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One-pot synthesis of diverse *N*,*N*′-disubstituted guanidines from *N*-chlorophthalimide, isocyanides and amines *via N*-phthaloyl-guanidines†

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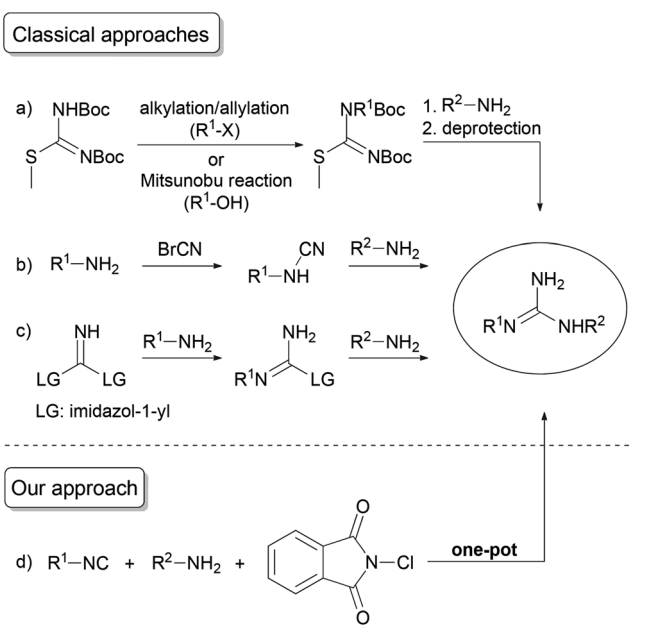
A sequential one-pot approach towards *N*,*N*′-disubstituted guanidines from *N*-chlorophthalimide, isocyanides and amines is reported. This strategy provides straightforward and efficient access to diverse guanidines in yields up to 81% through previously unprecedented *N*-phthaloylguanidines. This protocol also features wide substrate scope and mild conditions.

Introduction

The guanidine functionality is a privileged structure in many natural products, biochemical processes and pharmaceuticals, playing key roles in various biological functions.[1] Moreover, guanidines also serve as valuable scaffolds in organocatalysis[2] and precursors for the synthesis of heterocycles.[3] The traditional synthesis of guanidines mainly relies on the addition of amines to carbodiimides,[4] or utilizes thioureas (usually bearing electron-withdrawing substituents) in conjunction with thiophilic metal salts,[5] Mukaiyama's reagent,[6] coupling reagents,[7] or other activating agents.[8] *S*-Oxidized thiourea derivatives[9] and guanylating agents[10] (such as *S*-methylisothioureas, pyrazole-1-carboximidamide and its derivatives, or triflyl guanidines) are also commonly employed. Beyond the well-known[11] and recently[12] developed approaches, a few isocyanide-based procedures have also been established, albeit each method exclusively affords *N*,*N*′,*N*″-substituted guanidines.[13]

Looking at the synthetic toolbox for the assembly of *N*,*N*′-disubstituted guanidines, *N*-protected *S*-methylisothioureas are often used as starting materials; however, the techniques available for the derivatization of isothioureas lack the achievable diversity (Scheme 1a).[14] *N*,*N*′-Disubstituted guanidines can also be obtained from amines through cyanamides, but utilization of toxic cyanogen bromide and harsh conditions are required (Scheme 1b).[15] The application of a commercially available guanylating reagent di(imidazole-1-yl)methanimine offers a more convenient access to *N*,*N*′-disubstituted guanidines through the stepwise displacement of its imidazole groups by amines (Scheme 1c).[16] Besides the necessary isolation of intermediates, the nucleophilicity of amines can strongly affect the sequence of substitution and the yield of products, or even limit the achievable substitution pattern. Therefore, the development of a facile and general one-pot procedure for the synthesis of diverse *N*,*N*′-substituted guanidines is still highly desired.



Scheme 1 Classical and new routes to *N*,*N*′-disubstituted guanidines.

