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A highly efficient method for the synthesis of guanidinium derivatives

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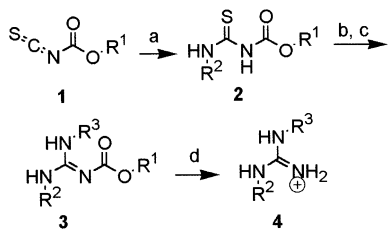
Abstract—A high yielding synthesis of guanidiniums with the use of the ethyl carbamate protecting group is presented. This strategy eliminates many steric hindrance and electronic problems. The deprotection of the products by Me_3SiBr is also demonstrated. © 2002 Published by Elsevier Science Ltd.

Guanidiniums are very weakly acidic molecules (pK_a around 12.5) with the capacity to form intermolecular contacts mediated by H-bonding interactions.[1] The guanidinium moiety is common in natural products[2] and is often used in molecular recognition.[3] They also play important biological roles.[4] Various methods exist for the synthesis of guanidiniums from different starting materials and reagents.[5] One of the well-known methods is the conversion of thioureas into guanidiniums in the presence of a coupling reagent.[6] The conversion of thioureas into guanidiniums is usually accomplished with an electron withdrawing protecting group on the thiourea. These protecting groups, such as *t*-Boc,[7] Fmoc,[6] and benzoyl,[8] are not only capable of facile deprotection, but also activate the thiourea for the coupling reaction. Most thioureas that contain these activating groups can be only coupled with primary amines. Furthermore, the efficiency of guanylation depends on the group attached to the primary amine. Thioureas mostly react with primary amines attached to primary carbons due to the bulkiness of the protecting groups. The efficiency of guanylation also depends upon whether the group that is attached to the amine is electron withdrawing or electron donating. Amines attached to electron withdrawing groups tend to give lower yields in guanylation.

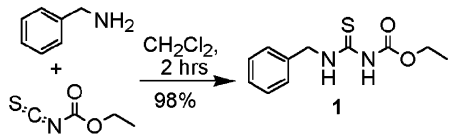
The general sequence of synthesizing guanidiniums via a thiourea is illustrated in Scheme 1. At first, potassium thiocyanate is allowed to react with an electrophile to give the protected thiocyanate. Addition of an amine to the protected thiocyanate results in the formation of thiourea **2**. An amine can then be coupled to the thiourea to form guanidinium **3** with coupling reagents



Scheme 1. (a) CH_2Cl_2, R^2NH_2; (b) EDCl, CH_2Cl_2, Et_3N; (c) R^3NH_2; (d) deprotection.

such as EDCl,[9] Sanger's reagent,[10] Mukaiyama's reagent,[11] and $HgCl_2$.[12] Deprotection of **3** then gives the guanidinium **4**.

We were interested in the use of ethyl thiocyanato formate since it is commercially available and the corresponding thiourea is readily prepared as shown in Eq. (1).[13] While we were working on the synthetic strategies of ethyl carbamate protected guanidines using various coupling reagents and their subsequent deprotection, Hamilton and co-workers published the aforementioned synthesis with various amines using EDCl as the coupling reagent.[14] Here, we would like to report our findings on the synthesis of ethyl carbamate protected guanidines using EDCl, Mukaiyama's reagent, and Sanger's reagent. We also looked at the electronic and steric effects of different amines on the guanylation as well as their deprotection using trimethyl silyl bromide (Me_3SiBr).



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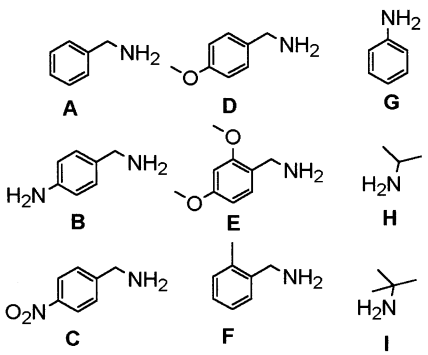
We envisioned that the much smaller ethyl carbamate-protecting group could alleviate steric hindrance problems created by bigger carbamate groups such as Boc, Fmoc, and Cbz. To investigate the electronic and steric limitations of the coupling in the presence of this protecting group, we decided to couple different amines to the carbamate protected benzyl thiourea.

The coupling of amines (**A**–**I**) to thiourea succeeds with EDCl coupling conditions without any major, undesirable side products in 48 h.[15] This same reaction was also attempted with Mukaiyama's and Sanger's reagent in place of EDCl under different reaction conditions. The use of Mukaiyama's reagent did not give any products. On the other hand, Sanger's reagent gave lower yields along with side products. The guanidines obtained via EDCl coupling were easily purified through flash chromatography. The yields of these guanidines are reported in Table 1.

