DOI: 10.1002/adsc.201501146

Guanidine Synthesis: Use of Amidines as Guanylating Agents

Mattijs Baeten[a] and Bert U. W. Maes[a,*]

[a] Organic Synthesis, Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, B-2020 Antwerp, Belgium
Fax: (+32)-(0)32-2653233; phone: (+32)-(0)32-2653205; e-mail: bert.maes@uantwerpen.be

Received: December 15, 2015; Published online: February 17, 2016

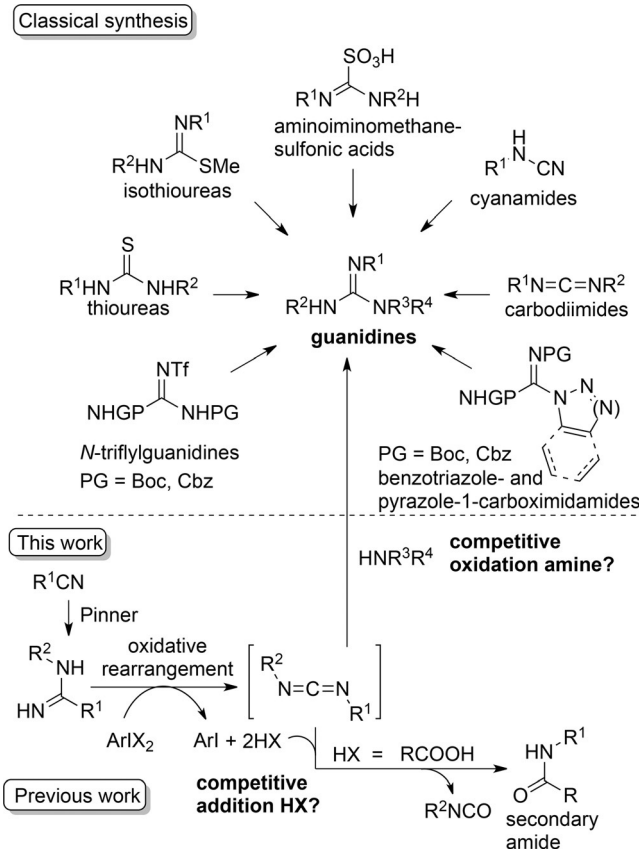
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201501146.

Abstract: The use of amidines for the tandem or one-pot synthesis of guanidines is reported. Guanidines are obtained by oxidative rearrangement of readily available and stable amidines into carbodiimides, followed by *in situ* reaction with amines. The protocol can be executed under mild reaction conditions (30 °C), in a green solvent (dimethyl carbonate). The amine scope is broad, including sterically hindered, oxidation-sensitive and chiral amines. Examples for the synthesis of both acyclic and cyclic guanidines are provided. 2-Propoxyphenyl iodide (2-PrOPhI) by-product, generated from the oxidant [*N*-(*p*-toluenesulfonyl)imino](2-propoxyphenyl)iodinane (2-PrOPhINTs), can be isolated in high yields making regeneration of the hypervalent iodine reagent possible. The utility and greenness of the synthetic method *versus* the state-of-the-art is demonstrated by a new route towards the antihypertensive drug Pinacidil. The *process mass intensity* (PMI) of the new route is only 24% of the classical one.

Keywords: amidines; guanidine synthesis; hypervalent iodine compounds; oxidative rearrangement

Introduction

The guanidine core is a very common functionality in natural products (e.g., guanine, creatine), pharmaceuticals (e.g., Argatroban, Imatinib) and agrochemicals (e.g., Imidacloprid).[1] Guanidines are also used as (chiral) catalysts, superbases, explosives, super potent sweeteners or as a chlorinating agent (Palau′ chlor).[2,3] Classical approaches towards the synthesis of guanidines involve reaction of an amine and a so-called guanylating agent (Scheme 1).[3] Although these classical approaches often allow efficient synthesis of guanidines, the precursors/reagents required for the synthesis [iso(thio)cyanate, cyanogen bromide derived] and/or activation of these guanylating agents pose health, flammability and reactivity issues. Considering the importance of the guanidine entity and the limitations associated with the classical synthetic methods, there is still a need for general, simple and more sustainable methods. We envisaged amidines as a potentially interesting new class of guanylating agents. After all, amidines are stable and can be easily obtained from readily available amines and nitriles *via* the Pinner reaction, requiring only an alcohol and hydrochloric acid.[3c,4] By rearrangement of amidines with an appropriate hypervalent iodine reagent, carbodiimides are obtained. Subsequent reaction of the carbodiimide with an amine gives access to guanidines in one step (Scheme 1).[5]



Scheme 1. Classical and new approaches towards guanidines.

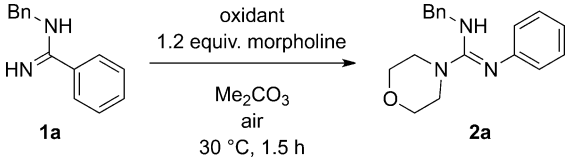
Our group recently described the synthesis of secondary amides *via* reaction of *in situ* generated carbodiimide and carboxylic acid.[6,7] However, the efficient oxidative rearrangement of amidines without competitive nucleophilic addition of *in situ* generated nucleophiles and amine oxidation with periodinane is not self-evident.[8] Hypervalent iodine compounds are interesting oxidants for rearrangement as they possess a low toxicity, are readily available and easily handled. Moreover, by changing the substituents their reactivity can be modulated and the nucleophile *in situ* generated selected.[9] The only drawback is the organic iodide by-product formed. However, when this can be easily separated from the reaction product and transformed into periodinane reagent a more sustainable approach is at hand.

