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Two New Reagents for the Guanylation of Primary, Secondary and Aryl Amines.

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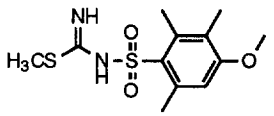
Abstract: Two new reagents for the preparation of monoprotected guanidines from primary, secondary and aryl amines are reported. These protected guanidines can be liberated under acidic conditions and are amenable to a variety of synthetic manipulations.

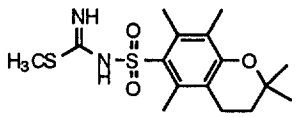
The guanidine functionality has been found in many natural products and guanidine-containing molecules are found to be a critical part of many biological processes. Consequently, many reagents have been used to prepare protected and unprotected guanidines including pyrazole-1-carboxamidine derivatives,[1] formamidinesulfinic acid[2] and isothiourea derivatives.[3]

It has been shown that 1,3-bis(benzyloxycarbonyl)-2-methyl-2-thiopseudourea can be used to prepare di-benzyloxycarbonyl (di-CBZ) protected guanidines.[3d] However, the di-CBZ protecting group is not always compatible with functional group manipulations. Therefore, we have utilized the 2,3,6-trimethyl-4-methoxybenzenesulfonyl (Mtr) and 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc) groups for protection of guanidines.[4] These groups are stable to most organometallics, base, hydrogenolysis, but require more vigorous conditions for removal, thus providing orthogonal protection to standard CBZ, *tert*-butyloxycarbonyl (Boc) and 9-fluorenylmethoxycarbonyl (Fmoc) protection strategies.

Previously, reagents for the direct conversion of amines to monoprotected Mtr or Pmc guanidines have not been described. Thus, the synthesis and reactions of reagents **1** and **2** for the preparation of mono Mtr or Pmc protected guanidines are described.



1



2

To prepare reagent **1**: 2-methyl-2-thiopseudourea (15.00 g, 53.9 mmol) was dissolved in a solution of THF (500 mL) and saturated sodium carbonate (700 mL) with stirring. Mtr-chloride (Mtr-Cl) (53.61 g, 215.6 mmol) was dissolved in THF (200 mL) and added dropwise. After stirring overnight, the THF was evaporated "in vacuo" and the aqueous solution was extracted with EtOAc (600 mL, 2 x 200 mL). The combined organic extracts were washed with H_2O, brine (2 x 100 mL, respectively) dried with $MgSO_4$, filtered, concentrated and recrystallized from EtOAc:Hex yielding **1** (27.42 g, 84 %) as a white crystalline solid.[5a] Reagent **2** was prepared similarly (79 %).[5b]

Piperidine and aniline were used as model substrates to test the utility of reagents **1** and **2**. Several conditions were evaluated to determine optimal conditions. Reagent **1** reacted with piperidine or aniline in the presence of triethylamine and $Hg(ClO_4)_2$ in refluxing THF (or toluene) to produce mono Mtr protected guanidines in moderate to good yields (Table 1). The reaction with more basic amines could proceed without added base (Row A). However, higher yields were obtained when the reactions were carried out in the presence of triethylamine (Row E). While mercury perchlorate proved to be the best salt, presumably due to its increased solubility in organic solvents, silver perchlorate could also be used (Rows C, D, E and G). The presence of a "soft" cation salt is required since no reaction occurred without addition of silver or mercury salt (data not shown). Elevated temperatures were also required for reaction to occur. Refluxing THF gave optimal yields, but refluxing toluene was also acceptable (Rows B-D, F, G).

Table 1. Optimization of the reaction conditions for guanylation reactions with reagent **1**.

Reaction	Substrate	Conditions	Isolated Yield (%)
A		$HgCl_2$ (1.1 eq.), THF, Δ	42
B		$HgCl_2$, TEA (1.1, 2 eq.), toluene, Δ	37
C		$Hg(ClO_4)_2$, TEA (1.1, 2 eq.), toluene, Δ	62
D		$AgClO_4$, TEA (1.1, 2 eq.), toluene, Δ	46
E		$Hg(ClO_4)_2$, TEA (1.1, 2 eq.), THF, Δ	80
F		$HgCl_2$, TEA (1.1, 2 eq.), toluene, Δ	a
G		$Hg(ClO_4)_2$, TEA (1.1, 2 eq.), toluene, Δ	47

a. This reaction proceeded to less than 20% completion.

Reagents **1** and **2** were evaluated with several other substrates under optimal conditions (Table 2).[6] Reagents **1** and **2** were reacted with Boc-Lys-OMe•HCl and Boc-p-aminophenylalanine-OMe. The lysine derivative has a primary aliphatic amine side chain but appears to react with **1** and **2** less readily, and in lower yield, than the other substrates (Rows B'[7], E'- H'). The Boc-*p*-aminophenylalanine-OMe substrate reacts efficiently with **1** and **2** in high yield to produce the target guanylated amino acids (Row F',G'). Reagent **2** was also reacted with 2,2,2-trifluoroethylamine also giving a reasonably high yield (Row H'). These results are interesting since reagents **1** and **2** react with the less nucleophilic electron deficient amines more readily than the more basic primary aliphatic amines.[1b,c]

To compare the efficiency of reagent **2**, which produces monoprotected guanidines in a single step, to a two step guanylation/protection reaction sequence, Boc-Lys-OMe•HCl was treated with 1*H*-pyrazole-

carboxamidine hydrochloride[1b] and base to produce the unprotected homoarginine derivative. The product was protected with Pmc by treatment with Pmc-Cl. This two-step procedure provided the protected homoarginine derivative in only 26% isolated yield which is much lower than the yield obtained using **2** in a single step under the best conditions (Row E').