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†Electronic supplementary information (ESI) available: Experimental procedures, mechanistic study, compound characterization data and copies of NMR spectra. See DOI: 10.1039/c7ob03109b

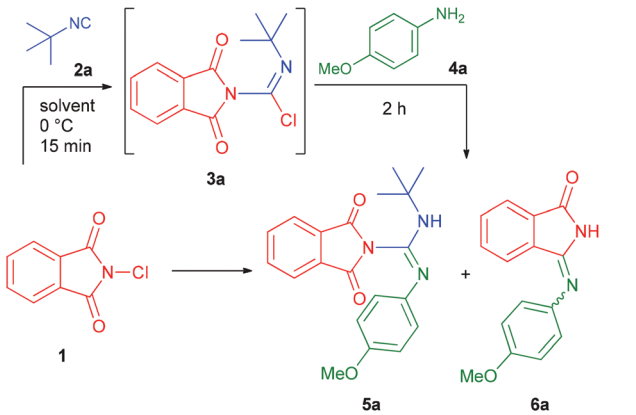
Herein, we report a new approach for the synthesis of *N*,*N*′-disubstituted guanidines employing *N*-chlorophthalimide, isocyanides and amines as substrates in a sequential one-pot protocol (Scheme 1d).

Results and discussion

At the outset of the study, the model reaction of *N*-chlorophthalimide (**1**) with *tert*-butyl isocyanide (**2a**) and *p*-anisidine (**4a**) was investigated (Table 1). On the basis of literature information on the addition of analogous *N*-chloroamines to isocyanides,[13a] we presumed the need for the prior formation of the imidoyl chloride intermediate **3a**, which can react with *p*-anisidine to furnish *N*-phthaloylguanidine **5a**. Pleasingly, the addition of *N*-chlorophthalimide to *tert*-butyl isocyanide took place rapidly in dichloromethane at 0 °C with full conversion. However, further reaction with *p*-anisidine led to the desired guanidine **5a** in only 12% HPLC yield, along with an unexpected side-product, which was identified as isoindolinone **6a** (Table 1, entry 1). In order to optimize the reaction conditions, various solvents were tested (entries 1–15). Acetonitrile was found to be the best medium affording **5a** in 75% HPLC yield, while non-polar solvents and ethers led to **6a** predominantly. In order to avoid the formation of the urea-type product, anhydrous solvents were used; however, "wet" acetonitrile provided **5a** in almost identical yield (entry 15). Decreasing the temperature gave **5a** in lower yields, while elevated temperatures had no significant effect on the outcome of the reaction (entries 16–20). It is noteworthy, that the replacement of **1** with *N*-bromo- or *N*-iodophthalimide resulted in complex reaction mixtures and no trace of **5a** or **6a**.[17]

Interestingly, performing the reaction with aromatic isocyanide **2b** under the optimized conditions failed to produce the corresponding guanidine **5b** (Table 2, entry 1). However, application of an equimolar amount of base (KO*t*Bu, DBU, Na_2CO_3 or tertiary aliphatic amine) in order to neutralize the liberated hydrogen chloride promoted the formation of **5b** (Table 2, entries 7–12). Other bases were ineffective and gave access only to isoindolinone **6a** (Table 2, entries 2–6). The best result

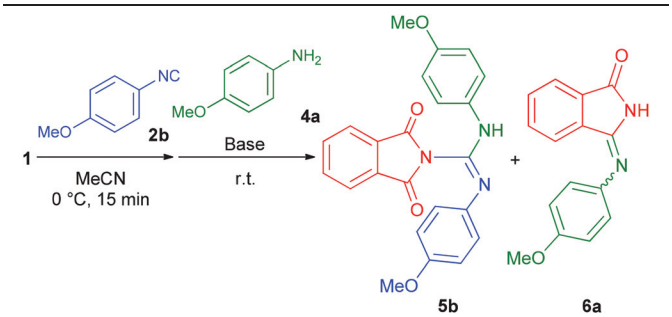
Table 1 Optimization of the model reaction[a]