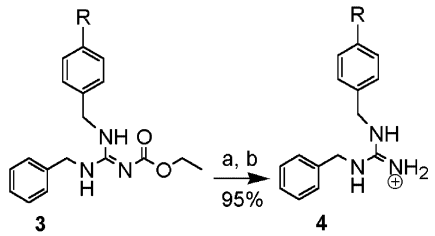
From Table 1 it is evident that all the amines gave comparably similar and good yields. It was concluded that ethyl carbamate protecting groups are very efficient in the synthesis of guanidinium derivatives especially for coupling an amine that is attached to a secondary or tertiary carbon, and even aryl amines. However, it was previously shown that secondary amines could not be used in this coupling process.[14]

The removal of the ethyl carbamate group was carried out using Me_3SiBr under reflux in DMF followed by protonation with methanol to give complete deprotection, as seen in Eq. (2), without cleaving the functional groups.[16] The product was easily purified by an acid work-up. The efforts to deprotect this group in the presence of reagents such as hydrazine monohydrate,[17] HBr,[18] Red-Al,[19] and NaOH,[20] that are known to cleave this group from amines, were unsuccessful. The use of ammonium hydroxide under mild heating, that is known to deprotect ethyl carbamate group from the guanidine of guanosine[21] also failed.

Table 1.



Amine	% Yield of guanidine **3**	Amine	% Yield of guanidine **3**
A	80	**F**	80
B	83	**G**	87
C	88	**H**	85
D	85	**I**	83
E	78		



R= H (**4A**), NH_2 (**4B**), O NO_2 (**4C**), and Me (**4D**)

a) Me_3SiBr, DMF, reflux, 18 hrs b) Methanol, 30 min

In conclusion, we report a highly efficient synthesis of guanidinium derivatives using ethyl carbamate protecting group and EDCl coupling followed by the deprotection with Me_3SiBr.

Acknowledgements

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13. Representative procedure for the preparation of ethyl carbamate protected thiourea: Synthesis of benzyl thiourea **1**. Benzylamine (2.3 g, 21.6 mmol) was added to ethyl isothiocyanatoformate (1.8 g, 13.7 mmol) dissolved in 10 ml of DCM. A gas evolution was noticed and a

yellow solid was formed immediately. The product was purified through flash chromatography (silica gel; eluant, DCM/hexanes (2:3)); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.86 (br, 1H), 8.05 (br, 1H), 7.21 (m, 5H), 4.77 (br, 2H), 4.12 (q, 2H), 1.19 (t, 3H); ^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 179.3, 152.7, 136.2, 128.7, 127.7, 127.6, 62.6; HRMS (CI^+) calcd for $C_{11}H_{14}N_2O_2S$ ($[M+H]^+$): 239.0854; found: 239.0846.

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15. Representative procedure for the preparation of protected guanidinium: synthesis of *N*,*N*-dibenzyl-guanidine carbamic acid ethyl ester **3A**. The thiourea **1** (0.5 g, 2.1 mmol) was dissolved in DMF and Et_3N (3 ml, 41.5 mmol) and EDCl (0.5 g, 2.6 mmol) were added to it. After 30 min, benzylamine (0.23 g, 2.1 mmol) was added. The reaction was run for 38 h. The product was isolated through flash chromatography to give an off-white solid (DCM/hexanes (2:3)); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (m, 10H), 4.41 (br, 4H), 4.10 (q, 2H), 1.26 (t, 3H); ^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 164.1, 159.9, 136.9, 128.5, 127.3, 126.9, 60.4; HRMS (CI^+) calcd for $C_{19}H_{21}N_3O_2$ ($[M+H]^+$): 312.1712; found: 312.1713.
16. Representative procedure for deprotecting the ethyl carbamate group: synthesis of *N*,*N*-dibenzyl-guanidine **4A**. Protected guanidinium **3A** (100 mg, 0.42 mmol) and trimethyl silyl bromide (0.32 g, 2.1 mmol) were dissolved in DMF and the solution was refluxed overnight. The DMF was distilled off and the residue was resuspended into 2 M HCl and was washed with ether. The solution was then made basic by adding NaOH and the guanidine was extracted with DCM. The DCM was rotary evaporated to give an white solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 13H), 4.31 (s, 4H); ^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 158.6, 139.2, 128.4, 127.1, 127.0; HRMS (CI^+) calcd for $C_{15}H_{17}N_3$ ($[M+H]^+$): 240.1500; found: 240.1497.
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