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FULL PAPER

Micelle-enabled one pot guanidine synthesis in water directly from isothiocyanate using hypervalent iodine(III) reagents under mild condition

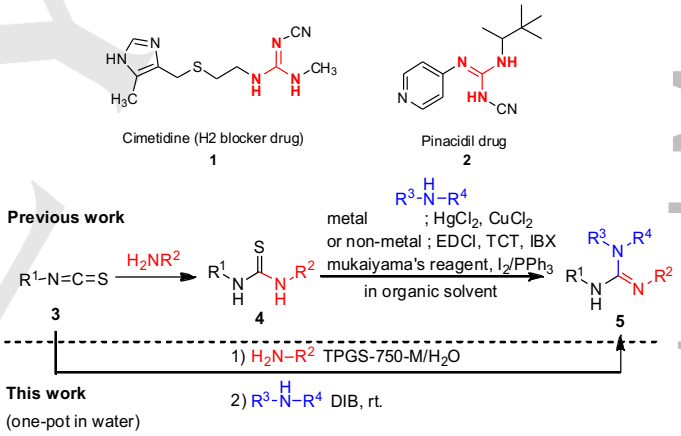
Jakkrit Srisa,[a,b] Theeranon Tankam,[a] Mongkol Sukwattanasinitt,[a,c] and Sumrit Wacharasindhu*[b,c]

Abstract: In this work, we developed a one-pot synthesis of guanidine directly from isothiocyanate using DIB (diacetoxyiodobenzene) as a desulfurizing agent under micellar condition in water. Our optimization study revealed that the use of 1% TPGS-750-M as a surfactant with NaOH as an additive base at room temperature can convert a variety of isothiocyanates and amines into corresponding guanidines in excellent yields (69 - 95%). This synthetic process in water can be applied to prepare guanidine at gram-scale quantity. Our aqueous micellar medium also demonstrated high reusability as the reaction can be performed for several cycles without losing its efficiency. The reaction is metal-free, utilize water as solvent and practical (room temperature and open flask).

Introduction

Organic solvents are the most widely used reaction medium in both academic and industry. However, its uses contribute to environmental pollution. In recent years, water has gained popularity as an alternative medium as it is safe, affordable and has low environmental footprint. Neat water or so called "*on-water*" reaction was first introduced by Sharpless.[1-3] Since then many elegant reactions have been reported.[4-12] Although on-water reactions offer much benefits, wide-spread adoption has been limited by inability of on-water reaction to be adapted to all traditional chemical transformation reactions due to heterogeneous behaviour. In recent years, new developments in surfactant technology created by Lipshutz[13-18] and others[19-34] have significantly made an improvement for aqueous reactions allowing reaction to occur *"in-water"* via the formation of micelles, thereby providing high reproducibility and reactivity.

Guanidines are important moieties that attract many interests in agricultural and pharmaceutical industry due to their broad spectrum of biological activities.[35-37] Many therapeutic agents have been constructed from this scaffold such as Cimetidine **1** (treatment of heartburn and peptic ulcers) and Pinacidil **2** (treatment of hypertension) (Scheme 1). Typical synthesis of guanidine involves reaction between an amine and guanylating agents such as isothioureas[38-40], carbodiimide[41-44], amidine[45], cyanamide[46-49], pyrrazole[50], triflylguanidines[51] and thiourea[52-54]. Among them, thiourea are the most promising guanylating agent because of their stability and ease of preparation. The two-step synthesis of guanidine from thiourea begins with the formation of thiourea (**4**) from isothiocyanate (**3**) and the corresponding amine (Scheme 1). The second step involves the coupling reaction between thiourea and amine using desulfurizing agents such as metals or non-metal mediators (Scheme 1). For metal mediators, oxidizing agent such as mercury chloride[55] and copper chloride[56] have been employed. Even though such reagents are highly efficient and compatible with wide verity of functional groups but the use of toxic metal and organic solvent are unavoidable. On the other hands, for non-metal mediators, ethyl-3-aminopropyl carbodiimide hydrochloride (EDCI)[57] and Mukaiyama's reagent [58] and TCT (trichloro cyanuric acid)[59] and I_2/PPh_3[60] have been used in a metal-free process.



Scheme 1. Guanidines with biological activities and synthetic approaches

Recently, hypervalent iodine have received much attention as oxidants due to their environmentally friendly character, ease of handling, selectivity and reasonable cost.[61-62] Because of the broad synthetic potential of hypervalent iodine, IBX (2-Iodoxybenzoic acid) have been reported as desulfurization agents for guanidine synthesis from thiourea.[63] However, for non-metal mediated guanidine synthesis including IBX, requires a two-step process from isocyanate (**3**) and the use of organic solvent as medium in combination with stoichiometric organic amine base are required. From green chemistry perspective, the use of harmful organic solvent/base and multiple-step process would increase the operating cost and risk in large scale production. Therefore, a mild, scalable, metal-free and more practical approach for guanidine synthesis in a greener medium would be highly desirable for both academia and industry. In view of this new development, herein we report an efficient one-pot synthesis

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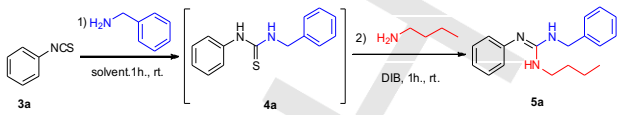
of guanidine directing from isothiocyanate (**3**) mediated by DIB (diacetoxyiodobenzene) as oxidant in water. The reaction was performed in a micellar system, TPGS-750-M/H_2O, in the presence of non-hazardous and inexpensive sodium hydroxide as base at room temperature under open-flask condition (Scheme 1).