Entry	Solvent	Temp.[b]	Yield of 5a[c] [%]	Yield of 6a[c] [%]
1	CH_2Cl_2	r.t.	12	40
2	DMSO	r.t.	0	0
3	MeOH	r.t.	1	8
4	1,4-Dioxane	r.t.	5	26
5	THF	r.t.	7	32
6	Et_2O	r.t.	11	24
7	$CHCl_3$	r.t.	16	30
8	Toluene	r.t.	4	46
9	EtOAc	r.t.	20	26
10	DMF	r.t.	26	3
11	Acetone	r.t.	45	18
12	CH_3NO_2	r.t.	48	8
13	IPA	r.t.	66	10
14	MeCN	r.t.	75	5
15	MeCN[d]	r.t.	72	7
16	MeCN	−40 °C	29	5
17	MeCN	−20 °C	30	13
18	MeCN	0 °C	47	11
19	MeCN	40 °C	73	2
20	MeCN	60 °C	66	6

[a] Reaction conditions: *N*-Chlorophthalimide (0.25 mmol), anhydrous solvent (0.50 ml), *t*-butyl isocyanide (1.1 equiv.), 15 min, 0 °C, then *p*-anisidine (1.2 equiv.), 2 h. [b] Temperature after the addition of *p*-anisidine. [c] Yield was determined by HPLC (each product was calibrated). [d] Non-dried solvent was used.

Table 2 The effect of base on the reaction performed with aromatic isocyanide **2b**[a]



Entry	Base	Yield of 5b[b] [%]	Yield of 6a[b] [%]
1	—	0	32
2	TMG	0	13
3	Proton Sponge	0	23
4	Pyridine	0	45
5	DMAP	0	46
6	*N*-Methylimidazole	0	48
7	KO*t*Bu	1	16
8	DBU	2	13
9	Na_2CO_3	10	32
10	DABCO	39	28
11	DIPEA	47	41
12	NEt_3	48	31

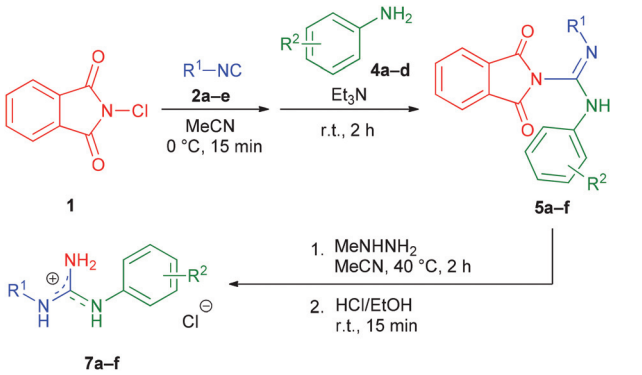
[a] Reaction conditions: *N*-Chlorophthalimide (0.25 mmol), anhydrous MeCN (0.50 ml), 4-methoxyphenyl isocyanide (1.1 equiv.), 15 min, 0 °C, then base (1.0 equiv.) and *p*-anisidine (1.2 equiv.), r.t., 2 h. [b] Yield was determined by HPLC (each product was calibrated).

was achieved when triethylamine was utilized, providing **5b** in an acceptable 48% HPLC yield (Table 2, entry 12).

To investigate the scope of the reaction and the cleavability of the phthaloyl moiety, six structurally different *N*-phthaloylguanidines **5a–f** were first synthesized by employing aliphatic (substrates **2a,c**), benzylic (substrate **2d**) or aromatic (substrates **2b,e**) isocyanides and anilines bearing both electron-donating (substrates **4a,c**) and electron-withdrawing groups (substrates **4b,d**) (Table 3, entries 1–6). The reactions proceeded smoothly in the presence of triethylamine under the optimized conditions providing **5a–f** in a non-protonated form in 28–68% isolated yields.[18] To our delight, further treatment of **5a–f** with methylhydrazine completely removed the phthaloyl group in all cases, leading to the desired *N*,*N*′-disubstituted guanidines **7a–f** in excellent yields under mild conditions (Table 3, entries 1–6).[19,20] Obtaining the products as hydrochloride salts facilitated the isolation procedure.