A related reaction to the aimed transformation is the Tiemann rearrangement starting from arenamidoximes. *O*-Activation of these substrates with RSO_2Cl and subsequent rearrangement followed by elimination yields an *N*-substituted cyanamide. *N*,*N*′-Substituted guanidines can be formed by subsequent reaction with an amine.[10] Activation of substrate and rearrangement/addition are performed in separate steps. No *N*,*N*′,*N*″-substituted guanidines can be obtained with this rearrangement. Aza-Hofmann rearrangement of *N*-alkanesulfonylarenamidines with diacetoxyiodotoluene into *N*-alkanesulfonyl-*N*′-arylcarbodiimide in glyme has been described by Yagupolskii.[11,12] Similar to the Tiemann rearrangement, the arenamidine requires a very strong electron-withdrawing sulfonyl group as activator for rearrangement and only reactions with morpholine (one-pot) were reported. Moreover, in general only low yields of *N*-aryl-*N*′-(alkanesulfonyl)morpholine-4-carboximidamides were obtained and no straightforward and sufficiently mild procedure for removal of the strong electron-withdrawing *N*-activating sulfonyl group was provided. Our aim was to develop a general and high yielding sustainable protocol based on amidine rearrangement featuring a broad substrate and amine scope without the need for pre-activation.

Results and Discussion

The reaction of *N*-benzylbenzamidine (**1a**) and morpholine was selected as model system. First several oxidants were tested using 1.2 equiv. morpholine in dimethyl carbonate (DMC) at 30 °C in air (Table 1). $PhI(OAc)_2$ and PhI(OH)OTs gave guanidine **2a** but with a low mass balance (entries 1 and 2). With $PhI(OCOCF_3)_2$ only decomposition of substrate was observed (entry 3). The most interesting result was obtained for PhINTs giving both a high mass balance and yield (entry 4).[9] A solvent screening with this oxidant revealed that a variety of solvents with different dielectric constants can be used (Supporting Information, Table S1).[13] As DMC is an environmentally benign and non-flammable solvent and it gave the highest yield it was retained.[14] Investigation of the effect of the amount of oxidant and amine on the conversion and yield revealed that 2.2 equiv. of oxidant and 1.2 equiv. morpholine were optimal (Supporting Information, Table S2). Unfortunately, when using only 1.2 equiv. of PhINTs no full conversion of **1a** was obtained (entry 5). Therefore we tested 2-PrOPhINTs as it possesses a higher reactivity and better solubility *versus* PhINTs.[15] Interestingly, the same yield was obtained with only 1.2 equiv. oxidant (entry 4 *versus* 6).

Table 1. Screening of hypervalent iodine reagents.



1a 2a

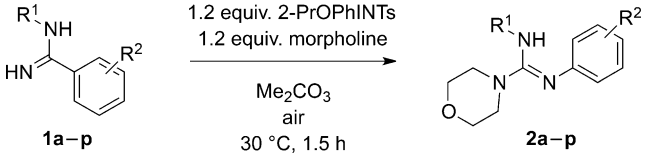
Entry	Oxidant	Equiv. Oxidant	Yield **1a**/**2a** [%][a,b]
1	$PhI(OAc)_2$	2.2	20/49
2	PhI(OH)OTs	2.2	12/7[c]
3	$PhI(OCOCF_3)_2$	2.2	57/0
4	PhINTs	2.2	0/89[d]
5	PhINTs	1.2	35/59
6	2-PrOPhINTs	1.2	6/84[e]

[a] *Reaction conditions:* 0.5 mmol **1a**, x equiv. oxidant, 1.2 equiv. morpholine, DMC, air, 30 °C, 1.5 h.
[b] NMR yield using 1,3,5-trimethoxybenzene as internal standard.
[c] 65% *N*-benzyl-*N*′-phenylurea was formed.
[d] 43% PhI was isolated.
[e] 92% 2-PrOPhI was isolated.

With the optimized conditions in hand, we investigated substrate scope with morpholine as amine. At first, different substituents on nitrogen of benzamidine and *p*-toluamidine were tested (Table 2). Both primary (entries 1 and 2), secondary (a)cyclic (entries 3 and 4) as well as aromatic substituents (entry 6) are compatible. A substrate with an *N*-*tert*-butyl group gave only 26% yield and remaining **1e**. With more oxidant and amine, 63% **2e** could be obtained (entry 5). In accordance with the observations of Yagupolskii a tosyl substituent gave a high yield of the corresponding guanidine (entry 7).[11] Next, different substituents in the phenyl ring of *N*-benzylbenzamidine were tested (Table 2). Both electron-donating (entries 8–11) and electron-withdrawing (entries 12–16) substituents are well tolerated. Even an SMe group gave a good yield, despite being a sensitive group towards oxidation (entry 8).

Subsequently, the amine scope was tested using **1a** as substrate (Table 3). Acyclic secondary amines gave a good result as exemplified by diethylamine (entry 2).

Table 2. Substituent scope in benzamidine (**1**) with morpholine.