Result and discussion

We selected phenyl isothiocyanate (**3a**) as a starting material to perform a two-step sequence guanidine synthesis using benzylamine as nucleophile for the formation of thiourea **4a** and subsequently added butylamine and hypervalent iodine (III), DIB, to facilitate guanidine formation. This is used as a representative one-pot reaction for the optimization investigation (table 1). We would like to note here that although related hypervalent (V) IBX were used in guanidine synthesis as mentioned above, the reagent poses serious drawback because of its potential shock sensitive nature.[64] Thus, we decided to use a non-explosive hypervalent iodine(III) such as DIB as oxidant instead. Initially, the reaction was conducted in acetonitrile. Resulting guanidine products **5a** were isolated in 50% yield along with unreacted intermediate thiourea **4a** in 28% yield (Table 1, entry1). Switching from traditional organic solvent to neat water, as expected, reduced guanidine **5a** to 19% yield along with increasing unreacted intermediate thiourea **4a** to 71% yield (Table 1, entry 2). Poor conversion is caused by heterogeneous nature of the on-water reaction. Next, efficiency of selected surfactants was examined in a model reaction in order to improve the in-water reaction. Among three surfactants, TPGS-750-M gave the best result, providing guanidine **5a** in 60% yield (Table 1, entry 3-5) . The superiority of this surfactant over the other could be explained by highly stable and suitable size of particle formed in water, which could accelerate the reaction.[15] Changing to more hydrophobic hypervalent iodine (III), BTB (Bis(*tert*-butylcarbonyloxy)iodobenzene) resulted in slightly lower yield of **5a** (Table 1, entry 6). We next surveyed the effect of base (Table 1, entry 7-9). To out delight, yield of guanidine **5a** increased to 75% along with only small amount of unreacted intermediate thiourea **4a** when 1.5 eq of NaOH was used (Table 1, entry 10). As we set the goal to create an atom-economy guanidine synthesis, large excess of reagents must be reduced as much as possible. In the guanidine formation step, amount of butylamine were then reduced from 3 to 1.5 equivalent. Fortunately, there was negligible effect on product **5a** yield (69%, Table 1, entry 11). Lowering TPGS-750-M from 2% to 1% w/w still provided a comparable yield but when 0.1% w/w were employed, only 40% yield of **5a** were isolated along with large amount of unreacted **4a** (41% yield) (Table 1, entry 12-13). This was likely because the reaction was carried near the critical micelle concentration of TPGS-750-M.[65] At such concentration, the micelle may not be formed effectively. Finally, we discovered that upon increasing the reaction concentration to 1.0 M, the reaction rate was enhanced, and it was completed within 30 min providing target compound **5a** in 83% yield (Table 1, entry 14).

Table 1. Optimization of the reaction condition[a]



Entry	Reaction medium	Additive	Yield (%)[b]	
			4a	**5a**
1	MeCN	None	28	50
2	H_2O	None	71	19
3	2WT%SDS	None	51	35
4	2wt%TritonX-100	None	42	39
5	2wt%TPGS-750-M	None	20	60
6[c]	2wt%TPGS-750-M	None	15	52
7	2wt%TPGS-750-M	1.0 eq. TEA	10	54
8	2wt%TPGS-750-M	1.0 eq. KOH	15	61
9	2wt%TPGS-750-M	1.0 eq. NaOH	17	67
10	2wt%TPGS-750-M	1.5 eq. NaOH	5	75
11[d]	2wt%TPGS-750-M	1.5 eq. NaOH	14	69
12[d]	1wt%TPGS-750-M	1.5 eq. NaOH	10	70
13[d]	0.1wt%TPGS-750-M	1.5 eq. NaOH	41	40
14[d,e]	**1wt%TPGS-750-M**	**1.5 eq. NaOH**	**-**	**83**

[a]Reaction conditions: **3a** (1.0 equiv. 0.37 mmol) and benzylamine (1.0 equiv.) butylamine (3.0 equiv.) DIB (1.2 equiv.) in water (0.5 M) under room temperature for 1 h.

[b]Isolated yield [c]BTB instead of DIB

[d]*n*-buthylamine (1.5 equiv.) [e]Reaction concentration = 1.0 M and stirred for 30 min after addition of DIB

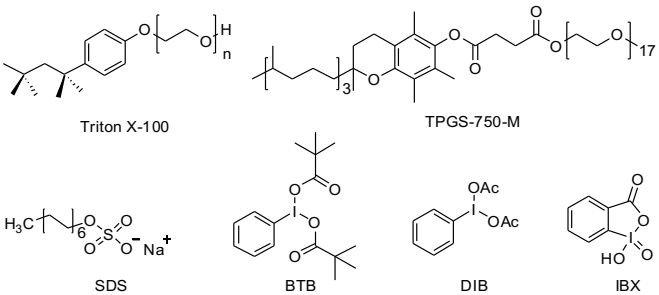


Figure 1. Structure of surfactants and hypervalent iodines used in this work

We would like to emphasize here that the newly developed "in water" reaction is very convenient and practical. The reaction was performed in an open test-tube and after the reaction was completed, crude products could be separated using only a small amount of ethyl acetate and transferred by a Pasteur pipet for

