Facile Guanidine Formation under Mild Acidic Condition

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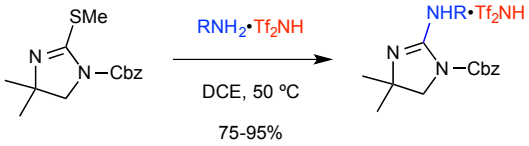

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Abstract: An efficient method for converting isothioureas into guanidines was developed. The use of amine salts of bis(trifluoromethanesulfonyl)imide as a nitrogen source was found to induce an efficient conversion under weak acidic condition at 50 °C. The conversion was applicable to the various amines and carbamate-protected thioureas, and various carbamate-protected cyclic guanidines were obtained in high yields. In particular, ammonium bis(trifluoromethanesulfonyl)imide salt is a useful N1 source with which to construct mono-protected cyclic guanidines.

Key words: guanidinylation, cyclic guanidine, isothiourea, bis(trifluoromethansulfonyl)imide, ammonium bis(trifluoromethansulfonyl)imidate.

Various types of natural products that contain guanidine moieties, including acyclic and/or cyclic ones, have been isolated thus far, such as tetrodotoxin[1], batzelladines[2], and guadinomine[3]. Furthermore, recently developed pharmaceutical compounds possessing guanidine moieties have been certified. For example, Inavir and Rapiacta[4] are used as neuraminidase inhibitors. In addition, interesting chemical properties of guanidines, such as high polarity and excellent hydrogen-bonding capacity[5], have been widely used to provide a strong base, such as tetramethylguanidine (TMG) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), and an active site of asymmetric catalysts[6] for organic synthesis. Therefore, various methods for guanidinylation of amines have been developed over many years (Figure 1).[7] These methods can be divided roughly into two groups. The first group (i) is defined by its use of activated thiourea or amidine reagents, e.g., isothioureas,[8] pyrazoles,[9] Goldman reagent,[10] and others.[11-12] The second group (ii) belongs to carbodiimide-type reagents, e.g., cyanamide[13] and Ag(I) or Hg(II)-activated isothiourea. These methods have been common and useful for constructing an acyclic guanidine moiety, and the above reagents normally possess a carbamate group as a protecting group (Figure 1a). Since the high polarity and reactivity of the guanidino group make it difficult to manipulate guanidine compounds, carbamate groups such as Boc and Cbz are first introduced to the guanidinylation reagents. On the other hand, in the case of cyclic guanidine formation, unprotected cyclic isothioureas have been frequently used,[14,15] and there have been surprisingly few examples of the conversion of carbamate-protected cyclic isothioureas into guanidines, for which harsh conditions are required (Figure 2a).[16] Probably, the steric hindrance and lower protonation ability caused by carbamate groups decrease the reactivity of isothioureas.

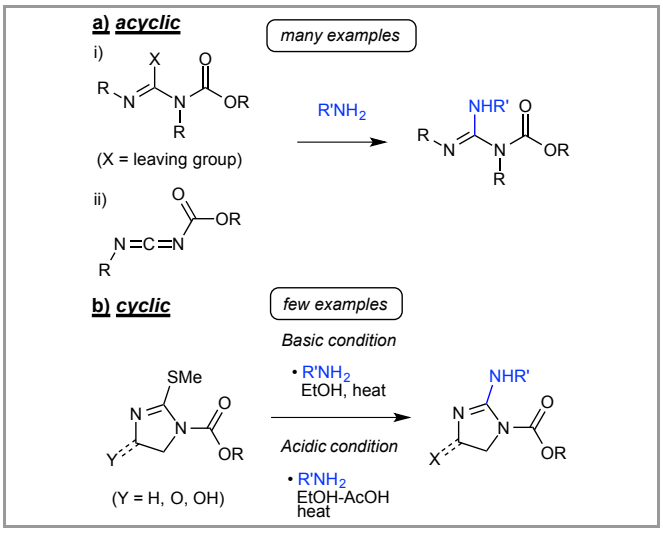


Figure 1. Guanidinylation reaction

Previously, we also had a problem with the guanidinylation of cyclic isothiourea possessing the Cbz group in a total synthesis of palau'amine.[17] Applications of common harsh conditions to the synthetic intermediates of palau'amine, which are unstable under basic conditions, resulted in only decomposition. Furthermore, removal of the Cbz group also induced decomposition of the intermediate, although various methods

for the guanidinylation of unprotected cyclic isothiourea have been reported. Moreover, the oxidative metals reacted with other parts in preference to the isothiourea moiety. Therefore, the development of a method for the direct conversion of Cbz-protected cyclic isothiourea into guanidines under acidic and mild conditions is indispensable to accomplish the total synthesis. Herein, we report the establishment of a concise and mild acidic method for the guanidinylation of carbamate-protected cyclic isothioureas.[18]

