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Iodine-catalyzed guanylation of amines with *N*,*N*′-di-Boc-thiourea†

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Herein, we report that iodine-catalyzed guanylation of primary amines can be accomplished with *N*,*N*′-di-Boc-thiourea and TBHP to afford the corresponding guanidines in 40–99% yields. Oxidation of the HI byproduct by TBHP eliminates the need for an extra base to prevent the protonation of substrates and makes the reaction especially useful for both electronically and sterically deactivated primary anilines.

Guanidine moieties are widespread in natural products, pharmaceuticals, sweeteners, and explosives.[1–6] Examples of guanidine-bearing compounds include peramine, a feeding deterrent that has been isolated from several plants;[1] zanamivir, a potent neuraminidase inhibitor;[7,8] rosuvastatin, which is used to treat high cholesterol and cardiovascular disease;[9] and nitroguanidine, a commonly used explosive propellant (Fig. 1). In addition, guanidines are organic superbases that have been shown to catalyze base-mediated reactions,[10–12] and the incorporation of a chiral auxiliary into the nitrogen atom makes guanidines useful for asymmetric reactions.[13,14] Owing to the versatility of guanidines, numerous methods have been developed for their synthesis,[1,15,16] the most direct and effective being the reaction of amines with guanylating agents.[1,15–17] Guanylating agents can be thiourea, isothiourea, carbodiimide, and pyrazole-1-carboximidamide; among these, *N*,*N*′-di-Boc-thiourea is one of the most commonly used agents because it is highly reactive and because subsequent removal of the Boc group is easy. A stoichiometric amount of a desulfurization reagent is usually necessary to promote the direct guanylation of amines with *N*,*N*′-di-Boc-thiourea because otherwise the desulfurization reaction is slow.[18] Reagents used for this purpose include metal salts (*e.g.*, Hg[19–23] and Cu[24–27]), Mukaiyama's reagent,[28] and iodine reagents.[29–32] In addition, an extra base (usually NEt_3) is needed to prevent the protonation of the amine. This strategy has been widely used for the late-stage functionalization of natural products and pharmaceuticals.[33–36] However, the catalytic guanylation of amines with *N*,*N*′-di-Boc-thiourea has not previously been reported.

Catalytic syntheses of guanidines with protected thiourea compounds often produce metal sulfides,[19,25,37–41] and therefore an excess of a desulfurization reagent is required. Recently, we discovered that I_2 could mediate the guanylation of amines with *N*,*N*′-di-Boc-thiourea.[42] Considering that the HI[43–50] produced as a byproduct could be reoxidized to I_2 with a suitable oxidant, we speculated that the I_2-catalyzed guanylation of amines with *N*,*N*′-di-Boc-thiourea would be possible. In addition, the oxidation of the HI would eliminate the need for an extra base to prevent the protonation of the amine substrates (Scheme 1).

To explore this possibility, we carried out reactions of 4-methoxyaniline as a model substrate for the I_2-catalyzed guanylation of amines with *N*,*N*′-di-Boc-thiourea (Table 1). After carefully screening various catalysts, oxidants, and solvents, we found that with I_2 as the catalyst, TBHP as the oxidant, and toluene as the solvent, the desired guanidine **3a** could be

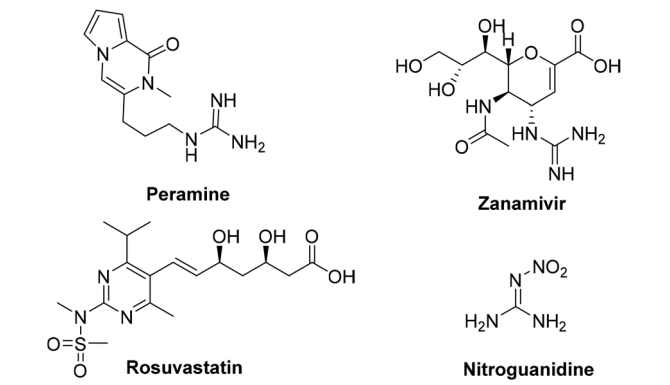

Fig. 1 Representative compounds with guanidine moieties.