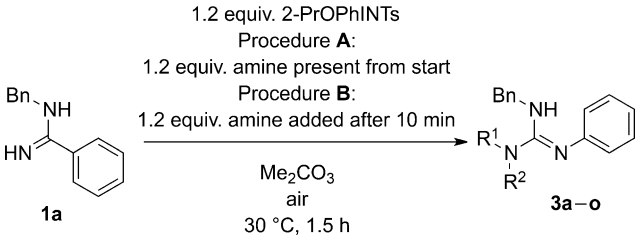
Entry	**1**	R^1	R^2	**2**	Yield [%][a]	ArI [%][b]
1	**1a**	Bn	H	**2a**	77	92
2	**1b**	Pr	H	**2b**	91	98
3	**1c**	*i*-Pr	*p*-Me	**2c**	91	94
4	**1d**	Cy	*p*-Me	**2d**	87	99
5	**1e**	*t*-Bu	*p*-Me	**2e**	63[c,d]	46
6	**1f**	Ph	H	**2f**	92	95
7	**1g**	Ts	H	**2g**	75	93
8	**1h**	Bn	*p*-SMe	**2h**	76	78
9	**1i**	Bn	*p*-Me	**2i**	78	96
10	**1j**	Bn	*m*-Me	**2j**	78	88
11	**1k**	Bn	*o*-Me	**2k**	81	92
12	**1l**	Bn	*p*-Cl	**2l**	69	94
13	**1m**	Bn	*m*-Cl	**2m**	76	84
14	**1n**	Bn	*o*-Cl	**2n**	88	90
15	**1o**	Bn	*p*-F	**2o**	70	92
16	**1p**	Bn	*p*-CO_2Et	**2p**	72	89

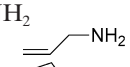
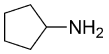
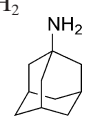
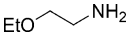
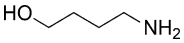
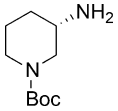
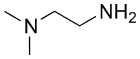
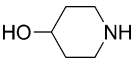
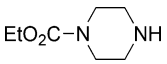
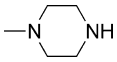
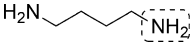
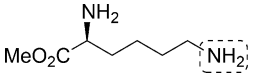
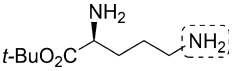
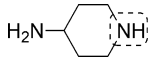
[a] *Reaction conditions:* 0.5 mmol **1**, 1.2 equiv. 2-PrOPhINTs, 1.2 equiv. morpholine, DMC, air, 30 °C, 1.5 h.
[b] 2-PrOPhI isolated.
[c] Under standard conditions: 26% **1e** and 26% **2e**.
[d] 2.2 equiv. PhINTs and 3.0 equiv. morpholine.

Besides butylamine (entry 1) more challenging primary amines such as benzylamine (entry 3) and allylamine (entry 4) can be used, although a benzylic position is oxidation sensitive and a double bond is known to react with the oxidant with formation of *N*-tosylaziridines.[14a] Primary amines which are secondary and tertiary at the alpha position also performed well (entries 5–7). Next, compatibility with heteroatom-containing functional groups which can potentially also be oxidized were tested. 2-Ethoxyethanamine gave 68% of the guanidine but 22% of the substrate was still remaining (entry 8). Also the reactions with 4-aminobutanol, (*S*)-1-Boc-3-aminopiperidine, *N*,*N*-dimethylethane-1,2-diamine, 4-hydroxypiperidine and

[a] 2-PrOPhI isolated.
[b] Procedure A: 0.5 mmol **1a**, 1.2 equiv. 2-PrOPhINTs, 1.2 equiv. amine (present from start), DMC, air, 30 °C, 1.5 h. Procedure B: similar, but amine added after 10 min.
[c] NMR yield with 1,3,5-trimethoxybenzene as internal standard.
[d] Amine (3.0 equiv.) used.
[e] Cyanamide (5.0 equiv.) and Et_3N (3.0 equiv.) were added after 10 min. Then increasing temperature to 80 °C and stirring for 3 h.

Table 3. Amine scope with *N*-benzylbenzamidine (**1a**).



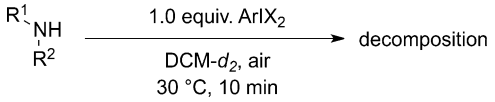
Entry	Amine	Product	Yield **1a**/**3** [%]	ArI [%][a]	Procedure[b]
1	$BuNH_2$	**3a**	0/84	89	A
2	Et_2NH	**3b**	0/78	89	A
3	$BnNH_2$	**3c**	0/66	88	A
4		**3d**	0/70	84	A
5		**3e**	0/82	87	A
6	*t*-$BuNH_2$	**3f**	0/82	87	A
7		**3g**	0/68	67	A
8		**3h**	22/68[c]	–	A
9			0/78	74	B
10		**3i**	25/64[c]	–	A
11			0/75	71	B
12		**3j**	13/73[c]	–	A
13			0/78	70	B
14		**3k**	29/55	98	A
15			0/90	93	B
16		**3l**	17/76[c]	–	A
17			0/87	78	B
18		**3m**	26/68[c]	–	A
19			0/79[c]	–	B
20			0/94[d]	76	B
21		**3n**	48/0[c]	–	A
22			0/67[c]	–	B
23			0/90[d]	91	B
24	$NCNH_2$	**3o**	55/0[c]	–	A
25			0/51[c]	-	B
26			0/70[e]	84	B
27		**3p**	0/68[d]	82	B
28		**3q**	0/57	67	B
29		**3r**	0/78	74	B
30		**3s**	0/82	82	B

ethyl piperazine-1-carboxylate suffered from an incomplete conversion and moderate yields were obtained (entries 10, 12, 14, 16, 18). With *N*-methylpiperazine no guanidine was obtained and 48% of the substrate remained (entry 21). To achieve full conversion in these challenging cases simply switching to a one-pot approach was tested. Gratifyingly, when nucleophile was added after just 10 min reaction of amidine with oxidant at 30 °C, full conversion and significantly improved isolated yields were obtained (up to 35%) (entries 11, 13, 15, 17, 19, 22). For piperazines the yield can be further increased to over 90% when three equivalents were added (entries 20 and 23). Even cyanamide, a very oxidative sensitive and poor nucleophile, can be used in the one-pot protocol (entry 25).[16] Addition of a base (NEt_3) and applying a higher reaction temperature (80 °C) were beneficial for the yield (entry 26). Next we investigated reagents featuring two primary amines. Applying the one-pot protocol on **1a** with butane-1,4-diamine gave selectively 68% of the desired mono guanidine product (entry 27). Only when the amidine was added in excess (3 equiv.) it was possible to functionalize both amino groups and obtain the bisguanidine **3t** in 96% (see the Supporting Information). With L-lysine and L-ornithine esters, featuring two chemically different primary amino groups, good yields were achieved with complete selectivity for the unbranched primary amino group, providing an easy access towards arginine mimetics (entries 28 and 29).[17] Finally, a bisamine consisting of a primary and secondary amine was tested. 4-Aminopiperidine gave selectively the guanidine including the secondary amine (entry 30).