Our plan is shown in Figure 2. We considered that the difficulty of converting cyclic isothiourea having Cbz protection arises from the low reactivity of the carbon center of isothiourea toward the nucleophilic addition of amine. Thus, activation of the imine moiety might help the addition of amines, and the acetic acid in the conventional method was not strong enough for the activation even when a large excess amount of acetic acid was treated. To protonate the nitrogen of thioisourea efficiently, we took particular note of strong acid (HX) salts of amines (R'NH_2). Based on this concept, various combinations of acids and amines were examined by using a cyclic substrate that was not applicable to conventional conditions.[14-16]

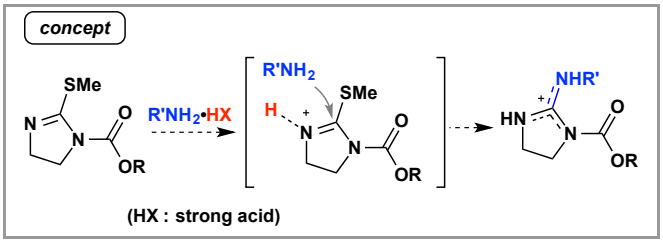
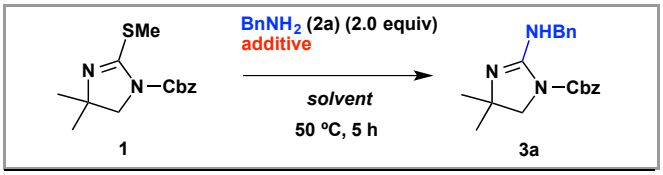


Figure 2. Acid-assisted guanidinylation reaction

We began the investigation with sterically hindered cyclic isothiourea **1** as a difficult substrate for guanidinylation (Table 1). First, the common condition was applied to **1**. Treatment of **1** with ammonia in methanol did not afford the desired guanidine, and only starting material was recovered (entry 1). Neither did another common condition using ammonium acetate at high temperature or sulfurphilic metal salts such as Ag(I) or Hg(II) (entries 2, 4, and 5). Although a small amount of the desired guanidine was obtained in the presence of a large excess amount of acetic acid, the yield was hardly enhanced (entry 3). Therefore, the conventional method for guanidinylation was found not to be applicable to **1**. Next, an appropriate strong acid was investigated based on our strategy as shown in Figure 2. The reaction of **1** with 2.0 equiv of benzylamine and equal amount of one of various strong acids in ethanol at 50 °C were examined. Among the strong acids of trifluoromethanesulfonic acid (TfOH), trifluoromethanesulfonimide (Tf_2NH), hydrogen chloride, toluenesulfonic acid (TsOH), and trifluoroacetic acid (TFA), Tf_2NH was found to give **3a** in highest yield (67%) (entries 6-10). The promising result of Tf_2NH is probably attributable to its sufficiently high acidity and good solubility in organic solvent. After identifying the best acid, we further optimized the reaction conditions. Although the use of THF as a solvent increased the yield of **3a** to 82%, the starting material **1** was not consumed completely (entry 11). The reactions in PhH, MeCN, and EtOAc gave **3a** in 90, 90, and 91% yields, respectively (entries 12-14). The reaction in 1,2-dichloroethane (DCE) proceeded much faster than any other solvent and furnished **3a** in 96% yield (entry 15). The reaction using prospectively prepared $BnNH_2$•Tf_2NH salt also proceeded smoothly to afford **3a** in high yield, similar to the yield achieved by the use of in situ–generated salt by the successive additions of $BnNH_2$ and Tf_2NH (entry 16). This method might help the reaction employing base-sensitive compounds.

