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A New Reagent for Solid and Solution Phase Synthesis of Protected Guanidines from Amines

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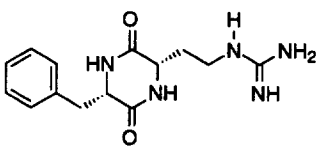
Abstract: A new reagent -- 4-nitro-1-*H*-pyrazole-1-[*N, N'*-bis(*tert*-butoxycarbonyl)]carboxamidine -- has been developed to effect the rapid and efficient synthesis of bis(carbamate)-protected guanidines from primary and secondary amines. The reagent is a more electrophilic, and consequently more reactive, derivative of the literature reagent 1-*H*-pyrazole-1-[*N, N'*-bis(*tert*-butoxycarbonyl)]carboxamidine. The increased reactivity of the new reagent affords it increased yields in solution and the need for fewer equivalents when guanylating resin-bound amines.

During the development of a solid-phase synthesis of a cyclic dipeptide catalyst (**1**) of the Strecker amino acid synthesis,[1-2] it became necessary to convert the primary amine of a resin-bound peptide (**2**) to a guanidine. While a number of different conditions have been developed to effect such a transformation[3-15] the restrictions imposed by solid phase synthesis (homogeneous reaction conditions, organic solvent) were found to severely limit the choice of reagents. Although the reagent 1-*H*-pyrazole-1-[*N, N'*-bis(*tert*-butoxycarbonyl)]-carboxamidine (**3**) was eventually adopted for the synthesis, it failed to completely guanylate the resin even when forcing conditions (8 equiv., 72 h) were used. This realization prompted an investigation of new reagents.



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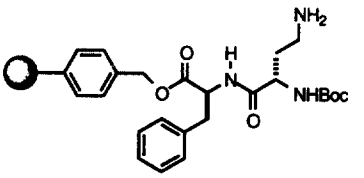

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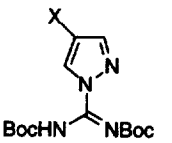

3 (X=H)
4 (X=NO_2)

Initial studies focused on the known guanylation of amines using *N, N'*-di(*tert*-butoxycarbonyl)thiourea in the presence of stoichiometric $HgCl_2$.[11-12] While this method cannot readily be used in a solid phase synthesis owing to its production of the insoluble precipitate HgS, replacement of $HgCl_2$ with Mukaiyama's reagent (2-chloro-*N*-methylpyridinium iodide) resulted in completely homogeneous conditions. While application of this method in solution and on two model resins gave satisfactory results,[14] later evidence has shown that many resin-bound amines fail to guanylate under these conditions, reacting instead with the Mukaiyama's reagent.[16] A new reagent for the gunaylation of resin-bound amines was therefore pursued and attention was turned to improving the reactivity of **3** by making it more electrophilic.

The most straightforward method for enhancing the electrophilicity of **3** was to replace the pyrazole leaving group with a more electronegative substituent. Of the various leaving groups examined in this study, the most effective proved to be a 4-nitro-1-*H*-pyrazole substituent. The new reagent incorporating this leaving

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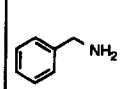
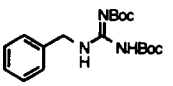
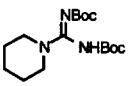
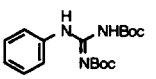
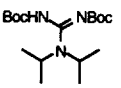
group, 4-nitro-1-*H*-pyrazole-1-[*N*, *N'*-bis(*t*-butoxycarbonyl)]carboxamidine (**4**) was readily synthesized from pyrazole and thiourea. Pyrazole was nitrated using a literature procedure[17] and converted to **4** using *N*, *N'*-di(*tert*-butoxycarbonyl)thiourea and either $HgCl_2$[11-12] or Mukaiyama's reagent,[14] though the latter reagent gave a lower yield.[18]

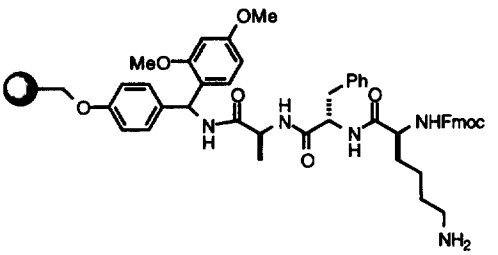
The efficacy of **4** as a guanylation agent was first established by comparison of it with **3** in the guanylation of several amine substrates (Table 1) in solution. The two reagents were each used in small excess and reacted with amine at 25° in anhydrous DMF.[19] Although benzylamine, a relatively reactive primary amine, reacted in high yield (80%), less reactive amines proved far less successful substrates. Thus, secondary amines failed to completely react with **3** even after 20 hours and the less nucelophilic amine aniline gave an unstaisfactorily low yield. Increasing the steric hindrance also severely inhibited reaction with **3**: *N*, *N*-diisopropylamine essentially failed to react under these conditions. Reaction of the same amines with **4** consistently gave higher isolated yields and faster reaction. Although the reactivity trends observed with **3** were mirrored by **4**, in no case was the isolated yield less than 50% and only *N*, *N*-diisopropylamine failed to completely react with **4**. Even in that case, an isolated yield of 64% was obtained for **4** under conditions where **3** failed to react.