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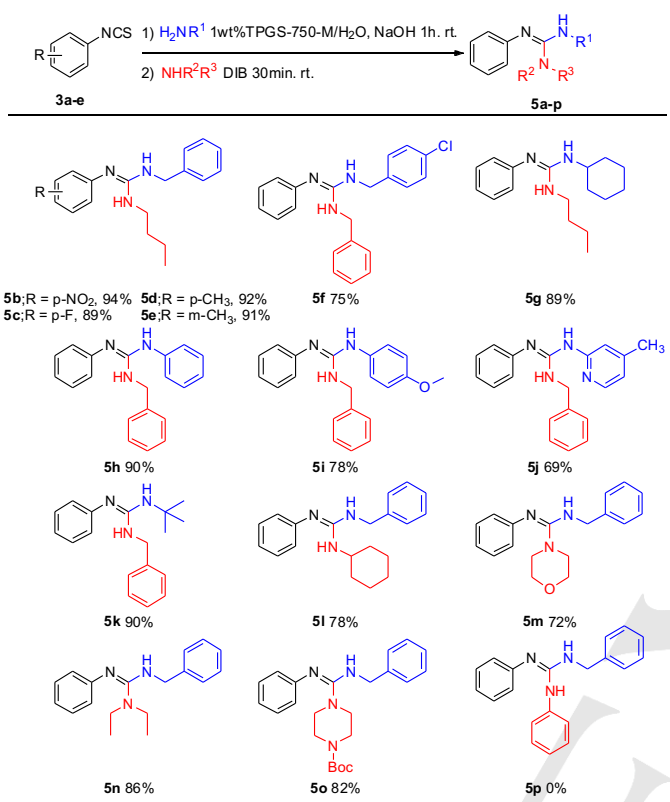
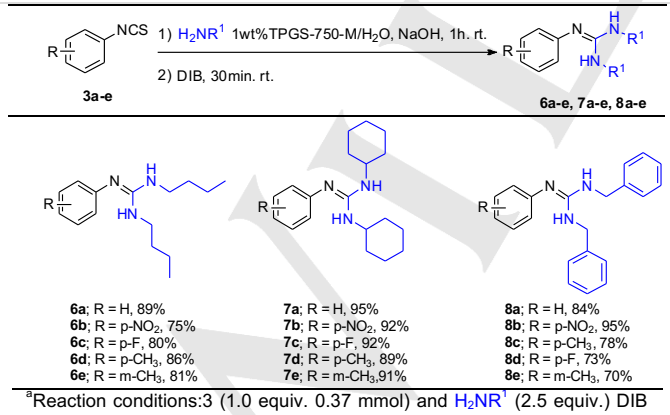
further purification (**Figure S1**). Having established an optimized reaction condition (Table 1, entry 14), we then explored the generality and scope of the reaction across a series of isothiocyanate and amine nucleophiles (**Scheme 2**).

Scheme 2. Substrate scope[a]



[a]Reaction condition: 3 (1.0 equiv. 0.37 mmol) and H_2NR^1 (1.0 equiv.), HNR^2R^3 (1.5 equiv.), DIB (1.2 equiv.) in water (1.0 M)

Scheme 3. Symmetric Guanidine Synthesis[a]



6a; R = H, 89%
6b; R = p-NO_2, 75%
6c; R = p-F, 80%
6d; R = p-CH_3, 86%
6e; R = m-CH_3, 81%

7a; R = H, 95%
7b; R = p-NO_2, 92%
7c; R = p-F, 92%
7d; R = p-CH_3, 89%
7e; R = m-CH_3,91%

8a; R = H, 84%
8b; R = p-NO_2, 95%
8c; R = p-CH_3, 78%
8d; R = p-F, 73%
8e; R = m-CH_3, 70%

[a]Reaction conditions:3 (1.0 equiv. 0.37 mmol) and H_2NR^1 (2.5 equiv.) DIB (1.2 equiv.) in water (1.0 M).

A panel of phenyl isothiocyanates (**3b-3e**) were reacted with benzylamine to form corresponding thioureas which were further coupled with *n*-butyl amine to generate desired guanidines (**5b-5e**) in good to excellent yields. Here, we demonstrated that phenyl isothiocyanates containing electron withdrawing group (nitro (**3b**) and fluorine groups (**3c**) and electron donating group (*p*-methyl(**3c**), *m*-methyl(**3e**) has no effect on the reaction efficiency. We next explored the scope of amine in the formation of thiourea. A variety of primary amines such as 4-chlorobenzylamine, *n*-buthylamine, cyclohexylamine, aniline, 4-mtoxyaniline and 2-aminopyridine were reacted smoothly with phenyl isothiocyanates **3a** which subsequently underwent guanidine formation with either benzyl or *n*-butyl amines to provide products **5f-5j** in satisfactory yields. Interestingly, bulky amine such as *tert*-butylamine also proceeded successfully, offering **5k** in excellent yield. Next, a variety of amines such as cyclohexylamine, morpholine and diethylamine were tested in the guanidine formation step. Under the optimized condition, products **5l-n** were isolated in high yields. Importantly, amine containing acid sensitive protecting group such as BOC protected piperazine were tolerated in our micellar in water system, and yielded product **5o** in 82% yield without any deprotected by-product. Unfortunately, reaction failed with aromatic amine (**5p**) and only corresponding thiourea intermediate was observed. This is probably due to the poor nucleophilic property of aniline. We also applied our micellar coupling reaction in water method to the synthesis of symmetrical guanidines. For symmetric guanidine, we were able to add an excess amount of amine (2.5 equivalents) at the first step. After stirring for 1 hour to ensure complete formation of thiourea, DIB was added to facilitate the guanidine formation with the remaining amine from the first step. As shown in **Scheme 3**, both electron-withdrawing and electron-donating group substituted on phenyl isothiocyanates (**3a-3e**) have almost no effect in thiourea and guanidine formation as they can react smoothly with butylamine, cyclohexylamine and benzylamine to provide the desired guanidines **6a-e**, **7a-e** and **8a-e,** respectively in excellent yields.

To demonstrate the recyclability of the waste water containing surfactant TPGS-750-M, we reacted phenyl isothiocyanate (**3a**) with benzylamine followed by cyclohexylamine (**Scheme 4**) under the optimized condition. After each reaction, small amount of ethyl acetate was added, and this organic layer containing product **5l** was collected and purified. The aqueous layer containing TPGS-750-M was then reused for three subsequent fresh reaction batches. Excellent results were obtained without any significant loss in product yields. Importantly, after 3 recycles, E-factor of 8.3 was found, indicating the low waste process of this protocol.