Although **5a–f** were readily formed, their isolation proved to be rather demanding and required individual chromatographic conditions (see the ESI† for details). Therefore, we decided to combine the steps of the *N*,*N*′-disubstituted guanidine synthesis into a sequential one-pot three-step protocol and omit the isolation of *N*-phthaloylguanidine intermediates. First, the scope of the combined method with respect to the isocyanide reagent was evaluated, using **4a** as an aniline input (Table 4). Gratifyingly, both aliphatic and benzylic, as well as

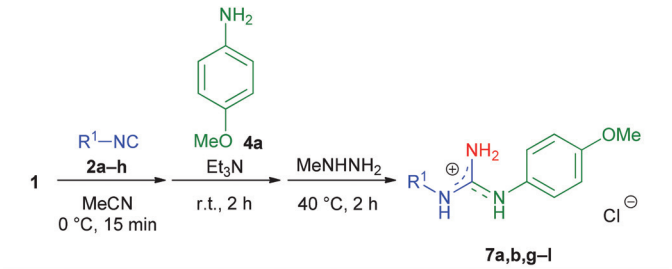
Table 3 Synthesis and hydrazinolysis of *N*-phthaloyl-guanidines[a,b]

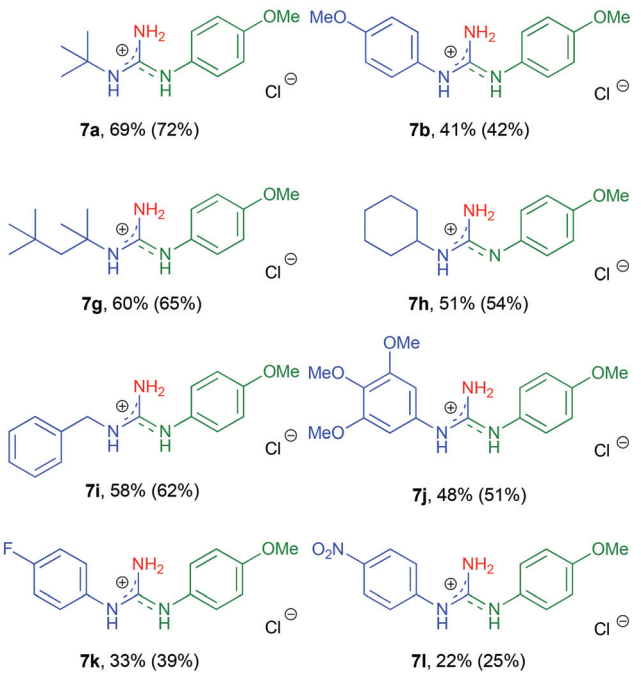


Entry	2	R^1	4	R^2	5	Yield[c] [%]	7	Yield[c] [%]
1	**2a**	*t*-Bu	**4a**	4-MeO	**5a**	68 (73)	**7a**	98 (99)
2	**2b**	4-MeOC$_6$H$_4$	**4a**	4-MeO	**5b**	31 (49)	**7b**	94 (98)
3	**2b**	4-MeOC$_6$H$_4$	**4b**	4-Br	**5c**	28 (44)	**7c**	96 (99)
4	**2c**	*c*-Hex	**4c**	3,5-Me	**5d**	29 (64)	**7d**	96 (98)
5	**2d**	Bn	**4d**	4-F	**5e**	48 (54)	**7e**	97 (99)
6	**2e**	4-FC$_6$H$_4$	**4e**	H	**5f**	30 (47)	**7f**	96 (99)

[a] Reaction conditions for the synthesis of **5a–f**: *N*-Chlorophthalimide (1.0 mmol), anhydrous MeCN (2.0 ml), isocyanide (1.1 equiv.), 0 °C, 15 min, then Et$_3$N (1.0 equiv.) and aniline (1.2 equiv.), r.t., 2 h. [b] Reaction conditions for the synthesis of **7a–f**: Guanidine **5a–f** (0.25 mmol), MeCN (0.5 ml), MeNHNH$_2$ (1.5 equiv.), 40 °C, 2 h, then HCl/EtOH (3 equiv.), r.t., 15 min [c] Isolated yield (NMR yield in parenthesis). NMR yield was determined by ^{1}H-NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

Table 4 Scope of the one-pot three-step synthesis with respect to isocyanide[a]