Table 1. Reactions of Selected Amines with Guanylation Reagents 3 and 4

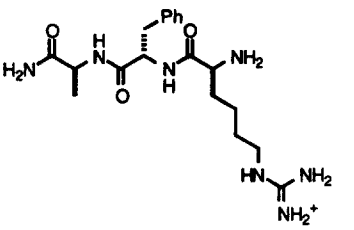
Substrate	Product[b]	Isolated Yield[a],% Using 3	Using 4
		80	94
		70[c]	82
		11[c]	78
		<5[c]	64[c]

[a] Reaction conditions: 1.2 equiv. reagent in anhydrous DMF at 25° for 1-20 h. [b]All products were characterized by ^{1}H-NMR, ^{13}C-NMR and correlation with reported data. [c] Unreacted amine remained after 20 h.

Having established that **4** was a more reactive guanylating agent than **3**, our attention was turned to its primary purpose: its ability to guanylate resin-bound amines. Two peptides (**2** and **5**), bound to two different resins and both bearing a primary amine on a sidechain, were guanylated using both **3** and **4**: **2** was the dipeptide precursor to our catalyst bound to the Merrifield polystyrene resin, and **5** was a lysine-containing tripeptide bound to the Rink amidation resin.[20] Reactions with the resin-bound amines were monitored using qualitative and quantitative ninhydrin assay.[21] In both cases, the enhanced reactivity of **4** produced substantial benefits. Thus, the literature reagent **3** failed to react completely with both **2** and **5** even when used in eightfold excess and given 3 days to react. In contrast, 4 equivalents of the reagent **4** completely guanylated both **2** and **5** within 20 hours, as judged by ninhydrin assay.



5



6

After guanylation with **4**, resin-bound dipeptide **2** was fully deprotected with TFA in CH_2Cl_2 and cyclized to **1**, with concomitant cleavage from the resin, by treatment with 1.25 M acetic acid in toluene at 90°.[2] The overall yield for this series of transformations was 81% and the material was found to be >90% pure by reverse phase HPLC. In contrast, resin-bound peptide **5** was cleaved from the resin immediately after guanylation with **4** by treatment with TFA in CH_2Cl_2.[20] The isolated yield of guanylated peptide **6** was 55% and the purity was determined to be >90% by reverse-phase HPLC. In all cases, product identity was established after cleavage from the resin by mass spectroscopy.[22]

Based on these studies, we believe that **4** should be the reagent of choice for conversion of resin-bound amines to protected guanidines. It is easily synthesized, stable, chromatographable and compatible with most solvents, including water. Reactions with **4** are reasonably rapid and afford bis(carbamate)-protected guanidines in good yields. Equally important, both **4** and 2-nitropyrazole are fully soluble in most organic solvents and consequently can easily be removed from resins by filtration. With the growing interest in the synthesis of guanidine-containing molecules for use as phosphate receptors,[23] oligonucleotide binders[24] and peptidomimetics[25] it is anticipated that this methodology will find application in a number of areas of chemistry.[26]

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18. Procedure for the preparation of **4**: A 0.3 M solution of *N, N'*-di(*tert*-butoxycarbonyl)thiourea[11] (1.2 equiv) in anhydrous DMF was treated with $HgCl_2$ (1.1 equiv), triethylamine (3.3 equiv) and 4-nitropyrazole[17] (1.0 equiv). After 12 h, the reaction was evaporated, redissolved in diethyl ether and washed with saturated aqueous $NaHCO_3$. Product **4** was obtained in 59% yield after purification by column chromatography. mp 51-53°. ^{1}H-NMR($CDCl_3$): δ9.04 (s, 1H), 8.17 (s, 1H), 1.45-1.55 (m,18H). ^{13}C-NMR($CDCl_3$): δ149.3, 138.5, 137.6, 128.0, 84.9, 83.0, 77.7, 28.5. IR (neat): ν_{max} 1775, 1718, 1687, 1554, 1506 cm^{-1}. Anal Calcd for $C_{14}H_{21}N_5O_6$: C, 47.32; H, 5.96; N, 19.71. Found: C, 47.51; H, 6.15; N, 19.86. Replacement of the $HgCl_2$ by Mukaiyama's reagent provided **4** in 43% yield.[14]
19. Procedure for guanylation of amines using **4**: A 0.2 M solution of amine in anhydrous DMF was treated with **4** (1.2 equiv) and stirred at 25° until reaction was judged complete by TLC. Upon completion, solvent was evaporated, the residue redissolved in diethyl ether and washed with water. The organic layer was dried over $MgSO_4$, the solvent evaporated and the product purified by flash chromatography.
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22. **1**: CIMS calcd for $C_{14}H_{20}N_5O_2$ [M+H$^+$] 290.1, found 290; **6**: FABMS calcd for $C_{19}H_{32}N_7O_3$ [M+H$^+$] 406, found 406.
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26. This work was supported by a grant from the National Institutes of Health (GM 53091).