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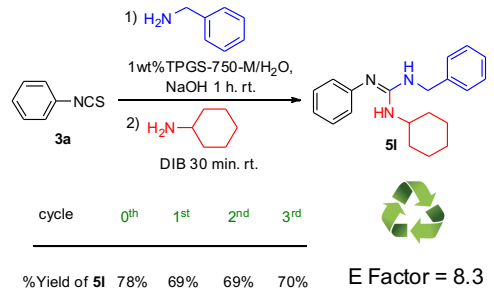
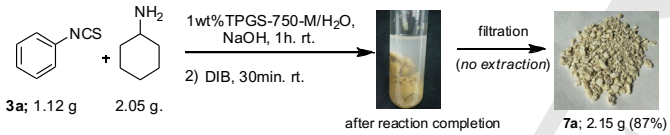


Scheme 4. Recycle Studies

To demonstrate the scalability of this protocol, the reaction was also performed on gram scale (**Scheme 5**). Treatment of **3a** (1.12 g.) with cyclohexylamine (2.05 g.) under optimized conditions. It resulted in the formation of **7a** in nearly excellent yield. Importantly, in large scale experiment, resulting product **7a** gradually underwent precipitation out of the reaction medium. Therefore, we were able to perform the simple filtration and then wash the solid with hexane/water without further purification by column chromatography. This suggested the possibility of reducing the use of organic solvent in extraction and purification process for large scale reaction. Notably, ^{1}H NMR of **7a** is clean showing no signal of surfactant, by-product iodobenzene or remaining amine (**Figure S43**).



Scheme 5. Gram scale synthesis of **7a**

Conclusions

In summary, we developed synthesis method for guanidine directly from isothiocyanate using DIB as desulfurizing reagent under aqueous micellar medium. The protocol has high selectivity and high functional group compatibility providing guanidines in high yields under mild reaction condition. The reactions are operationally very simple performing at room temperature in an open-air system. Importantly, micellar medium can be reused, providing a green and low waste process. Our methodology offers an alternative route for large-scale synthesis of guanidine for the chemical industries.

Experimental Section

All chemicals were obtained from commercial suppliers (Sigma Aldrich), Fluka (Switzerland) or Merck (Germany) and were used without further purification. All solvents were used directly without drying. Analytical thin-layer chromatography (TLC) was performed on Kieselgel F254 pre-coated plastic TLC plates from EM Science. Visualization was performed with a 254 nm ultraviolet lamp. Column chromatography was performed by using Merck and silica gel (60,230–400 mesh) from ICN Silitech. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 or BrukerAvance 400 for ^{1}H (400 MHz) and Bruker Avance 400 for ^{13}C (100 MHz) in $CDCl_3$ solution. Mass spectrometry was performed with a MicroTOF Bruker mass spectrometer and triple quadrupole GC/MS from Agilent Technologies.

General experimental procedure A: asymmetry guanidines 5a-5p

In a 5.0 mL reaction vial containing a magnetic stir bar, isothiocyanate (1.0 equivalent), amine (1.0 equivalent), NaOH (1.5 equivalent) and TPGS-750-M/H_2O (1wt%, 0.4 mL, 1.0 M) were sequentially added. The reaction mixture was stirred at room temperature for 1h. After starting material was completely consumed, as monitored by TLC, amine (1.5 equivalent) and DIB (1.2 equivalent) were sequentially added and stirring continued for 30 minutes. Then ethyl acetate (2x1mL) was added to the reaction mixture, which was stirred for 2 minutes. The organic layer was transferred using a Pasteur pipet and evaporated under reduced pressure to give the crude product. The residue was purified by column chromatography over silica gel by using 25%ethyl acetate in hexane to 100%ethyl acetate as eluent to obtain guanidine derivative.

General experimental procedure B: symmetry guanidines 6a-8e

In a 5.0 mL reaction vial containing a magnetic stir bar, isothiocyanate (1.0 equivalent), amine (2.5 equivalent), NaOH (1.5 equivalent) and TPGS-750-M/H_2O (1wt%, 0.4 mL, 1.0 M) were sequentially added. The reaction mixture was stirred at room temperature for 1h. after starting material was completely consumed, as monitored by TLC, DIB (1.2 equivalent) was sequentially added and stirring continued for 30 minutes. Then ethyl acetate (1 mL x 2) was added to the reaction mixture, which was stirred for 2 minutes. The organic layer was transferred using a Pasteur pipet and evaporated under reduced pressure to give the crude product. The residue was purified by column chromatography over silica gel by using 25%ethyl acetate in hexane to 100%ethyl acetate as eluent to obtain guanidine derivative.

Synthesis of guanidines

1-benzyl-3-butyl-2-phenylguanidine (**5a**)

General procedure A was followed, using phenyl isothiocyanate **3a** (51.1 mg, 0.3780 mmol), benzylamine (40.5 mg, 0.3780 mmol) and butylamine (41.4 mg, 0.5671 mmol). The compound was obtained in yellow oil (0.9489 g, 83% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (m, 7H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 2H), 4.39 (s, 2H), 3.12 (t, *J* = 7.2 Hz, 2H), 1.48-1.41 (m, 2H), 1.31-1.22 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 148.8, 138.9, 129.3, 128.7, 127.5, 127.3, 123.5, 122.0, 46.0, 41.8, 31.7, 19.9, 13.7 $[M+H]^+$: calcd 282.1970, found 282.1983.

