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Urethane Protected Derivatives of 1-Guanylpyrazole for the Mild and Efficient Preparation of Guanidines

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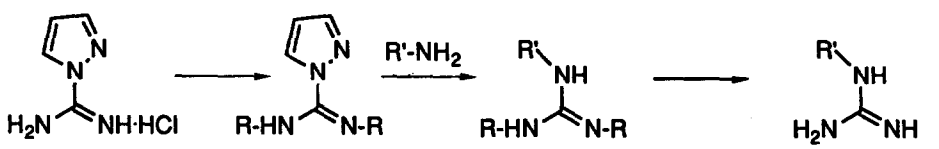
Abstract: **Bis-urethane protected derivatives of 1-guanylpyrazole were prepared and found to readily react with relatively unreactive amines at room temperature to produce bis-protected guanidines in good yields. Simultaneous removal of both protecting groups from these products efficiently produced monosubstituted guanidines.**

This laboratory recently reported on the utility, scope and limitations of 1H-pyrazole-1-carboxamidine hydrochloride (**1**, "1-guanylpyrazole hydrocloride") as a reagent for the conversion of amines to monosubstituted guanidines and its use in the synthesis of arginine containing peptides.[1] This led to further studies of the relative reactivity and potential synthetic utility of substituted derivatives of **1**. For example, although an N-allyl derivative of **1** was found to be less reactive than **1**, its use nonetheless led to a greatly improved synthesis of N^G-allyl-(L)-arginine,[2] a nitric oxide synthase inhibitor.[3] Diacyl substituted derivatives of **1** became very interesting, partly because of a recent report describing the use of acylated thioureas for the mild and efficient conversion of amines to protected guanidines,[4] and also because of the potential synthetic importance of such derivatives. Here we report the preparation and synthetic utility of N,N'-bis protected derivatives (**2a,b**) of **1** for the preparation of guanidines. Scheme 1 summarizes the work thus far accomplished with the N,N'-bis-Boc (**2a**)[5] and bis-Cbz (**2b**) derivatives.[6]

Scheme 1



1

2a, R= Boc
2b, R= Cbz

3a, R=Boc, R'= phenyl
3b, R=Boc, R'= CF_3CH_2-
3c, R=Boc, R'= *p*-nitrophenyl
4a, R=Cbz, R'= phenyl
4b, R=Cbz, R'= CF_3CH_2-

5a, R'= phenyl
5b, R'= CF_3CH_2-
5c, R'= *p*-nitrophenyl

The bis-Cbz derivative **2b** was noticeably more reactive toward amines than bis-Boc derivative **2a**[7] and both **2a** and **2b** were substantially more reactive than the unsubstituted parent compound **1**. For example, both 2,2,2-trifluoroethylamine and aniline failed to produce guanidines by displacement of pyrazole from **1** at

room temperature, conditions which allow facile conversion of **1** to guanidines by reaction with unhindered primary and secondary amines.[1] In the case of 2,2,2-trifluoroethylamine and aniline only the diguanidine self-condensation product of **1**[1] was slowly formed. In contrast, urethane protected derivatives **2a** and **2b** reacted readily as expected with these relatively non-nucleophilic amines at room temperature, using slight excesses of amines in THF,[8] to produce protected guanidines **3a,b** and **4a,b** respectively in good yields (Table 1).[9] Because of urethane protection, no self-condensation side-product was observed under the mild conditions employed for the reactions of **2a** and **2b** with these amines.

Table 1. Results for Amine Guanylation by **2a** and **2b**.

Product Entry	Reaction Time (h)	% Yield	m.p. (°C)[a]
3a	5	90	132-4
3b	17	85	136-8
3c	70	39	190[b]
4a	2.5	96[c]	115-6
4b	22	94	oil

a. All melting points were taken on a Fisher-Johns hotplate apparatus and are uncorrected.
b. Decomposes.
c. Only in this case was the reaction quantitative as evidenced by TLC in the time period indicated.

All bis-Boc protected guanidines (**3a-c**) reported were completely deprotected under typical conditions for Boc group cleavage to give monosubstituted guanidines **5a-c** in good yields. Both Boc groups were smoothly cleaved from **3a-c** by treatment with TFA:CH_2Cl_2 (1:1 by volume) at room temperature for 1-2 h.[10] These results are summarized in Table 2. Because the TFA salts of **5a** and **5b** did not readily crystallize, these guanidines were isolated as flavianate salts.