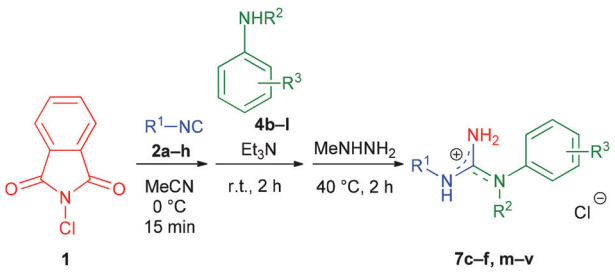
[a] Reaction conditions: *N*-Chlorophthalimide (1.0 mmol), anhydrous MeCN (2.0 ml), isocyanide (1.1 equiv.), 0 °C, 15 min, then Et$_3$N (1.0 equiv.) and aniline (1.2 equiv.), r.t., 2 h, then MeNHNH$_2$ (1.5 equiv.), 40 °C, 2 h. The products were isolated as hydrochloride salts. Isolated yield (NMR yield in parenthesis). NMR yield was determined by ^{1}H-NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

aromatic isocyanides could be subjected to the reaction; however, their electronic nature had a notable impact on the overall yield of the products. Benzylic and aliphatic isocyanides (including the sterically hindered 1,1,3,3-tetramethylbutyl isocyanide) provided the best results (**7a** and **7g–i**, 51–69% isolated yields), while aromatic isocyanides bearing electron-donating MeO or electron-withdrawing F substituents delivered the corresponding guanidine hydrochlorides **7b,j** and **7k** in moderate yields (33–48%).

Unfortunately, the strongly electron-deficient 4-nitrophenyl isocyanide was barely tolerated (**7l**, 22% isolated yield), while methyl isocyanoacetate, TosMIC and 2-isocyano- or 3-isocyanopyridine did not afford the desired products.

To further explore the generality of our protocol, various anilines were subjected to the one-pot reaction applying the

Table 5 Scope of the one-pot three-step synthesis with respect to aniline[a]

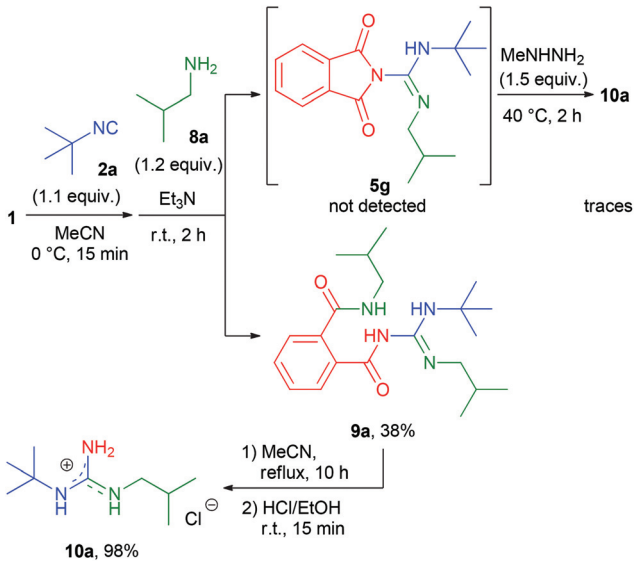


Entry	2	R^1	4	R^2	R^3	7	Yield[b] [%]
1	**2a**	*t*-Bu	**4f**	H	2,4-F	**7m**	73 (78)
2	**2a**	*t*-Bu	**4g**	Me	H	**7n**	66 (71)
3	**2f**	*t*-Octyl	**4h**	H	4-CF_3	**7o**	55 (61)
4	**2f**	*t*-Octyl	**4i**	H	3-I	**7p**	64 (68)
5	**2c**	*c*-Hex	**4c**	H	3,5-Me	**7d**	56 (58)
6	**2c**	*c*-Hex	**4j**	H	4-Me-3-NO_2	**7q**	35 (38)
7	**2d**	Bn	**4d**	H	4-F	**7e**	52 (54)
8	**2d**	Bn	**4k**	H	4-(NMe_2)	**7r**	47 (51)
9	**2b**	4-$MeOC_6H_4$	**4e**	H	H	**7s**	42 (43)
10	**2b**	4-$MeOC_6H_4$	**4b**	H	4-Br	**7c**	34 (42)
11	**2g**	3,4,5-$MeOC_6H_2$	**4e**	H	H	**7t**	43 (45)
12	**2e**	4-FC_6H_4	**4e**	H	H	**7f**	37 (39)
13	**2e**	4-FC_6H_4	**4l**	H	4-CN	**7u**	27 (33)
14	**2h**	4-$NO_2C_6H_4$	**4e**	H	H	**7v**	35 (37)