As full conversion could be obtained with the one-pot protocol when amidine substrate was remaining in the tandem approach, a link between the rate of oxidation of amine *versus* amidine was assumed. To demonstrate this, the stability of the different amines used in this study towards 2-PrOPhINTs was tested by ^{1}H NMR analysis in CD_2Cl_2 (Table 4). On the basis of the remaining amine (10 min after oxidant addition) a good correlation between the rate of amine decomposition and performance in the tandem approach was revealed. A similar study with PIDA indicated that always less amine remained *versus* 2-PrOPhINTs (and in most cases none) justifying why it is not a good oxidant in this process. Control experiments on **1a** for several amines with PIDA as oxidant confirmed the superiority of 2-PrOPhINTs irrespective of the protocol applied (tandem or one pot) (Table 5).

Next we looked at the suitability of other amidines than *C*-aryl-*N*-alkylamidines as substrates. The use of isomeric *C*-alkyl-*N*-arylamidines as substrate does not offer any added value as these would go through the same carbodiimide intermediate delivering the same guanidines. In fact, *C*-alkyl-*N*-arylamidines lead to

Table 4. Reaction of amines with $ArIX_2$ reagents.

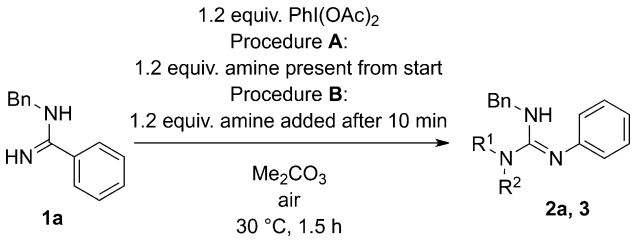


Entry	Amine	$ArIX_2$	Amine [%][a,b]
1	butylamine	2-PrOPhINTs	68
2	butylamine	$PhI(OAc)_2$	48
3	diethylamine	2-PrOPhINTs	51
4	diethylamine	$PhI(OAc)_2$	12
5	*t*-butylamine	2-PrOPhINTs	73
6	*t*-butylamine	$PhI(OAc)_2$	60
7	adamantylamine	2-PrOPhINTs	98
8	adamantylamine	$PhI(OAc)_2$	19
9	allylamine	2-PrOPhINTs	0
10	allylamine	$PhI(OAc)_2$	0
11	2-ethoxyethanamine	2-PrOPhINTs	0
12	2-ethoxyethanamine	$PhI(OAc)_2$	0
13	4-hydroxypiperidine	2-PrOPhINTs	0
14	4-hydroxypiperidine	$PhI(OAc)_2$	0
15	*N*-methylpiperazine	2-PrOPhINTs	0
16	*N*-methylpiperazine	$PhI(OAc)_2$	0
17	cyanamide	2-PrOPhINTs	0
18	cyanamide	$PhI(OAc)_2$	0
19	4-aminopiperidine	2-PrOPhINTs	0
20	4-aminopiperidine	$PhI(OAc)_2$	0
21	morpholine	2-PrOPhINTs	25
22	morpholine	$PhI(OAc)_2$	0
23	cyclopentylamine	2-PrOPhINTs	51
24	cyclopentylamine	$PhI(OAc)_2$	0
25	benzylamine	2-PrOPhINTs	42
26	benzylamine	$PhI(OAc)_2$	0
27	4-aminobutanol	2-PrOPhINTs	52
28	4-aminobutanol	$PhI(OAc)_2$	0
29	(*S*)-1-Boc-3-aminopiperidine	2-PrOPhINTs	69
30	(*S*)-1-Boc-3-aminopiperidine	$PhI(OAc)_2$	0
31	ethyl piperazine-1-carboxylate	2-PrOPhINTs	32
32	ethyl piperazine-1-carboxylate	$PhI(OAc)_2$	0
33	$Me_2NCH_2CH_2NH_2$	2-PrOPhINTs	32
34	$Me_2NCH_2CH_2NH_2$	$PhI(OAc)_2$	0
35	butane-1,4-diamine	2-PrOPhINTs	49
36	butane-1,4-diamine	$PhI(OAc)_2$	0
37	L-lysine, Me ester	2-PrOPhINTs	42
38	L-lysine, Me ester	$PhI(OAc)_2$	0
39	L-ornithine, *t*-Bu ester	2-PrOPhINTs	41
40	L-ornithine, *t*-Bu ester	$PhI(OAc)_2$	0

[a] *Reaction conditions:* 0.2 mmol amine, 1.0 equiv. hypervalent iodine reagent, 0.5 mL DCM-d_2, 30 °C, 10 min.
[b] Remaining amine calculated by NMR with 1,3,5-trimethoxybenzene as internal standard.

1*H*-benzimidazoles rather than to a carbodiimide *via* a faster direct amination reaction.[6] Unfortunately, *N*-unsubstituted benzamidines and alkanimidamides did not rearrange to the corresponding carbodiimide/cyanamide under our reaction conditions. Therefore *N*-protection on these substrates was explored (Table 6). Gratifyingly, *N*-Boc-benzamidine (**4a**) and *N*-Boc-

Table 5. Control experiments using PIDA in the oxidative rearrangement and nucleophilic addition protocol with *N*-benzylbenzamidine (**1a**) and selected amines.



