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A new entry for the synthesis of *N*-acyl-*N*′-substituted guanidines

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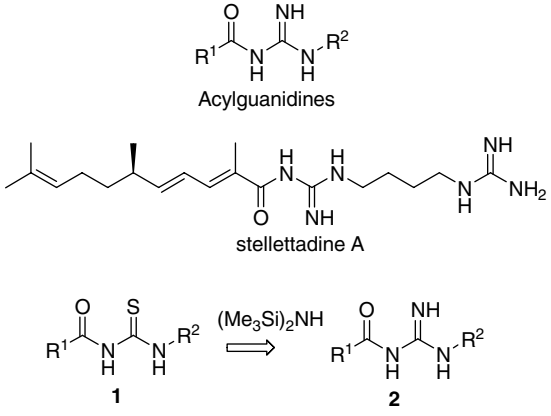
Abstract—An efficient synthesis of *N*-acyl-*N*′-substituted guanidines by condensation reaction of thiourea and $(Me_3Si)_2NH$ in the presence of EDCI is described. Various guanidines were synthesized in a simple manner.

N-Acyl-*N*′-substituted guanidines are abundant source of biologically active compounds.[1–3] The α_2-adrenoceptor agonist guanfacine,[4] the multiple ion-channel blocker amiloride,[5] and its derivatives such as caripolide,[6] eniporide,[7] and BMS-284640,[8] are representative examples.[9] Moreover, natural products bearing the *N*-acylguanidine moiety have been isolated.[10] For example, stellettadine A, a sesquiterpene amide of 1,4-diguanidinobutane possessing unique biological profiles, for example, larval metamorphosis-inducing activity in an ascidian, was isolated from a kind of marine *Stelletta* sponges.[11] *N*-Acylguanidines are of great synthetic value as starting materials for the synthesis of highly substituted guanidines[3s,12] and heterocycles such as 2-imidazolines,[13] 1,2,4-oxadiazoles,[14] and guanosines.[3k]

These facts lead to extensive efforts for the synthesis of this class of acylguanidines. Herein, we wish to report a simple method to access *N*-acyl-*N*′-substituted guanidines by condensation of *N*-acyl-*N*′-substituted thiourea **1** with hexamethyldisilazane (HMDS) as a nitrogen source under the mild reaction conditions (Scheme 1).

In contrast to a large number of methods for synthesis of *N*-acyl- and *N*-acyl-*N*′,*N*″-disubstituted guanidines,[3–9] only a few methods have been reported to access the titled guanidines. Typical procedures are summarized as follows: (i) acylation of guanidines that often accompanied with the undesired diacylation reaction,[3r,9b,15] (ii) addition reaction of an amine to an acylcyanamide derived from toxic cyanamide,[9b] and (iii) the use of a protected imino group (=NH of **2**) as the starting material followed by its deprotection to give **2**.[3d,e,i] We envisioned that reaction of thioureas **1** with HMDS in the presence of a condensation reagent would provide **2** in a simple operation. The feasibility was tested by using *N*-benzoyl-*N*′-phenyl thiourea (**3**) as a model substrate that was prepared by addition reaction of aniline to commercially available benzoyl isothiocyanate. Thiourea **3** was treated with 10 equiv of HMDS with several condensation reagents **5**–**9** in the presence or absence of a base (Scheme 2, Table 1). The corresponding benzoylguanidine **4** was obtained in good to moderate yields in all cases. However, the resulting products derived from condensation reagents **5**–**8** and *N*-acylguanidine **4** were



Scheme 1.

Keywords: Thiourea; Guanidine; Condensation reaction; EDCI; HMDS.
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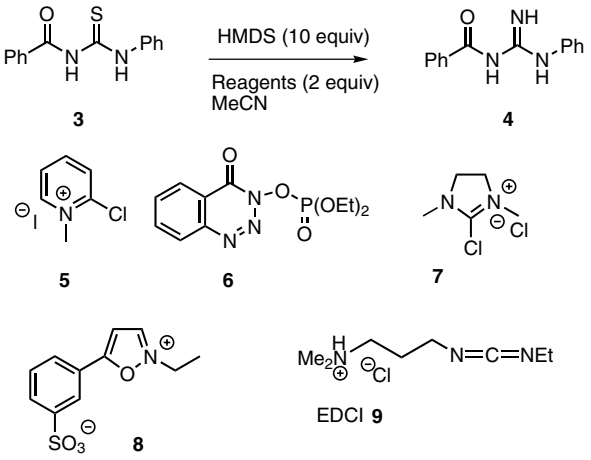


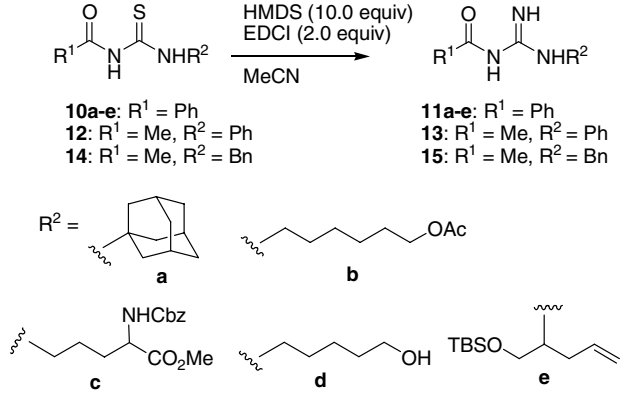
Scheme 2.