[a] Reaction conditions: *N*-Chlorophthalimide (1.0 mmol), anhydrous MeCN (2.0 ml), isocyanide (1.1 equiv.), 0 °C, 15 min, then Et_3N (1.0 equiv.) and aniline (1.2 equiv.), r.t., 2 h, then $MeNHNH_2$ (1.5 equiv.), 40 °C, 2 h. The products were isolated as hydrochloride salts. [b] Isolated yield (NMR yield in parenthesis). NMR yield was determined by ^{1}H-NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

previously utilized isocyanides (Table 5, entries 1–14). Interestingly, both electron-rich and electron-poor anilines were equally tolerated. The electronic effect of substituents was not significant, with the exception of the nitro group (substrate **4j**, Table 5, entry 6). Even *N*-substituted anilines could be used, as exemplified by *N*-methylaniline (Table 5, entry 2). Guanidines derived from aliphatic and benzyl isocyanides were obtained in the highest yields (**7d**,**e** and **7m–r**, up to 73% isolated yield), while aromatic isocyanides, especially with electron-withdrawing substituents, furnished the corresponding **7c**,**f** and **7s–v** products in lower yields ranging from 27 to 43%. These results suggest that the overall performance of our method principally depends on the reactivity of the isocyanide component.

As an extension of the one-pot protocol towards *N*,*N*′-dialkylguanidines, we next surveyed the reaction of isobutylamine (**8a**) with **1** and **2a** under standard conditions (Scheme 2). Surprisingly, no appreciable amount of guanidine **10a** was produced and no trace of the expected intermediate **5g** could be detected. Instead, compound **9a** was isolated as the main product, presumably as a result of the subsequent reaction of **5g** with an additional molecule of amine. Unfortunately, preventing the instantaneous ring-opening reaction by decreasing



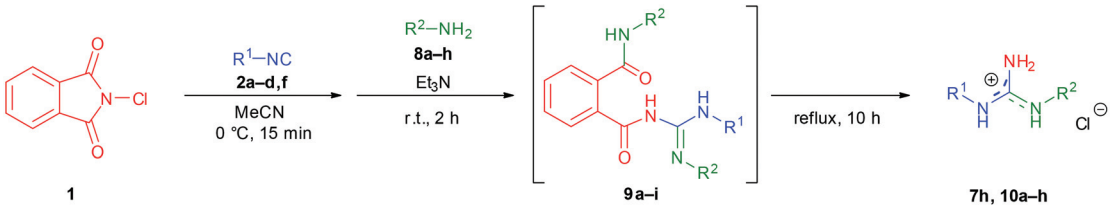
Scheme 2 Unexpected ring-opening with aliphatic amine **8a**.

the temperature (−40 °C) was not successful. Nevertheless, we reasoned that product **9a** might also be transformed to the desired *N*,*N*′-disubstituted guanidine **10a** by a straightforward intramolecular cleavage. Our hypothesis was supported by the reaction mechanism of phthalimide deprotection with aliphatic amines.[21] Indeed, simply heating **9a** alone in refluxing acetonitrile for 10 h readily generated guanidine **10a** in an almost quantitative yield (Scheme 2).