Entry	Amine	Product	Yield **1a**/**2a** or **3** [%][a]	Procedure[b]
1	butylamine	**3a**	8/63	A
2			10/52	B
3	morpholine	**2a**	48/32	A
4			42/17	B
5	allylamine	**3d**	25/23	A
6			6/20	B
7	4-hydroxypiperidine	**3l**	27/17	B
8	*N*-methylpiperazine	**3n**	42/6	B
9	cyanamide	**3o**	32/12	B

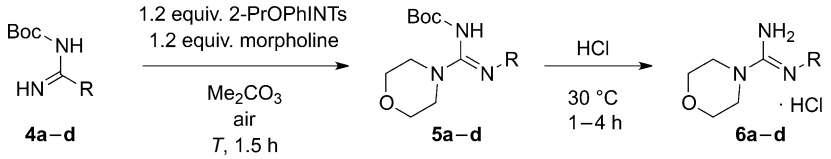
[a] NMR yield with 1,3,5-trimethoxybenzene as internal standard.
[b] Procedure A: 0.5 mmol **1a**, 1.2 equiv. $PhI(OAc)_2$, 1.2 equiv. amine (present from start), DMC, air, 30 °C, 1.5 h. Procedure B: similar, but the amine was added after 10 min.

phenylethanimidamide (**4b**) worked smoothly under the standard reaction conditions yielding the corresponding *N*-Boc-guanidines (**5**) in good yields (entries 1 and 2). Other *N*-Boc-alkanimidamides required a higher reaction temperature to obtain full conversion to **5** in 1.5 h (entries 4–7). Addition of HCl to the crude reaction mixture of **5** before work-up allowed for quantitative deprotection of the Boc group and yielded the target guanidines **6** in a one-pot reaction (Table 6).

Subsequently, we investigated whether our protocol could be used to make cyclic guanidines. When aminoacetals are used as the nucleophiles followed by an additional deprotection and condensation step on the crude reaction mixture 2-amino-1*H*-imidazoles can be synthesized. With *N*-benzylbenzamidine (**1a**) as substrate and 2,2-dimethoxyethan-1-amine as the nucleophile, 78% of the corresponding guanidine **7** was obtained under the standard reaction conditions. Addition of HCl immediately after the tandem reaction without prior work-up provided 2-benzylamino-1-phenyl-1*H*-imidazole (**8a**) in 75% yield (Scheme 2). Even with a bismethylated analogue, 3,3-dimethoxybutan-2-amine, the same protocol delivered 2-benzylamino-3,4-dimethyl-1-phenyl-1*H*-imidazole (**8b**) in good yield (Scheme 2). When we tested this procedure on *N*-Boc-benzamidine (**4a**) and *N*-Boc-ethanimidamide (**4c**) with 2,2-dimethoxyethan-1-amine, 2-phenylamino-1*H*-imidazole (**8d**) and 1-ethyl-2-amino-1*H*-imidazole (**8c**) respectively, were obtained (Scheme 2).

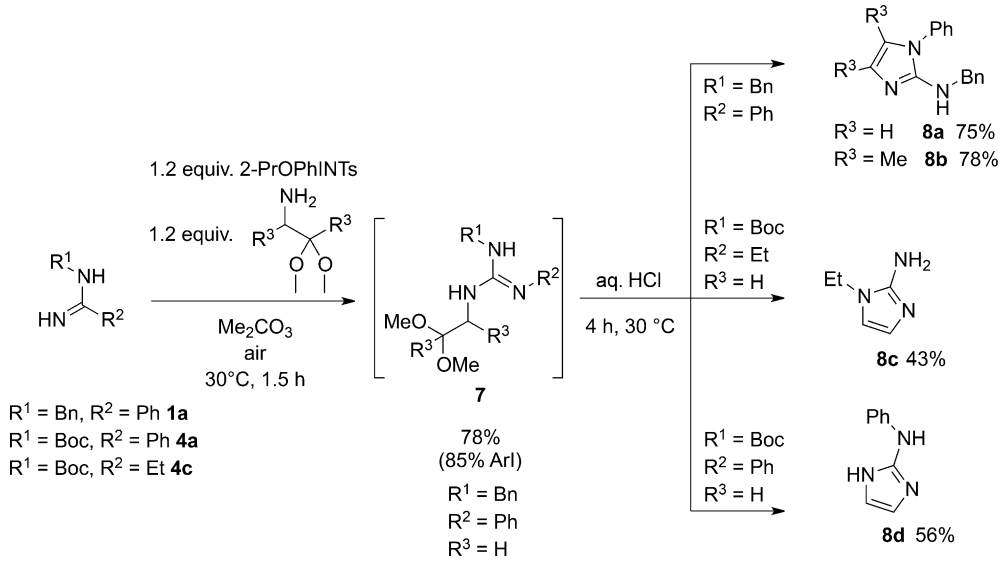
To demonstrate the applicability of the synthetic method developed, we synthesized the antihypertensive drug Pinacidil (**10**) in an alternative manner, starting from the same substrate (Scheme 3). 4-Cyanopyridine was transformed into amidine **9** *via* a Pinner-like reaction.[18] By evaporation of the solvent and subsequent washing with aqueous NaOH, crude **9** could be isolated. Without further purification **9** was converted into **10** applying the one-pot oxida-

Table 6. Guanylation with *N*-unsubstituted amidines *via* Boc protection.

