solid (0.0828 g, 84%); mp 109–110 °C. R_f = 0.33 (30% EtOAc–hexane). FTIR (neat): ν_{max} = 3393, 3275, 2931, 2854, 1617, 1572, 1451, 1307, 1108 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.8 Hz, 2 H), 7.38–7.28 (m, 5 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 4.39 (s, 2 H), 3.41–3.36 (m, 1 H), 1.92–1.88 (m, 2 H), 1.65–1.61 (m, 2 H), 1.57–1.53 (m, 1 H), 1.32–1.22 (m, 2 H), 1.17–1.06 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 151.6, 141.4, 138.0, 128.9, 127.8, 127.4, 125.5, 122.6, 50.7, 46.3, 33.4, 25.4, 24.6.

1-Benzyl-3-butyl-2-(4-nitrophenyl)guanidine (3q, Table 3, Entry 2)

Yellow oil (0.0813 g, 89%). R_f = 0.30 (30% EtOAc–hexanes). FTIR (neat): ν_{max} = 3417, 3298, 2957, 2930, 2871, 1571, 1493, 1306, 1107 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.8 Hz, 2 H), 7.38–7.29 (m, 5 H), 6.97 (d, *J* = 8.8 Hz, 2 H), 4.42 (s, 2 H), 3.14 (t, *J* = 7.2 Hz, 2 H), 1.50–1.43 (m, 2 H), 1.30–1.22 (m, 2 H), 0.87 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 152.1, 141.6, 138.0, 129.0, 127.9, 127.4, 125.5, 122.8, 46.2, 42.0, 31.6, 19.9, 13.7.

***N*-Cyclohexyl-*N'*-phenylmorpholine-4-carboximidamide (3w, Table 3 Entry 8)**

Colorless oil (0.0418 g, 52% yield). R_f = 0.25 (40% EtOAc–hexanes). FTIR (neat): ν_{max} = 3374, 2928, 2853, 1620, 1588, 1116 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26 (t, *J* = 7.6 Hz, 2 H), 6.99 (t, *J* = 7.6 Hz, 1 H), 6.83 (d, *J* = 7.6 Hz, 2 H), 3.71 (t, *J* = 4.8 Hz, 4 H), 3.22 (t, *J* = 4.8 Hz, 4 H), 3.11–3.04 (m, 1 H), 1.88–1.84 (m, 2 H), 1.68–1.62 (m, 2 H), 1.57–1.53 (m, 1 H), 1.27–1.16 (m, 2 H), 1.10–1.01 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 147.2, 129.3, 122.5, 66.6, 53.8, 48.6, 33.8, 25.3, 25.2.

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