1-benzyl-3-butyl-2-(4-nitrophenyl)guanidine (**5b**)

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General procedure A was followed, using 4-nitrophenylisothiocyanate **3a** (52.0 mg, 0.2886 mmol), benzylamine (31.5 mg, 0.2886 mmol) and butylamine (31.6 mg, 0.4329 mmol). The compound was obtained in yellow solid (0.0855 g, 94% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.6 Hz, 2H), 7.38-7.29 (m, 5H), 6.94 (d, *J* = 7.6 Hz, 2H), 4.41 (s, 2H), 3.14 (t, *J* = 7.2 Hz, 2H), 1.50-1.43 (m, 2H), 1.32-1.23 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 152.5, 141.1, 138.1, 128.8, 127.7, 127.3, 125.5, 122.6, 46.1, 41.9, 31.5, 19.9, 13.6. $[M+H]^+$: calcd 327.1821, found 327.1849

1-benzyl-3-butyl-2-(4-fluorophenyl)guanidine (**5c**)

General procedure A was followed, using 4-fluorophenylisothiocyanate **3a** (51.0 mg, 0.3330 mmol), benzylamine (36.0 mg, 0.3330 mmol) and butylamine (36.1 mg, 0.4995 mmol). The compound was obtained in colorless oil (0.0917 g, 92% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.27 (m, 5H), 6.98 (t, *J* = 8.8 Hz, 2H), 6.84 (dd, *J* = 8.2, 5.2 Hz, 2H), 4.40 (s, 2H), 3.13 (t, *J* = 7.2 Hz, 2H), 1.54-1.37 (m, 2H), 1.35-1.20 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4 (d, J_{C-F} = 237.7 Hz), 151.7, 145.9, 138.9, 128.7, 127.5, 127.3, 124.6 (d, J_{C-F} = 7.7 Hz), 115.9 (d, J_{C-F} = 21.8 Hz), 46.0, 41.6, 31.8, 19.9, 13.7. $[M+H]^+$: calcd 300.1876, found 300.1893

1-benzyl-3-butyl-2-(*p*-tolyl)guanidine (**5d**)

General procedure A was followed, using p-tolylphenylisothiocyanate **3a** (50.0 mg, 0.3351 mmol), benzylamine (36.1 mg, 0.3351 mmol) and butylamine (37.3 mg, 0.5027 mmol). The compound was obtained in yellow oil (0.0881 g, 89% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.22 (m, 3H), 7.17 (m, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.73 (d, *J* = 8.0 Hz, 2H), 4.28 (s, 2H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.20 (s, 3H), 1.40-1.28 (m, 2H), 1.21-1.11 (m, 2H), 0.78 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 146.9, 139.1, 130.9, 129.9, 128.7, 127.4, 127.3, 123.3, 46.0, 41.6, 31.8, 20.7, 20.0, 13.7. $[M+H]^+$: calcd 296.2127, found 296.2150

1-benzyl-3-butyl-2-(*m*-tolyl)guanidine (**5e**)

General procedure A was followed, using m-tolylphenylisothiocyanate **3a** (52.2 mg, 0.3497 mmol), benzylamine (37.3 mg, 0.3497 mmol) and butylamine (38.1 mg, 0.5246 mmol). The compound was obtained in yellow oil (0.0940 g, 91% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.27 (m, 5H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.85-6.70 (m, 3H), 4.39 (s, 2H), 3.12 (t, *J* = 7.2 Hz, 2H), 2.32 (s, 3H), 1.49-1.42 (m, 2H), 1.33-1.23 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 148.8, 139.0, 129.1, 128.7, 127.4, 127.3, 124.2, 122.7, 120.3, 46.1, 41.8, 31.8, 21.4, 19.9, 13.7. $[M+H]^+$: calcd 296.2127, found 296.2158

1-benzyl-3-(4-chlorobenzyl)-2-phenylguanidine (**5f**)

General procedure A was followed, using phenylisothiocyanate **3a** (50.9 mg, 0.3771 mmol), 4-chlorobenzylamine (53.2 mg, 0.3771 mmol) and benzylamine (60.9 mg, 0.5657 mmol). The compound was obtained in yellow oil (0.0989 g, 75% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.18 (m, 9H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.02 (t, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 2H), 4.34 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 148.6, 138.6, 137.4, 133.1, 129.5, 128.8, 128.8, 128.6, 127.6, 127.2, 123.5, 122.3, 46.1, 45.2. $[M+H]^+$: calcd 350.1424, found 350.1430

1-butyl-3-cyclohexyl-2-phenylguanidine (**5g**)

General procedure A was followed, using phenylisothiocyanate **3a** (50 mg, 0.3734 mmol), butylamine (27 mg, 0.3734 mmol) and cyclohexylamine (55 mg, 0.5601 mmol) The compound was obtained in yellow solid (0.0908 g, 89% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.6 Hz, 2H), 6.87 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 2H), 3.34-3.29 (m, 1H), 3.07 (t, *J* = 7.2 Hz, 2H), 1.92-1.89 (m, 2H), 1.68-0.93 (m, 12H), 0.85 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 129.2, 123.5, 121.6, 50.4, 41.9, 33.7, 31.9, 25.6, 24.8, 20.1, 13.8. $[M+H]^+$: calcd 274.2283, found 274.2284

1-benzyl-2,3-diphenylguanidine (**5h**)

General procedure A was followed, using phenylisothiocyanate **3a** (50.5 mg, 0.3746 mmol), aniline (35.5 mg, 0.3746 mmol) and benzylamine (60.1 mg, 0.5620 mmol) The compound was obtained in yellow solid (0.1016 g, 90% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.12 (m, 9H), 6.94-6.90 (m, 6H), 4.38 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 138.8, 129.5, 128.7, 127.6, 127.4, 123.5, 123.0, 46.0. $[M+H]^+$: calcd 302.1657, found 302.1652.