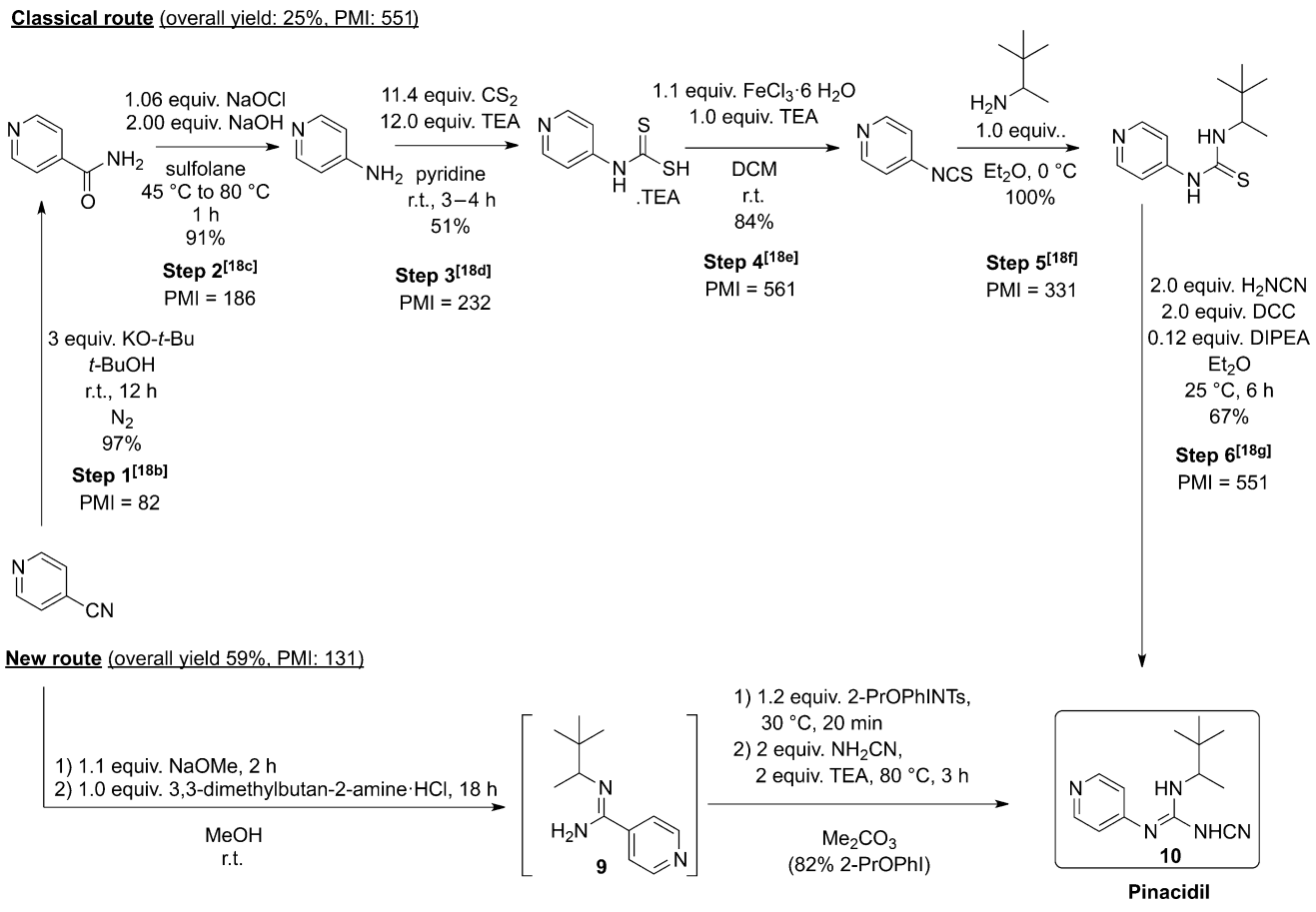


Entry	Substrate	R	*T* [°C]	Product	Yield **4**/**5** [%][a]	ArI [%][b]	Product	Yield **6** [%]
1	**4a**	Ph	30	**5a**	0/89	89	**6a**	88[c]
2	**4b**	Bn	30	**5b**	0/83	70	**6b**	61[d]
3	**4c**	Et	30	**5c**	18/70	–	**6c**	–
4	**4c**		30	**5c**	0/78[e]	–	**6c**	–
5	**4c**		50	**5c**	21/70	–	**6c**	–
6	**4c**		80	**5c**	0/88	82	**6c**	62[d]
7	**4d**	Cy	80	**5d**	0/90	82	**6d**	73[d]

[a] *Reaction conditions:* 0.5 mmol **4**, 1.2 equiv. 2-PrOPhINTs, 1.2 equiv. morpholine, DMC, air, *T*, 1.5 h.
[b] 2-PrOPhI isolated for the synthesis of **5**.
[c] As in [a] but one-pot deprotection by addition of conc. aq. HCl, 30 °C, 1 h.
[d] As in [a] but one-pot deprotection by addition of 2 mL HCl (4 M in dioxane), 30 °C, 4 h.
[e] The reaction time was 3 h instead of 1.5 h.



Scheme 2. One-pot 2-amino-1*H*-imidazole (**8a–d**) formation starting from amidines (**1a** or **4**).



Scheme 3. New and classical synthesis of Pinacidil (**10**) from 4-cyanopyridine.

tive rearrangement and nucleophilic addition protocol with cyanamide as the nucleophile.[19] The reaction product **10** could be purified by crystallization. The classical Pinacidil route is a 6-step process with an overall yield of 25%[19] while our approach reduces the synthesis to only 2 steps, with an overall yield of 59%. To further demonstrate the greenness of the guanidine synthesis we compared the *process mass in-*

tensity (PMI) of both approaches towards this API.[21] The PMI is defined as the total mass of substrates, reagents and chemicals (e.g., solvents) needed for work-up, divided by the mass of the product. Therefore the PMI is not only a measure for the mass efficiency of the reaction, but also for its sustainability. After all, a lower PMI also means less waste production. The classical synthesis revealed a PMI of 551 while the new process features a PMI of only 131. Moreover, the use of undesirable reagents (from a health and flammability point of view) such as CS_2 is avoided. Interestingly, the 2-PrOPhI by-product generated by reduction of the oxidant can be isolated in high yield (82%) in the Pinacidil synthesis by simple extraction with heptane. This recovery has not been taken into account in the PMI calculation.