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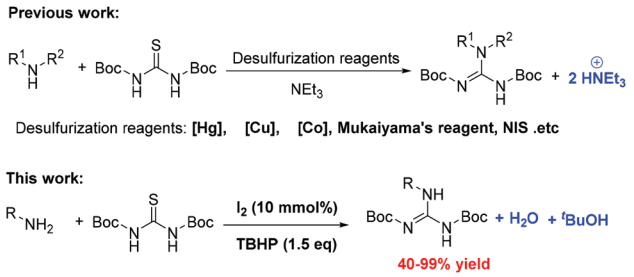
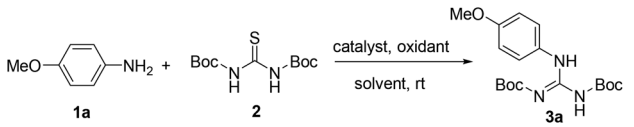


Scheme 1 Guanylation of amines using *N*,*N*′-di-Boc-thiourea.

Table 1 Optimization of guanylation conditions[a]

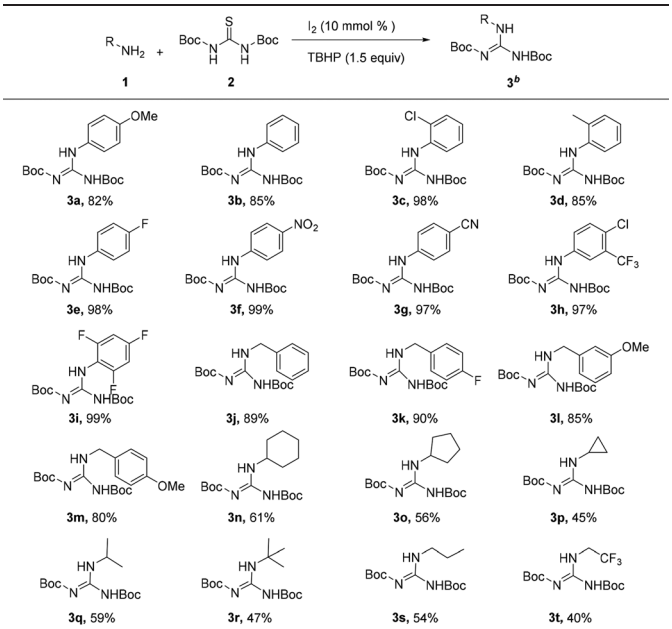


Entry	Catalyst	Oxidant (equiv.)	Solvent	Yield[b] (%)
1	NIS (10 mmol%)	TBHP (1.5)	PhMe	64
2	I_2(10 mmol%)	TBHP (1.5)	PhMe	82
3	Bu_4NI (10 mmol%)	TBHP (1.5)	PhMe	47
4	I_2(10 mmol%)	H_2O_2 (1.5)	PhMe	58
5	I_2(10 mmol%)	TBHP (1.5)	EtOAc	75
6	I_2 (10 mmol%)	TBHP (1.5)	EtOH	68
7	I_2(5 mmol%)	TBHP (1.5)	PhMe	79
8	I_2(20 mmol%)	TBHP (1.5)	PhMe	83
9	I_2 (10 mmol%)	TBHP (1.2)	PhMe	70

[a] Conditions: To a solution of **1a** (0.2 mmol) and **2** (0.24 mmol) in solvent (2 mL) at rt were added catalyst and oxidant, in this order. [b] Isolated yield.

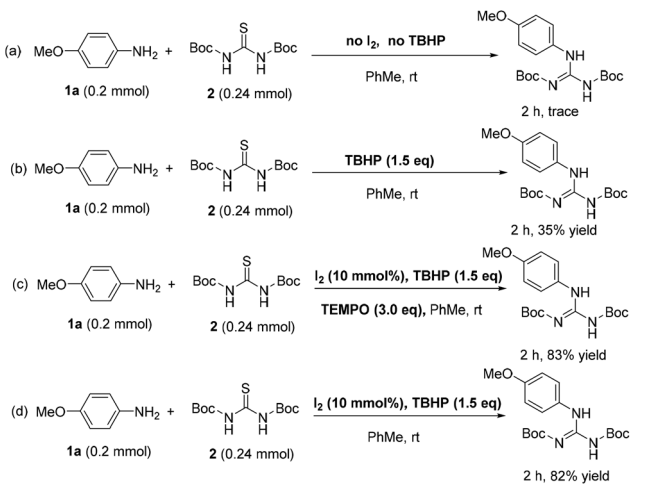
obtained in 82% yield (entry 2). With the optimal conditions in hand, we carried out the reactions of primary anilines (**2a–2i**), benzyl amines (**2j–2m**), and alkyl amines (**2n–2t**) to explore the substrate scope of the reaction (Table 2). Most of the tested substrates afforded the corresponding guanidines in moderate to excellent yields (40–99%). Notably, the method worked well for electronically or sterically deactivated primary anilines, which often give only moderate yields of the corresponding guanidines when previously reported methods are used.[25,28,29,51–53] Under our conditions, such substrates gave the desired products (**3e–3i**) in 95–99% yields. We propose the following explanation for this difference in reaction outcome. When the guanylation reactions of electronically or sterically deactivated primary anilines with *N*,*N*′-di-Boc-thiourea are carried out in the presence of an excess of a desulfurization reagent, the active intermediate is rapidly generated; but the addition of this intermediate to the carbodiimide is slow, and the byproducts are therefore produced. In contrast, in our I_2-catalyzed guanylation reaction, the desulfurization reagent (I_2) was regenerated by the oxidation of the byproduct HI, and the formation of the active intermediate therefore depended on the nucleophilic addition of the amine to *N*,*N*′-di-Boc-thiourea. When electronically or sterically deactivated primary anilines were used, the slow addition of these anilines to *N*,*N*′-di-Boc-