Table 1. Optimization of the condensation reaction

Entry	Reagent	Time (h)	Yield (%)
1	**5**, Et_3N	18	31
2	**6**, Et_3N	5	42
3	**7**, Et_3N	5	76
4	**8**, Et_3N	2	75
5	**9**	2	84

difficult to separate by silica gel column chromatography (entries 1–4). This practical problem was solved by the use of EDCI **9**. The resulting thiourea of EDCI was easily removed by extractive work-up and silica gel column chromatography. As a result, EDCI **9** was found to be the best reagent in terms of high yield and practical convenience.[16]

With the optimized reaction conditions in hand, the scope and limitation of this method were examined (Scheme 3, Table 2). Various kinds of thioureas **10a**–**e**, **12**, and **14** were smoothly condensed with HMDS in the presence of EDCI **9**. Functional groups such as hydroxy, acetyl, silyl, vinyl, Cbz, and ester groups were tolerated under the reaction conditions to give the corresponding *N*-acylguanidines **11a**–**e**, **13**, and **15** in excellent yields.



Scheme 3.

Table 2. Synthesis of *N*-acyl-*N*′-substituted guanidines

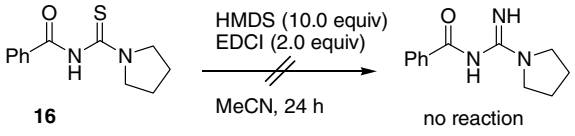
Entry	Substrate[a]	Time (h)	Product	Yield (%)
1	**3**	3	**4**	84
2	**10a**	4	**11a**	92
3	**10b**	3	**11b**	83
4	**10c**	4	**11c**	86
5	**10d**	4	**11d**	83
6	**10e**	24	**11e**	93
7	**12**[b,c]	48	**13**	90
8	**14**[b,c]	48	**15**	72

[a] 1 mmol scale.
[b] 0.2 mmol scale.
[c] 4 equiv of EDCI was used.

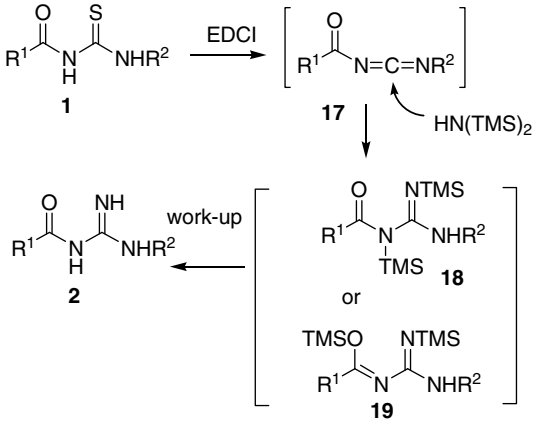
Sterically bulky thiourea **10a** underwent condensation reaction to give *N*′-adamantyl guanidine **11a** in 92% yield. Acetyl thioureas **12** and **14** were also converted to guanidines **13** and **15** in 90% and 72% yields, respectively.

The condensation reaction of *N*-benzoyl-*N*′,*N*′-disubstituted thiourea **16** having a pyrrolidine moiety was not proceeded at all to result in a recovery of the starting material (Scheme 4). This indicates that –NHR^2 moiety of acyl thioureas **1** plays an important role in this condensation reaction.

Based on the above observation, a plausible reaction pathway via a carbodiimide intermediate is proposed in Scheme 5. Treatment of **1** with EDCI would afford *N*-acyl carbodiimide **17** as a reactive intermediate.[17] HMDS smoothly reacts with **17** to give **18** or **19**. The silyl groups of **18** or **19** are removed to give *N*-acyl-*N*′-substituted guanidine **2** under the work-up condition.



Scheme 4.



Scheme 5.

In summary, we developed a simple method to access *N*-acyl-*N*′-substituted guanidines from *N*-acylthioureas by the use of HMDS. Various *N*-acylguanidine derivatives were prepared from the corresponding thioureas in a facile manner. Application of this method for the synthesis of biologically active guanidines and guanidine-containing natural products is currently underway.

Acknowledgments

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16. Typical procedure for the condensation reaction. To a solution of **10a** (314 mg, 1 mmol) and HMDS (2.09 mL, 10 mmol) in CH_3CN (10 mL) was added EDCI (383 mg, 2 mmol) at 0 °C with stirring. The mixture was stirred for 2 h, poured into water, and extracted with AcOEt (50 mL × 2). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (AcOEt/hexane (1:4) to AcOEt) to give **11a** (271 mg, 92%) as colorless crystals. Mp 194–196 °C (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, $J = 6.6$ Hz, 2H), 7.40–7.36 (m, 3H), 7.15 (br s, 1H), 2.10 (br s, 3H), 2.02 (br s, 6H), 1.67 (br s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 160.7, 138.8, 130.8, 128.8, 127.8, 51.9, 42.2, 36.1, 29.3. HRMS (FAB$^+$) calcd for $[C_{18}H_{23}N_3O+H]^+$ 298.1919, found 298.1914.
17. Carbodiimide derivatives bearing an electron-withdrawing group have been synthesized by dehydration reaction of urea derivatives using $COCl_2$ and Et_3N.[2a,3k] See also references cited in 2a and 3k.