Afterwards, a series of primary aliphatic and aralkyl amines were tested in a combined one-pot three-step manner (Table 6, entries 1–9). Intermediates **9a–i** were formed smoothly by reacting **1** with isocyanides and amines under slightly modified conditions (2.2 equivalents of primary amine were used). Subsequent heating of the reaction mixtures at reflux temperature gave complete conversion of **9a–i** within 10 h furnishing, in all cases, guanidine hydrochlorides in moderate to good yields (44–81%). We were pleased to find that bifunctional aliphatic amines, such as aminoalcohol **8b** and Boc-protected diaminobutane **8d**, were compatible with the protocol and provided the corresponding guanidines **10b** and **10d** in 80% and 55% isolated yields, respectively (Table 6, entries 2 and 4). Moreover, propargylamine (**8e**) and the sterically demanding *tert*-butylamine (**8f**) were also well tolerated (Table 6, entries 5 and 6). Alternatively, *N*-alkyl-*N*′-aryl guanidines are readily accessible from aromatic isocyanides as well, as demonstrated by the synthesis of **7h** (Table 6, entry 9). Although their synthetic routes are somewhat different, it is noteworthy that aliphatic and aralkyl amines provided the corresponding guanidines generally in better yields compared to anilines (see the two complementary synthesis of **7h**). This, most probably, is due to their higher nucleophilicity.

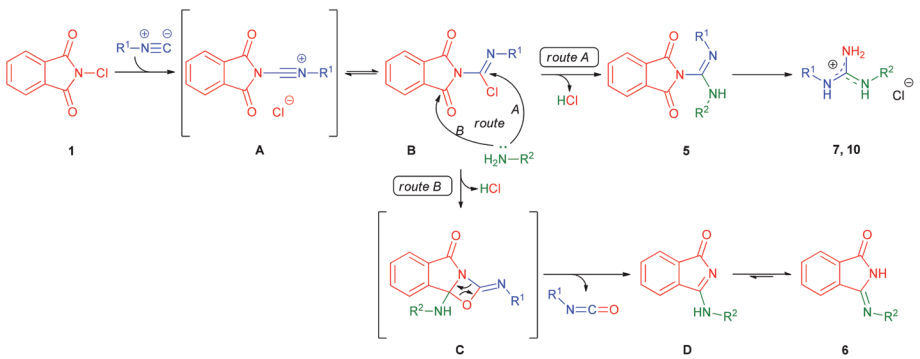
Based on the above results and observations, a plausible mechanism is proposed (Scheme 3). In the first step, *N*-chlorophthalimide **1** undergoes α-addition to isocyanide to

Table 6 One-pot three-step synthesis of *N,N'*-disubstituted guanidines from aliphatic and aralkyl amines[a]



Entry	2		8		Product	Yield[b] [%]
1	**2a**	R^1 = *t*-Bu	**8a**	R^2 = i-Bu	**10a**	81 (84)
2	**2a**	R^1 = *t*-Bu	**8b**	R^2 = $HO(CH_2)_5$	**10b**	80 (85)
3	**2f**	R^1 = *t*-Octyl	**8c**	R^2 = $C_6H_5(CH_2)_2$	**10c**	72 (78)
4	**2f**	R^1 = *t*-Octyl	**8d**	R^2 = $BocNH(CH_2)_4$	**10d**	55 (62)
5	**2c**	R^1 = *c*-Hex	**8e**	R^2 = $HCCCH_2$	**10e**	44 (47)
6	**2c**	R^1 = *c*-Hex	**8f**	R^2 = *t*-Bu	**10f**	64 (68)
7	**2d**	R^1 = Bn	**8g**	R^2 = *c*-Hex	**10g**	71 (75)
8	**2d**	R^1 = Bn	**8h**	R^2 =	**10h**	53 (64)
9	**2b**	R^1 = 4-$MeOC_6H_4$	**8g**	R^2 = *c*-Hex	**7h**	66 (70)

[a] Reaction conditions: *N*-Chlorophthalimide (1.0 mmol), anhydrous MeCN (2.0 ml), isocyanide (1.1 equiv.), 0 °C, 15 min, then Et_3N (1.0 equiv.) and amine (2.2 equiv.), r.t., 2 h, then reflux, 10 h. The products were isolated as hydrochloride salts. [b] Isolated yield (NMR yield in parenthesis). NMR yield was determined by ^{1}H-NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.