In fact, generally high yields of 2-PrOPhI were obtained in all experiments (Tables 2–4). It can be easily separated from the guanidine product by eluting with 100% heptane at the start of the purification by column chromatography on silica gel. No attempts were made to recover $TsNH_2$. Based on its polarity, a simple and general applicable separation is not straightforward. Moreover, 2-iodophenol from which 2-PrOPhI is made is 30 times more expensive than $TsNH_2$.[22] As 2-PrOPhINTs is synthesized from 2-PrOPhI, *via* oxidation with Ac_2O/H_2O_2 followed by treatment with $TsNH_2$ under basic conditions,[15] 2-PrOPhI recovery positively contributes to the overall sustainability of the process as initially aimed. Although we standardly applied column chromatography for the purification of the guanidines, the synthesis of Pinacidil illustrates that it is certainly possible to purify by crystallization while maintaining the interesting feature of 2-PrOPhI recovery.

Conclusions

In conclusion, we have developed a general method for the transformation of readily available and stable amidine substrates (Pinner reaction) into substituted guanidines using 2-PrOPhINTs as an oxidant and an amine as the reagent. The rate of rearrangement of amidine into carbodiimide *versus* the competitive oxidation of amine determines which approach has to be used; tandem or one-pot. The use of 2-PrOPhINTs as hypervalent iodine reagent is crucial to obtain a good mass balance and a high yield of guanidine target compound, irrespective of whether the amine is added from the start or after 10 min reaction. The amine scope is broad, including (alpha) chiral, non-nucleophilic (cyanamide) and sterically hindered representatives. When aminoacetals are selected as reagents, cyclic guanidines can be synthesized by *in situ* deprotection of the guanidine acetals initially obtained. The guanylation reactions can be performed in a sustainable solvent (DMC) under mild reaction conditions (30 °C) and 2-PrOPhI by-product generated can be reused. The new synthesis of Pinacidil illustrates the usefulness of the developed protocol. Comparison of the PMI of the new and classical synthesis of this API underlines the greenness of the new approach.

Experimental Section

General Procedure for the Synthesis of Guanidines

A vial was loaded with 0.5 mmol of amidine and amine (0.6 mmol). Me_2CO_3 (1 mL) and 2-PrOPhINTs (259 mg, 0.6 mmol) were added. Subsequently, the vial was sealed and the reaction mixture was stirred for 1.5 h at 30 °C. The solvent was removed under vacuum and the crude product was purified *via* an automated chromatography system using a Silica Flash Cartridge. For oxidation-sensitive amines, a one-pot protocol where the amine was added after 10 min was used.

Acknowledgements

This work was supported by the Agency for Innovation by Science and Technology (IWT-Flanders), the University of Antwerp (BOF) and the Hercules Foundation. The research leading to these results has also received funding from the Innovative Medicines Initiative (www.imi.europa.eu) Joint Undertaking under grant agreement 115360, resources of which are composed of financial contribution from the European Union's Seventh Framework Program and EFPIA companies in kind contribution. The authors thank Philippe Franck, Heidi Seykens and Norbert Hancke for technical assistance and Dr. John Hayler (GSK) for discussions on the green metrics.

References

[1] a) F. Saczewski, L. Balewski, *Expert Opin. Ther. Pat.* **2013**, *23*, 965–995; b) A. F. Pozharskii, A. Soldatenkov, A. R. Katritzky, *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications*, 2nd edn., Wiley, **2011**.

[2] a) T. Ishikawa, *Superbases for Organic Synthesis*, John Wiley & Sons, U.K., **2009**; b) R. A. Rodriguez, C.-M. Pan, Y. Yabe, Y. Kawamata, M. D. Eastgate, P. S. Baran, *J. Am. Chem. Soc.* **2014**, *136*, 6908–6911.

[3] For reviews about guanidine synthesis and their applications, see: a) W.-X. Zhang, L. Xu, Z. Xi, *Chem. Commun.* **2015**, *51*, 254–265; b) C. Alonso-Moreno, A. Antinolo, F. Carrillo-Hermosilla, A. Otero, *Chem. Soc. Rev.* **2014**, *43*, 3406–3425; c) T. R. M. Rauws, B. U. W. Maes, *Chem. Soc. Rev.* **2012**, *41*, 2463–2497; d) A. R. Katritzky, B. V. Rogovoy, *ARKIVOC (Gainesville, FL, U.S.A.)* **2005**, 49–87.

[4] Typically, the Pinner reaction uses a large excess of gaseous HCl. This is because it is bubbled through the re-

action mixture and the quantity is therefore hard to control. More recently, a more environmentally friendly synthesis of imido esters using anhydrous solutions of HCl was developed. In this case only 4 equiv. of HCl were required: H. C. Kolb, R. C. Kanamarlapudi, P. F. Richardson, G. Khan, U.S. Patent 6,806,380 B2.

[5] For examples of guanidine synthesis from carbodiimides and amines, see: a) Q. Li, S. Wang, S. Zhou, G. Yang, X. Zhu, Y. Liu, *J. Org. Chem.* **2007**, *72*, 6763–6767; b) X. Zhu, Z. Du, F. Xu, Q. Shen, *J. Org. Chem.* **2009**, *74*, 6347–6349; c) R. E. Looper, T. J. Haussener, J. B. C. Mack, *J. Org. Chem.* **2011**, *76*, 6967–6971; d) L. Xu, W.-X. Zhang, Z. Xi, *Organometallics* **2015**, *34*, 1787–1801.