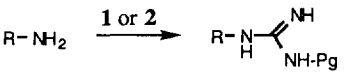
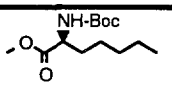
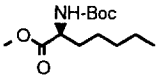
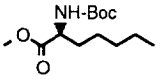
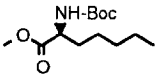
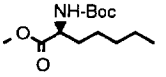
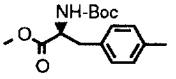
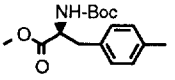


Table 2. Reactions using reagents **1** and **2**.

Reaction	R	Reagent and Conditions	Isolated Yield (%)
A'		**1**, $HgCl_2$, TEA, (1.1, 1.1, 1.5 eq.), THF, Δ, 120h	51
B'		**1**, $AgClO_4$, TEA (1.25, 1.1, 2 eq.), toluene, Δ, 16h	71[a]
C'		**2**, $Hg(ClO_4)_2$, TEA (1.3, 1.1, 2 eq.), toluene, Δ, 16h	24
D'		**2**, $Hg(ClO_4)_2$, TEA (1.3, 1.1, 2 eq.), THF, Δ, 48 h	35
E'		**2**, $Hg(ClO_4)_2$, TEA (1.3, 1.1, 2 eq.), THF, Δ, 60 h	41
F'		**1**, $Hg(ClO_4)_2$, TEA (1.25, 1.1, 2 eq.), THF Δ, 16h	84
G'		**2**, $Hg(ClO_4)_2$, TEA (1.3, 1.1, 2 eq.), THF, Δ, 60 h	93
H'	CF_3CH_2-	**2**, $Hg(ClO_4)_2$, TEA (1.3, 1.1, 2 eq.), neat trifluoro-ethylamine, Δ, 16h	72

a. To examine whether or not racemization occurred, this material was Boc-deprotected and coupled to Boc-L-leucine. Only one diastereomer was detected by HPLC and NMR.

In summary, reagents **1** and **2** react efficiently with amines in the presence of triethylamine and mercury or silver perchlorate to produce mono Mtr or Pmc protected guanidines. These reagents provide useful alternatives to the standard Boc or CBZ protecting group strategies commonly employed in guanylating reagents. In addition, these reagents provide routes to guanidines that are complementary to those already known and should serve as useful tools for the preparation of arginine peptidomimetics and other biologically active molecules.

ACKNOWLEDGEMENTS

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5. a. Reagent **1**. mp 155 - 157 °C; R_f = 0.30 (EtOAc/Hex 1:1); ^{1}H NMR ($CDCl_3$) δ 6.56 (s, 1H), 3.84 (s, 3H), 2.71 (s, 3H), 2.62 (s, 3H), 2.35 (s, 3H), 2.14 (s, 3H); MS M/H$^+$: 303; Anal. calc. for $C_{12}H_{18}N_2O_3S_2$: C, 47.66; H, 6.00; N, 9.26; Found: C, 47.73; H, 5.92; N, 8.87.

   b. Reagent **2**. mp 127 - 129 °C; R_f = 0.48 (EtOAc/Hex 1:1); ^{1}H NMR ($CDCl_3$) δ 2.64 (t, J = 6.8 Hz, 2H), 2.58 (s, 3H), 2.57 (s, 3H), 2.35 (s, 3H), 2.12 (s, 3H), 1.81 (t, J = 6.6 Hz, 2H), 1.31 (s, 6H); MS M/H$^+$: 357; Anal. calc. for $C_{16}H_{24}N_2O_3S_2$: C, 53.91; H, 6.79; N, 7.86; Found: C, 53.91; H, 6.70; N, 7.62.

6. General procedure: Boc-(*p*-Mtr-guanidino)-phenylalanine methyl ester. Boc-*p*-aminophenylalanine methyl ester (0.34 g, 1.1 mmol) and **1** (0.43 g, 1.4 mmol) were dissolved in dry THF (30 mL). TEA (0.32 mL, 2.2 mmol) and $Hg(ClO_4)_2$ (0.57 g, 1.2 mmol) were added and the mixture was refluxed overnight. An additional 0.20 g of **1** was added and refluxing continued for an additional 4 h. The mixture was concentrated and the remaining residue was dissolved in EtOAc (150 mL), filtered through celite which was washed with EtOAc (50 mL). The combined filtrate was washed with H_2O, sat. $NaHCO_3$, 4N $NaHSO_4$ and brine (2 x 50 mL, respectively), dried with $MgSO_4$, filtered and concentrated "in vacuo" to yield a white foam. The foam was chromatographed on silica gel (EtOAc/Hex 1:3 to 1:2 gradient) to yield the title compound (0.52 g, 84 %) as a white solid. mp 182 - 183 °C; R_f = 0.28 (EtOAc/Hex 1:1); $[\alpha]_D^{20}$ = + 6.1° (c = 1.8, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.75 (br s, 1H), 7.12 (dd, J = 17.9, 8.5 Hz, 4H), 6.53 (s, 1H), 6.04 (br s, 2H), 5.04 (d, J = 9.1 Hz, 1H), 4.54 (m, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.11 (dd, J = 14.6, 6.4 Hz, 1H), 2.98 (dd, J = 12.8, 6.4 Hz, 1H), 2.69 (s, 3H), 2.61 (s, 3H), 2.13 (s, 3H), 1.40 (s, 9H); MS M/H$^+$: 549; Anal. calc. for $C_{26}H_{36}N_4O_7S$: C, 56.92; H, 6.61; N, 10.21; Found: C, 56.78; H, 6.45; N, 9.69.

7. The highest yield for this reaction was obtained using these conditions. The difference in reactivity is even more pronounced when one compares Row E' to the others.

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