1-benzyl-3-(4-methoxyphenyl)-2-phenylguanidine (**5i**)

General procedure A was followed, using phenylisothiocyanate **3a** (50.8 mg, 0.3764 mmol), 4-methoxyphenylisothiocyanate (46.1 mg, 0.3764 mmol) and benzylamine (60.3 mg, 0.5646 mmol) The compound was obtained in yellow solid (0.0973 g, 78% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (m, 7H), 7.05 (d, *J* = 7.6 Hz, 3H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.37 (s, 2H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 138.6, 129.4, 128.6, 127.6, 127.4, 125.6, 123.4, 123.2, 114.8, 55.4, 46.1. $[M+H]^+$: calcd 332.1763, found 332.1757.

1-benzyl-3-(4-methylpyridin-2-yl)-2-phenylguanidine (**5j**)

General procedure A was followed, using phenylisothiocyanate **3a** (52.1 mg, 0.3854 mmol), 2-amino-4-metylpyridine (42.3 mg, 0.3854 mmol) and benzylamine (62.1 mg, 0.5782 mmol) The compound was obtained in yellow solid (0.0841 g, 69% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 5.2 Hz, 1H), 7.27-7.06 (m, 8H), 6.88 (m, 2H), 6.39 (d, *J* = 5.2 Hz, 1H), 6.22 (s, 1H), 4.26 (s, 2H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 151.3, 148.8, 147.6, 138.7, 129.4, 128.7, 127.4, 127.2, 123.5, 122.0, 115.5, 108.9, 46.0, 20.9. $[M+H]^+$: calcd 317.1766, found 316.1808

1-benzyl-3-(*tert*-butyl)-2-phenylguanidine (**5k**)

General procedure A was followed, using phenylisothiocyanate **3a** (53.0 mg, 0.3921 mmol), t-butylamine (27.3 mg, 0.3921 mmol) and benzylamine (63.2 mg, 0.5881 mmol) The compound was obtained in yellow solid (0.0993 g, 90% yield.); 1H NMR (400 MHz, CDCl3) δ 7.42-7.26 (m, 7H), 6.98 (t, *J* = 7.2 Hz, 1H), 6.91 (d, *J* = 7.2 Hz, 2H), 4.41 (s, 2H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 139.1, 129.3, 128.7, 127.4, 127.4, 123.2, 121.6, 50.9, 46.4, 30.1. $[M+H]^+$: calcd 282.1970, found 282.1964.

1-benzyl-3-cyclohexyl-2-phenylguanidine (**5l**)

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General procedure A was followed, using phenylisothiocyanate **3a** (50.0 mg, 0.3702 mmol), benzylamine (40.0 mg, 0.3702 mmol) and cyclohexylamine (55.1 mg, 0.5553 mmol) The compound was obtained in yellow solid (0.0887 g, 78% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.25 (m, 7H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 2H), 4.41 (s, 2H), 3.42-3.38 (m, 1H), 1.95-1.92 (m, 2H), 1.69-1.51 (m, 3H), 1.39-0.99 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 149.3, 139.1, 129.3, 128.7, 127.4, 127.4, 123.5, 121.8, 50.2, 46.0, 33.6, 25.5, 24.7. $[M+H]^+$: calcd 308.2127, found 308.2120

***N*-benzyl-*N'*-phenylmorpholine-4-carboximidamide** (**5m**)

General procedure A was followed, using phenylisothiocyanate **3a** (51.0 mg, 0.3772 mmol), benzylamine (40.5 mg, 0.3772 mmol) and morpholine (49.4 mg, 0.5658 mmol) The compound was obtained in yellow oil (0.0802 g, 72% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.17 (m, 7H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 2H), 4.32 (s, 2H), 3.73 (t, *J* = 4.4 Hz, 4H), 3.29 (t, *J* = 4.4 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 138.6, 129.4, 128.9, 127.7, 127.6, 122.8, 122.1, 66.7, 49.2, 48.5. $[M+H]^+$: calcd 296.1763, found 296.1785

3-benzyl-1,1-diethyl-2-phenylguanidine (**5n**)

General procedure A was followed, using phenylisothiocyanate **3a** (51.0 mg, 0.3775 mmol), benzylamine (40.4 mg, 0.3775 mmol) and diethylamine (41.2 mg, 0.5663 mmol) The compound was obtained in yellow oil (0.0913 g, 86% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.19 (m, 7H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 2H), 4.20 (s, 2H), 3.30 (q, *J* = 7.2 Hz, 4H), 1.18 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 150.3, 139.2, 129.0, 128.5, 127.5, 127.3, 122.1, 121.1, 49.3, 42.7, 13.1. $[M+H]^+$: calcd 282.1970, found 282.1977

***tert*-butyl-4-(*N*-benzyl-*N'*-phenylcarbamimidoyl)piperazine-1-carboxylate** (**5o**)

General procedure A was followed, using phenylisothiocyanate **3a** (50.1 mg, 0.3705 mmol), benzylamine (40.4 mg, 0.3705 mmol) and tert-Butyl-piperazine-1-carboxylate (103.2 mg, 0.5558 mmol) The compound was obtained in yellow oil (0.1198 g, 82% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.11 (m, 7H), 6.99-6.90 (m, 1H), 6.70 (d, J = 8.4 Hz, 2H), 4.20 (s, 2H), 3.45 (s, 4H), 3.21 (s, 4H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 154.7, 148.4, 138.7, 129.2, 128.7, 127.5, 127.4, 127.2, 122.2, 122.2, 79.9, 49.1, 47.6, 46.1, 28.4. $[M+H]^+$: calcd 395.2447, found 395.2433

1,3-dibutyl-2-phenylguanidine (**6a**)