Table 1. Optimization of the guanidinylation reaction

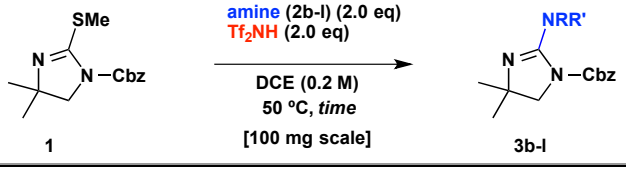


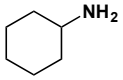
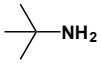
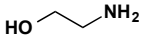
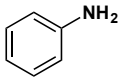
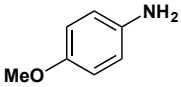
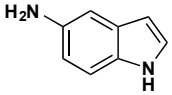
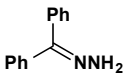
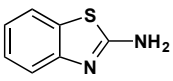
Entry	Additive (equiv)	Solvent	Yield (%)[a]
1[b]	NH_3[c]	MeOH	0
2[b]	NH_4OAc (10)[c]	EtOH	0
3	NH_4OAc (10)[c]	EtOH-AcOH (9:1)	31
4	AgOTf (2), Et_3N (3)	DMF	0
5	$HgCl_2$ (2), Et_3N (3)	DMF	0
6	TsOH (2)	EtOH	0
7	TFA (2)	EtOH	47
8	HCl (2)[d]	EtOH	5
9	TfOH (2)	EtOH	52
10	Tf_2NH (2)	EtOH	67
11	Tf_2NH (2)	THF	82
12	Tf_2NH (2)	PhH	90
13	Tf_2NH (2)	MeCN	90
14	Tf_2NH (2)	EtOAc	91
15	Tf_2NH (2)	DCE	96
16[e]	Tf_2NH (2)	DCE	95

[a]NMR yield using pyrazine as an internal standard. [b]The reaction mixture was heated to reflux. [c]The reagent was used instead of $BnNH_2$. [d]$BnNH_2$•HCl was used. [e]$BnNH_2$•Tf_2NH (2 equiv) was used.

Having established the optimized conditions,[19] we applied this methodology to various amine reagents (Table 2). The reaction of isothiourea **1** with primary amines **2b** and **2c** efficiently provided corresponding guanidine derivatatives **3b** and **3c** in 96 and 95% yields, respectively (entries 1 and 2). On the other hand, *tert*-butylamine **2d** did not react at even 100 °C, and only starting material was recovered (entry 3). The reaction of ethanolamine **2e** also afforded guanidine **3e** in 92% yield without a side product that reacted with the hydroxyl group (entry 4). A secondary amine, pyrrolidine **2f**, was allowed to react cleanly and furnish guanidine **3f** in 80% yield (entry 5), although piperidine did not react at all. The reaction of arylamines such as **2g** and **2h** also proceeded to form guanidines **3g** and **3h** in 65% and 82% yields, respectively, although the reaction time of aniline **2g** had to be prolonged to 36 h (entries 6 and 7).

Table 2. Amine scope of the guanidinylation reaction

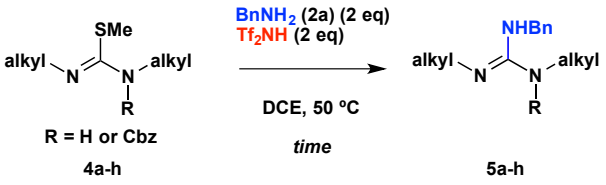


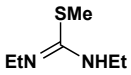
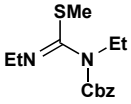
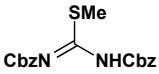
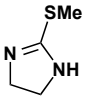
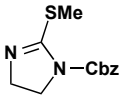
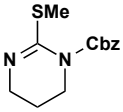
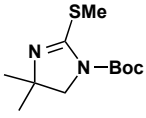
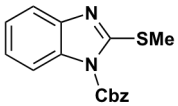
Entry	Amine	Time (h)	Product	Yield (%)[a]
1	 **2b**	5	**3b**	96
2	 **2c**	5	**3c**	95
3[b]	 **2d**	24	**3d**	n.d.
4	 **2e**	5	**3e**	92
5	 **2f**	5	**3f**	81
6	 **2g**	36	**3g**	65
7	 **2h**	12	**3h**	82
8	 **2i**	5	**3i**	85
9	 **2j**	12	**3j**	75
10	NH_2OBn **2k**	12	**3k**	84
11	 **2l**	50	**3l**	n.d.

[a]Isolated yield. [b]The reaction was conducted at 100 °C.

The indole derivative **2i** provided the desired guanidine **3i** that was selectively reacted with the amino group at the C-5 position of **2i**, and no byproduct that reacted with an indole nitrogen at the N1 position was observed (entry 8) in a case similar to the protocol reported by Tanaka and colleagues[13g]. The reactions with the hydrazine **2j** and hydroxylamine **2k** also afforded corresponding guanidines **3j** and **3k**, respectively, in good yield (entries 9 and 10). Unfortunately, benzothiazole **2l** hardly reacted with **1** to give **3k** under this condition.