Scheme 3 Proposed reaction mechanism.

form imidoyl chloride **B** through nitrilium species **A**. Then, nucleophilic attack of the amine takes place, which can occur either on the imidoyl carbon to provide guanidine products (route A), or on the carbonyl carbon to give intermediate **C** (route B). The subsequent rearrangement of **C** results in isoindolone **D** along with an isocyanate by-product. Finally, **D** undergoes tautomerization to afford the more stable[22] isoindolinone **6**. To support the mechanism, the formation of isocyanate was confirmed by control experiments and a representative example of **B** was also isolated (see the ESI† for details).

Conclusions

In conclusion, we have developed a new and efficient synthesis of *N*,*N*′-disubstituted guanidines from readily available *N*-chlorophthalimide, isocyanides and amines in a sequential one-pot manner. The reactions proceed through the formation of *N*-phthaloylguanidines, which represent a novel class of guanidines. This operationally simple method tolerates both aromatic and aliphatic substrates in all possible combinations, providing general and diverse access to *N*-alkyl-*N*′-aryl, *N*-aryl-*N*′-aryl and *N*-alkyl-*N*′-alkyl guanidines with broad substrate scope.

Experimental section

General procedure for the one-pot synthesis of guanidines 7a–v

To a cooled suspension of *N*-chlorophthalimide (1.0 mmol, 182 mg) in anhydrous acetonitrile (2 mL) isocyanide (1.1 mmol) was added and stirred at 0 °C for 15 min. Then triethylamine (1.0 mmol, 140 μL) and subsequently the corresponding aniline (1.2 mmol) were added and the reaction mixture was allowed to warm to room temperature. After stirring for 2 h, methylhydrazine (1.5 mmol, 79 μL) was added, and the stirring was continued at 40 °C for 2 h. Then the reaction mixture was poured into aqueous NaOH solution (30 mL, 1 M) and extracted with chloroform (4 × 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* until complete removal of the solvent and triethylamine. The residue was purified by flash column chromatography on neutral alumina (RediSep Rf; EtOAc : hexanes 0 : 100–100 : 0 gradient, then eluent switch to methanol : chloroform 0 : 100–1 : 10 gradient) to afford the pure guanidine base, which was then treated with HCl in ethanol (1 M, 2–3 equiv.) and stirred at room temperature for 15 min. Finally, evaporation to dryness followed by trituration with *n*-hexane or diisopropyl ether or diethyl ether (if necessary) gave pure guanidine hydrochlorides **7a–v**.

General procedure for the one-pot synthesis of guanidines 10a–h

To a cooled suspension of *N*-chlorophthalimide (1.0 mmol, 182 mg) in anhydrous acetonitrile (2 mL) isocyanide (1.1 mmol) was added and stirred at 0 °C for 15 min. Then triethylamine (1.0 mmol, 140 μL) and subsequently primary amine (2.2 mmol) were added and the mixture was warmed to room temperature. After stirring for 2 h, the reaction mixture was warmed to reflux temperature and the stirring was continued for 10 h. Then the reaction mixture was poured into aqueous NaOH solution (30 mL, 1 M) and extracted with chloroform (4 × 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* until the complete removal of the solvent and triethylamine. The residue was purified by flash column chromatography on neutral alumina (RediSep Rf; EtOAc : hexanes 0 : 100–100 : 0 gradient, then eluent switch to methanol : chloroform 0 : 100–1 : 10 gradient) to afford the pure guanidine base, which was then treated with HCl in ethanol (1 M, 2–3 equiv.) and stirred at room temperature for 15 min. Finally, evaporation to dryness followed by trituration with *n*-hexane or diisopropyl ether or diethyl ether (if necessary) gave pure guanidine hydrochlorides **10a–h**.

Conflicts of interest

There are no conflicts to declare.

Notes and references

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19 It should be noted that similar efficiencies were observed when hydrazine monohydrate was utilized, but the separation of the byproduct phthalhydrazide from *N*,*N*′-disubstituted guanidines was tedious.

20 The succinimidyl analogue of **5a** (see ref. 17) could not be transformed to the desired *N*,*N*′-disubstituted guanidine **7a** by hydrazinolysis ($MeNHNH_2$, MeCN) even at reflux temperature.

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