General procedure B was followed, using phenylisothiocyanate **3a** (51.7 mg, 0.3748 mmol) and butylamine (68.1 mg, 0.9370 mmol). The compound was obtained in yellow oil (0.082.5 g, 89% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (t, *J* = 8.0 Hz, 2H), 6.95 (t, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 2H), 3.13 (t, *J* = 8.0 Hz, 4H), 1.53-1.46 (m, 4H), 1.37-1.28 (m, 4H), 0.90 (t, *J* = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 148.2, 129.2, 123.4, 122.0, 42.0, 31.8, 20.0, 13.7. $[M+H]^+$: calcd 248.2127, found 248.2127

1,3-dibutyl-2-(4-nitrophenyl)guanidine (**6b**)

General procedure B was followed, using 4-nitroaniline **3b** (51.9 mg, 0.3481 mmol), butylamine (63.6 mg, 0.8704 mmol) The compound was obtained in yellow oil (0.0632 g, 75% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.55 (s, 2H), 3.15 (t, *J* = 7.2 Hz, 4H), 1.61-1.42 (m, 4H), 1.36-1.29 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 152.3, 141.2, 125.7, 123.0, 41.9, 31.9, 20.2, 13.9. $[M+H]^+$: calcd 293.1978, found 293.1972.

1,3-dibutyl-2-(4-fluorophenyl)guanidine (**6c**)

General procedure B was followed, using 4-fluorophenylisothiocyanate **3c** (50.1 mg, 0.3271 mmol) and butylamine (59.8 mg, 0.8177 mmol). The compound was obtained in yellow oil (0.0694 g, 80% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (t, *J* = 8.4 Hz, 2H), 6.78 (dd, *J* = 8.4, 4.8 Hz, 2H) 3.12 (t, *J* = 7.2 Hz, 4H), 1.48 (m, 4H), 1.32 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3 (d, $J_{C\text{-}F}$ = 237.6 Hz), 152.0, 145.8, 124.5 (d, $J_{C\text{-}F}$= 7.7 Hz), 115.8 (d, $J_{C\text{-}F}$ = 21.8 Hz), 41.6, 31.8, 20.0, 13.7. $[M+H]^+$: calcd 266.2033, found 266.2044

1,3-dibutyl-2-(*p*-tolyl)guanidine (**6d**)

General procedure B was followed, using p-tolylphenylisothiocyanate **3d** (51.0 mg, 0.3418 mmol) and butylamine (62.5 mg, 0.8546 mmol). The compound was obtained in yellow oil (0.0768 g, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 8 Hz, 2H), 6.75 (d, *J* = 8 Hz, 2H), 3.14 (t, *J* = 7.2 Hz, 4H), 2.27 (s, 3H), 1.53-1.45 (m, 4H), 1.39-1.29 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 147.3, 130.6, 129.8, 123.4, 41.7, 31.9, 20.7, 20.1, 13.8. $[M+H]^+$: calcd 262.2283, found 262.2277

1,3-dibutyl-2-(*m*-tolyl)guanidine (**6e**)

General procedure B was followed, using m-tolylphenylisothiocyanate **3e** (52.1 mg, 0.3491 mmol) and butylamine (64.4 mg, 0.8728 mmol). The compound was obtained in yellow oil (0.0739 g, 81% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (td, *J* = 7.6, 1.2 Hz, 1H), 6.73(d, *J* =7.6 Hz, 1H), 6.69(s, 1H), 6.66(d, *J* = 7.6 Hz, 1H), 3.12 (t, *J* = 7.2 Hz, 4H), 2.27 (s, 3H), 1.54-1.44 (m, 4H), 1.39-1.27 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 150.0, 138.9, 129.0, 124.4, 122.3, 120.4, 41.7, 31.9, 21.3, 20.1, 13.8. $[M+H]^+$: calcd 262.2283, found 262.2295

1,3-dicyclohexyl-2-phenylguanidine (**7a**)

General procedure B was followed, using phenylisothiocyanate **3a** (52.5 mg, 0.3887 mmol) and cyclohexylamine (96.3 mg, 0.9717 mmol). The compound was obtained in yellow solid (0.1015 g, 95% yield.);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.6 Hz, 2H), 6.92 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 7.6 Hz 2H), 3.37-3.32 (m, 2H), 1.94-1.92 (m, 4H), 1.67-1.53 (m, 6H), 1.29-1.06 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.93, 129.29, 123.47, 122.01, 50.62, 33.67, 25.61, 24.93. $[M+H]^+$: calcd 300.2440, found 300.2447

1,3-dicyclohexyl-2-(4-nitrophenyl)guanidine (**7b**)

General procedure B was followed, using 4-nitrophenylisothiocyanate **3b** (50.1 mg, 0.2782 mmol) and cyclohexylamine (69.2 mg, 0.6955 mmol). The compound was

obtained in yellow solid (0.0881 g, 92% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.2 Hz, 2H), 6.93 (d, *J* = 9.2 Hz, 2H), 3.40-3.33 (m, 2H), 1.98-1.90 (m, 4H), 1.72-1.53 (m, 6H), 1.33-1.12 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 151.2, 141.1, 125.5, 122.1, 50.9, 33.4, 25.3, 24.7. $[M+H]^+$: calcd 345.2291, found 3345.2294

1,3-dicyclohexyl-2-(4-fluorophenyl)guanidine (**7c**)

General procedure B was followed, using 4-fluorophenylisothiocyanate **3c** (51.1 mg, 0.3337 mmol) and cyclohexylamine (82.7 mg, 0.8343 mmol). The compound was obtained in colorless solid (0.0974 g, 92% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (t, *J* = 8.0 Hz, 2H), 6.77 (dd, *J* = 8.0, 4.0 Hz, 2H), 3.35 (s, 2H), 1.95-1.92 (m, 4H), 1.66-1.54 (m, 6H), 1.37-0.96 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, (d, J_{C-F} = 237.6 Hz), 150.7, 124.5 (d, J_{C-F} = 7.7 Hz), 115.7 (d, J_{C-F} = 21.8 Hz), 50.3, 33.7, 25.6, 24.9. $[M+H]^+$: calcd 318.2346, found 318.2363