Table 3. Substrate scope of the guanidinylation reaction

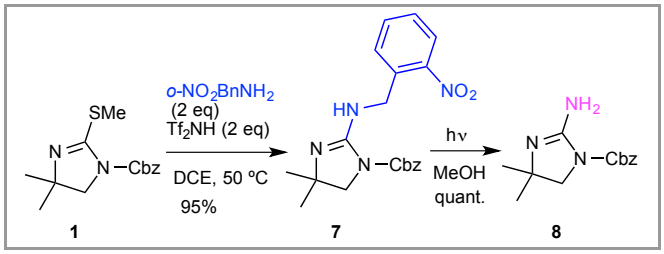


Entry	Amine	Time (h)	Product	Yield (%)[a]
1	 **4a**	3	**5a**	quant.
2	 **4b**	3	**5b**	95
3	 **4c**	3	**5c**	90
4	 **4d**	3	**5d**	quant.
5	 **4e**	5	**5e**	95
6	 **4f**	12	**5f**	92
7	 **4g**	5	**5g**	98
8[b]	 **4h**	60	**5h**	n.d.

[a]isolated yiled. [b]The reaction was conducted at 80 °C

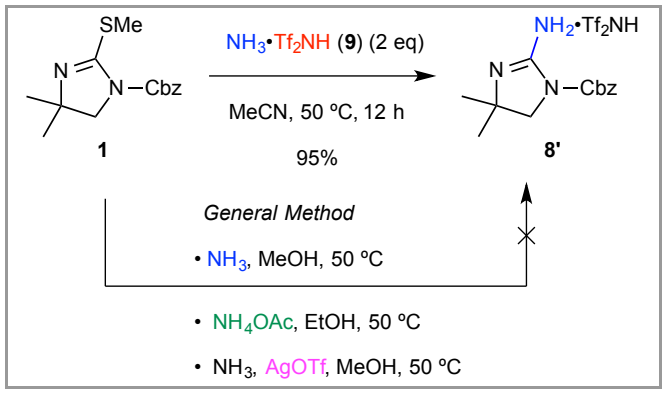
Next, we attempted to investigate the substrate scopes of the guanidinylation reaction. As we expected, the use of acyclic methylthioureas **4a**-**4c** efficiently resulted in the formation of corresponding guanidines **5a**-**5c** in 3 h (entries 1-3). Unprotected cyclic derivative **4d** was also applicable to this reaction (entry 4), and the reaction of Cbz-protected isothiourea **4e** uneventfully proceeded to give guanidine **5e** in high yield as well as dimethyl substrate **1** (entry 5). Furthermore, six-membered substrate **4f**also resulted in a high yield of guanidine **5f** (entry 6). In the case of Boc-protected derivative **4g**, the corresponding guanidine **5g** was obtained in 98% yield without the removal of the Boc group (entry 7). On the other hand, the reaction of benzoimidazole-type isothiourea **4h** did not proceed under this condition, probably due to the low basicity of the isothiourea moiety for protonation by Tf_2NH•$BnNH_2$ salt (entry 8). Therefore, the guanidinylation reaction using Tf_2NH•amine salt was proved to be applicable to various aliphatic isothioureas regardless of the protecting groups, cyclic substrates, or acyclic substrates.

Having established an efficient method for a guanidinylation, we demonstrated a photo-induced deprotection[20-21] of a nitrobenzyl group as a useful method for preparing mono-protected guanidine (Scheme 1). Treatment of **1** with 2 equiv of *o*-nitrobenzylamine and Tf_2NH afforded guanidine **7** in 95% yield. The *o*-nitrobenzyl group of **7** was cleanly removed by photo-irradiation using Hg-lump, and the mono-protected guanidine **8** was obtained in quantitative yield (NMR).



Scheme 1. Deprotection of guanidine **7**.