Table 2 Iodine-catalyzed guanylation of amines[a]

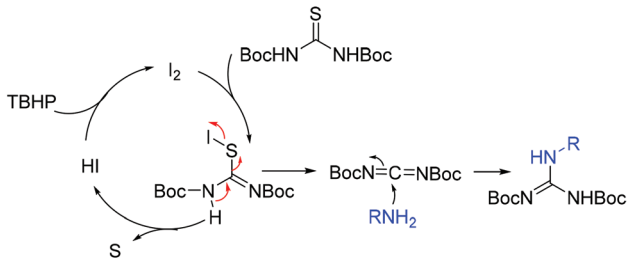


[a] Conditions: To a solution of **1** (0.2 mmol) and **2** (0.24 mmol) in PhMe (2 mL) at rt were added I_2 (0.02 mmol) and 70% aq. TBHP (0.3 mmol), in this order. [b] Isolated yield.

thiourea led to a slow generation of I_2 and the active intermediate which make our strategy work well with these substrates. Benzyl amines with different substituents (**2j–2m**) can afford the desired guanidines in 80–90% yields. When electronically or sterically deactivated primary alkyl amines (**2n–2t**) were used as the substrates, the desired guanidines can also be obtained in 40–61% yields. However, when it comes to heteroaromatic amines such as 3-aminopyridine and 4-aminopyridine, none of the desired guanidines were detected. To elucidate the mechanism of the reaction, we conducted a series of control experiments (Scheme 2). Specifically, the reaction of **1a**



Scheme 2 Control experiments.



Scheme 3 Proposed mechanism.

and **2** in toluene in the absence of I_2 and TBHP generated only a trace amount of the guanidine product after 2 h (Scheme 2a). When TBHP, but not I_2, was present as a desulfurization reagent, the desired guanidine product was isolated in 35% yield (Scheme 2b). The product was possibly generated by the substitution of an amine to aminoiminomethanesulfonic and -sulfinic acids which were formed by the oxidation of the thiourea.[54] These experiments demonstrated that both I_2 and TBHP were essential. Radical trapping experiments using TEMPO as a scavenger show that none of the trapping products were detected which indicate that the ionic pathway is more feasible (Scheme 2c).

On the basis of our control experiments and iodine-mediated desulfurization process of thiourea,[32,53,55–59] we propose the reaction pathway outlined in Scheme 3. The reaction begins with the I_2-mediated desulfurization of *N*,*N*′-di-Boc-thiourea to give S and active carbodiimide, and the resulting activated carbodiimide is attacked *in situ* by the free amine substrate to give the corresponding guanidine. The HI generated in the desulfurization step is oxidized by TBHP to regenerate I_2.

Conclusions

In conclusion, we have developed a protocol for the I_2-catalyzed guanylation of primary amines with *N*,*N*′-di-Boc-thiourea in the presence of TBHP. Oxidation of the HI byproduct by TBHP eliminates the need for an extra base to prevent protonation of the free amine. Because I_2 and the active intermediate are generated depending on the nucleophilic addition of the amine to *N*,*N*′-di-Boc-thiourea, this strategy works well for electronically or sterically deactivated primary anilines.

Conflicts of interest

There are no conflicts to declare.

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