[6] P. Debnath, M. Baeten, N. Lefèvre, S. V. Daele, B. U. W. Maes, *Adv. Synth. Catal.* **2015**, *357*, 197–209.

[7] For the oxidative rearrangement of amidines into carbodiimides with PIDA, see: a) M. Bobosikova, W. Clegg, S. J. Coles, M. Dandarova, M. B. Hursthouse, T. Kiss, A. Krutosikova, T. Liptaj, N. a. Pronayova, C. A. Ramsden, *J. Chem. Soc. Perkin Trans. 1* **2001**, 680–689; b) C. A. Ramsden, H. L. Rose, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2319–2327; c) C. A. Ramsden, H. L. Rose, *J. Chem. Soc. Perkin Trans. 1* **1995**, 615–617.

[8] A. Varvoglis, *Hypervalent Iodine in Organic Synthesis*, Academic Press, San Diego, **1997**.

[9] For reviews and a book, see: a) P. J. Stang, V. V. Zhdankin, *Chem. Rev.* **1996**, *96*, 1123–1178; b) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2002**, *102*, 2523–2584; c) T. Wirth, *Top. Curr. Chem.* **2003**, *224*, 185–208; d) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299–5358; e) V. Zhdankin, *Hypervalent Iodine Chemistry*, John Wiley & Sons, U.K., **2013**; f) F. V. Singh, T. Wirth, *Synthesis* **2013**, *45*, 2499–2511; g) R. Narayan, S. Manna, A. P. Antonchick, *Synlett* **2015**, *26*, 1785–1803.

[10] a) M. W. Partridge, H. A. Turner, *J. Pharm. Pharmacol.* **1953**, *5*, 103–110. b) For a more recent example of the use of the Tiemann rearrangement for the synthesis of guanidines, see: C.-J. Zeng, C.-J. Chen, C.-W. Chang, H.-T. Chen, T.-C. Chien, *Aust. J. Chem.* **2014**, *67*, 1134–1137.

[11] L. M. Yagupolskii, I. I. Maletina, L. V. Sokolenko, Y. G. Vlasenko, S. A. Buth, *J. Fluorine Chem.* **2008**, *129*, 486–492.

[12] For Hofmann rearrangements with hypervalent iodine compounds, see: a) A. A. Zagulyaeva, C. T. Banek, M. S. Yusubov, V. V. Zhdankin, *Org. Lett.* **2010**, *12*, 4644–4647; b) A. Yoshimura, K. R. Middleton, M. W. Luedtke, C. Zhu, V. V. Zhdankin, *J. Org. Chem.* **2012**, *77*, 11399–11404; c) A. Yoshimura, M. W. Luedtke, V. V. Zhdankin, *J. Org. Chem.* **2012**, *77*, 2087–2091.

[13] a) R. K. Henderson, C. Jimenez-Gonzalez, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, A. D. Curzons, *Green Chem.* **2011**, *13*, 854–862; b) D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada, P. J. Dunn, *Green Chem.* **2015**, *17*, 3111–3121.

[14] S. Huang, B. Yan, S. Wang, X. Ma, *Chem. Soc. Rev.* **2015**, *44*, 3079–3116.

[15] a) A. Yoshimura, V. N. Nemykin, V. V. Zhdankin, *Chem. Eur. J.* **2011**, *17*, 10538–10541; b) V. V. Zhdankin, J. D. Protasiewicz, *Coord. Chem. Rev.* **2014**, *275*, 54–62.

[16] A. Varvoglis, *Chem. Soc. Rev.* **1981**, *10*, 377–407.

[17] M. A. Estiarte, D. H. Rich, D. J. Abraham, in: *Burger's Medicinal Chemistry and Drug Discovery*, John Wiley & Sons, Hoboken N.J., **2003**.

[18] S. M. Sondhi, R. Rani, P. Roy, S. K. Agrawal, A. K. Saxena, *Eur. J. Med. Chem.* **2010**, *45*, 902–908.

[19] For an example of guanidine synthesis with cyanamide and carbodiimide see: R. Mestres, C. Palomo, *Synthesis* **1980**, 755–757.

[20] a) A. Kleeman, J. Engel, *Pharmaceutical substances: syntheses, patents, applications*, Thieme, Suttgart, **2001**; b) G. C. Midya, A. Kapat, S. Maiti, J. Dash, *J. Org. Chem.* **2015**, *80*, 4148–4151; c) D. S. Rane, M. M. Sharma, *J. Chem. Technol. Biotrans.* **1994**, *59*, 271–277; d) E. B. Knott, *J. Chem. Soc.* **1956**, 1644–1649; e) D. J. Le Count, D. J. Dewsbury, W. Grundy, *Synthesis* **1977**, 582–583; f) E. T. Hansen, H. J. Petersen, *Synth. Commun.* **1984**, *14*, 537–546; g) H. J. Petersen, C. K. Nielsen, E. Arrigoni-Martelli, *J. Med. Chem.* **1978**, *21*, 773–781.

[21] a) C. Jimenez-Gonzalez, C. S. Ponder, Q. B. Broxterman, J. B. Manley, *Org. Process Res. Dev.* **2011**, *15*, 912–917; b) A. P. Dicks, A. Hent, *Green Chemistry Metrics. A Guide to Determining and Evaluating Process Greenness*, Springer, **2015**.

[22] Prices taken from the Sigma–Aldrich website (http://www.sigmaaldrich.com/) in December 2015.