Since the above transformation leading to **8** required two steps, we focused on the direct introduction of a free amino group (Scheme 2). Although several direct conversions from a methylthio group into a free amino group were previously reported,[16] these conventional methods were not applicable to **1**. For example, none of the conditions of ammonia in methanol, ammonium acetate in ethanol, or ammonia and silver triflate in methanol gave the desired mono-protected cyclic guanidine. Thus, we attempted to apply ammonium bis(trifluoromethanesulfonyl) imide **9** (NH_3•Tf_2NH, see supporting information) to the conversion of **1**. Although there have been a few reports in which ammonium bis(trifluoromethanesulfonyl) imide **9** was used as the main source of bistrifluoromethanesulfonate as a counter anion,[22] there are no reports of its use for organic synthesis as an amine source. The reaction of **1** with **9** in MeCN proceeded smoothly to give cyclic guanidine **8'** as a bis(trifluoromethanesulfonyl)imide salt in 95% isolated yield. This is the first example of the use of NH_3•Tf_2NH for the direct introduction of a free amino group into isothiourea, and the Tf_2NH•amine salt is proven to be a powerful reagent for guanidinylation of isothiourea. Moreover, it is noteworthy that the salt form of **8'** with bis(trifluoromethanesulfonyl)imide was useful not only to keep the guanidine stable but also to readily obtain **8'** due to its good solubility in organic solvent, thus enabling efficient extraction and column chromatography. In contrast, the highly polar guanidine **8** as a salt-free form showed up to a 65% decline in yield during isolation and purification. Ammonium salt NH_3•Tf_2NH **9** is readily prepared[22a] and is bench-stable for more than a year without hygroscopicity, unlike ammonium acetate and bis(trifluoromethanesulfonyl)imide. Thus, we established a convenient method for synthesizing a cyclic isothiourea having carbamate protection.



Scheme 2. Direct conversion into mono-protected guanidine.

In summary, we have developed an efficient method for the guanidinylation of cyclic isothiourea having a carbamate group. The reaction of isothiourea with amines as a salt of bis(trifluoromethanesulfonyl)imide proceeded smoothly to give corresponding guanidines in high yield under a mild acidic condition. The various cyclic isothioureas and amines were readily applicable in most cases. Ammonium bis(trifluoromethanesulfonyl)imide (NH_3•Tf_2NH) **9** efficiently gave the corresponding mono-protected guanidine, and Tf_2NH salt actually made it easier to manipulate the resulting guanidine for isolation and purification using silica gel column chromatography. Hence this method can be broadly applicable to guanidine synthesis from isothiourea derivatives possessing base- or heat-sensitive functional groups. The application of **9** to another synthetic source of free amine units is ongoing in our laboratories.

Acknowledgment

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Supporting Information

Yes

Primary Data

NO

References and Notes

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(19) **General procedure for the transformation of isothiourea 1 into guanidine 3a**: to a solution of isothiourea **1** (100 mg, 0.359 mmol) in DCE (1.8 mL) were added $BnNH_2$ (39.2 µL, 0.718 mmol) and 1 M DCE solution of Tf_2NH (718 µL, 0.718 mmol) at 0 ºC. After being stirred at 50 ºC for 5 h, the reaction was quenched with 1 M NaOH. The mixture was extracted with CH_2Cl_2 (5 mL x3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 1/2 to 0/1) to afford guanidine **3a** (116 mg, 0.345 mmol, 96%) as yellow oil.

Analytical Data for Compound 3a: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.25 (m, 10H), 7.05 (br-s, 1H), 5.17 (s, 2H), 4.48 (s, 2H), 3.58 (s, 2H), 1.30 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.16, 151.12,

138.01, 135.21, 128.65, 128.58, 128.55, 128.13, 127.60, 127.37, 67.73, 60.93, 58.63, 46.76, 29.70.; IR (KBr): 3378, 3032, 2962, 2926, 2360, 2341, 1710, 1648, 1532, 1460, 1402, 1353, 1324, 1183, 1127, 1005, 913, 801, 742, 697, 610, 442, 418 cm^{-1} ; HRMS (ESI, m/z): $[M+H]^+$ calcd for $C_{20}H_{24}N_3O_2$, 338.1869; found, 338.1863.

Compound 3b: ^1H NMR (500 MHz, $CDCl_3$): δ 7.43-7.33 (m, 5H), 6.58-6.45 (br-s, 1H), 5.16 (s, 2H), 3.85 (oct, J = 6.5 Hz, 1H), 3.50 (s, 2H), 1.25 (s, 6H), 1.20 (d, J = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ ı□□̃16, ı□□̃8□, ı□□̃□3, ı□□̃58, ı□□̃□□, ı□□̃40, □□̃34, □̃□8, □□̃24, □3.93, □□̃82, □□̃73; IR (KBr): 3374, 2967, 2928, 2360, 1712, 1646, 1529, 1457, 1402, 1358, 1322, 1280, 1190, 1165, 1131, 1059, 988, 913, 765, 743, 698, 597, 576, 419 cm^{-1} ; HRMS (ESI, m/z): $[M+H]^+$ calcd for $C_{16}H_{24}N_3O_2$, 290.1862; found, 290.1863.

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