1,3-dicyclohexyl-2-(*p*-tolyl)guanidine (**7d**)

General procedure B was followed, using p-tolylphenylisothiocyanate **3d** (50.2 mg, 0.3364 mmol) and cyclohexylamine (73.5 mg, 0.8410 mmol). The compound was obtained in ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 7.6 Hz, 2H), 6.76 (d, *J* = 7.6 Hz, 2H), 3.36 (s, 2H), 2.26 (s, 3H), 1.96-1.94 (m, 4H), 1.67-1.54 (m, 6H), 1.35-1.02 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 131.1, 129.8, 123.2, 50.4, 33.6, 25.5, 24.8, 20.7. $[M+H]^+$: calcd 314.2596, found 314.2604

1,3-dicyclohexyl-2-(*m*-tolyl)guanidine (**7e**)

General procedure B was followed, using m-tolylphenylisothiocyanate **3e** (50.2 mg, 0.3364 mmol) and cyclohexylamine (83.4 mg, 0.8410 mmol). The compound was obtained in colorless solid (0.0959 g, 91% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.69 (s, 1H), 6.65 (d, *J* = 7.6 Hz), 3.41-3.36 (m, 2H), 2.27 (s, 3H), 2.06-1.87 (m, 4H), 1.73-1.54 (m, 6H), 1.39-1.03 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 138.8, 128.9, 124.3, 122.3, 120.3, 50.2, 33.7, 25.6, 24.9, 21.3. $[M+H]^+$: calcd 314.2596, found 314.2611

1,3-dibenzyl-2-phenylguanidine (**8a**)

General procedure B was followed, using phenylisothiocyanate **3a** (51.4 mg, 0.3802 mmol) and benzylamine (101.8 mg, 0.9505 mmol). The compound was obtained in yellow oil (0.1008 g, 84% yield.) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.00 (m, 12H), 6.91-6.85 (m, 3H), 4.23 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 148.3, 138.6, 129.4, 128.7, 127.4, 127.2, 123.4, 122.2, 46.1. $[M+H]^+$: calcd 316.1814, found 316.1839

1,3-dibenzyl-2-(4-nitrophenyl)guanidine (**8b**)

General procedure B was followed, using 4-nitrophenylisothiocyanate **3b** (52.0 mg, 0.2886 mmol) and benzylamine (77.3 mg, 0.7216 mmol). The compound was obtained in yellow solid (0.0998 g, 95% yield.);^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.0 Hz, 2H), 7.53-7.06 (m, 10H), 7.00 (d, *J* = 8.0 Hz, 2H), 4.41 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 151.6, 137.9, 128.9, 127.7, 127.2, 125.5, 123.0, 46.1. $[M+H]^+$: calcd 361.1665, found 361.1659

1,3-dibenzyl-2-(4-fluorophenyl)guanidine (**8c**)

General procedure B was followed, using 4-fluorophenylisothiocyanate **3c** (50.9 mg, 0.3328 mmol) and benzylamine (89.1 mg, 0.8320 mmol). The compound was obtained in yellow oil (0.086.5 g, 78% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (m, 10H), 7.00 (t, *J* = 8.4 Hz, 4H), 6.90 (dd, *J* = 8.4, 5.2 Hz), 4.37 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7 (d, J_{C-F} = 238.2 Hz), 151.7, 145.0, 138.5, 128.7, 127.5, 127.2, 124.6 (d, J_{C-F} = 7.7 Hz), 116.0 (d, J_{C-F} = 11.8 Hz), 46.0. $[M+H]^+$: calcd 3334.17206, found 334.1719

1,3-dibenzyl-2-(*p*-tolyl)guanidine (**8d**)

General procedure B was followed, using p-tolylphenylisothiocyanate **3d** (53.9 mg, 0.3615 mmol) and benzylamine (96.8 mg, 0.9039 mmol). The compound was obtained in yellow oil (0.0869 g, 73% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.17 (m, 10H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 4.38 (s, 4H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 146.3, 138.8, 131.3, 130.0, 128.7, 127.4, 127.2, 123.3, 46.0, 20.8. $[M+H]^+$: calcd 330.1970, found 330.1977

1,3-dibenzyl-2-(*m*-tolyl)guanidine (**8e**)

General procedure B was followed, using m-tolylphenylisothiocyanate **3e** (52.9 mg, 0.3548 mmol) and benzylamine (95.0 mg, 0.8870 mmol). The compound was obtained in yellow oil (0.0818 g, 70% yield.) ;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.15 (m, 11H), 6.85-6.79 (m, 3H), 4.39 (s, 4H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 149.2, 139.1, 138.9, 129.2, 128.7, 127.4, 127.3, 124.3, 122.9, 120.4, 46.0, 21.5. $[M+H]^+$: calcd 330.1970, found 330.1975

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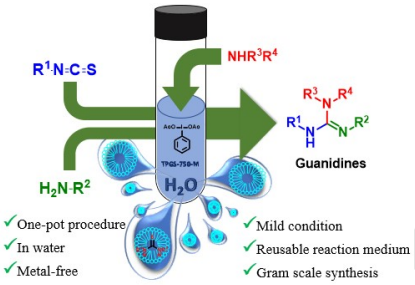
FULL PAPER

A new one-pot synthesis of guanidine directly from isothiocyanates is developed using mild oxidizing agent, hypervalent iodine (III), in green medium TPGS-750-M/H_2O. Waste medium from the reaction can be reused up to 3 time providing E-factor of 8.3 which indicates the low waste process of this protocol.



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Micelle-enabled one pot guanidine synthesis in water directly from isothiocyanate using hypervalent iodine(III) reagents under mild condition