Table 2. Results for Deprotection of N,N'-Bis-Boc Guanidines **3a-c**.

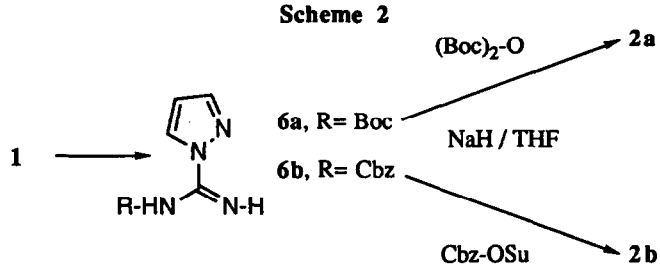
Product Entry	% Yield	m.p. (°C)
5a	80[a]	225-7[b]
5b	90[a]	263-4[b]
5c	83[c]	214-5

a. Yield of flavianate salt crystallized from MeOH/ether.
b. Decomposes.
c. Isolated as TFA salt.

The Cbz groups of **4a** and **4b** were cleanly and completely cleaved by catalytic hydrogenolysis (H_2, 1 atm, 10% Pd on carbon in MeOH or MeOH/THF, 18-20 h, room temp.) to give free bases **5a** and **5b** as crystalline solids (**5a**, m.p. 85-6 °C, **5b**, m.p. 68-9 °C) in essentially quantitative yields.

Bis-protected 1-guanyl pyrazole derivatives **2a** and **2b** were both readily synthesized from **1** via monourethane protected intermediates **6a** and **6b** as depicted in Scheme 2. Initial protection of **1** was

Scheme 2



accomplished using $(Boc)_2$-O or benzylchloroformate in CH_2Cl_2/DMF plus DIEA (1-2 h, room temp.) to give good yields (89-95%) of crystalline **6a** and **6b**,[11] respectively. The anions of **6a-b** were generated at 4 °C using NaH (3.5 mole NaH / mole **6**) in dry THF. Further reaction of the anions with excess amounts of $(Boc)_2$-O[12] or Cbz-OSu produced the bis-protected derivatives **2a-b** in good yields (76% for **2a**, 77% for **2b**) after extractive workup and crystallization.[13]

Interestingly, it was found that the monourethane protected derivatives **6a-b** failed to react with cyclohexylamine in DMF at room temperature after several hours. The same observation was made with the N-acetyl derivative of **1**. In contrast, reaction of **1** with cyclohexylamine under the same conditions is rapid. Thus, monoacylation of **1** dramatically reduces its reactivity as a guanylating agent while diacyl derivatives have dramatically enhanced reactivity. Possible explanation for the observed relative reactivity involves consideration of differences in basicity and electrophilicity of these derivatives. It has been observed that protonation of **1** is required for its reaction with amines.[1] Electrophilic activation of monoacyl derivatives by protonation is not as likely due to their reduced basicity. In the case of diacyl derivatives **2a** and **2b**, protonation for reaction is not required as the second acyl group can serve the same purpose as protonation but even more dramatically enhances electrophilicity and therefore results in greater reactivity.

A recent practical application of **2a** in this laboratory has been the synthesis of Fmoc-Arg$^{\omega,\omega'}$$(Boc)_2$-OH,[14] which has been recently reported to be a valuable intermediate in the synthesis of arginine containing peptides.[15] Reaction of Cu(II)-ornithine complex[16] with equimolar **2a** in formamide/p-dioxane mixture at room temperature provided Cu(II)$\{Arg^{\omega,\omega'}(Boc)_2\}_2$ in 90% yield. Subsequent acylation of this copper complex with Fmoc-OSu in the presence of EDTA/Na_2HCO_3/acetone/H_2O provided Fmoc-Arg$^{\omega,\omega'}$$(Boc)_2$-OH in 75% yield.

In summary, two bis-urethane protected (Boc, Cbz) derivatives of 1-guanylpyrazole were easily prepared and found to be more reactive than **1** as reagents for amine guanylation. These derivatives can serve as valuable synthetic tools where the guanylation of relatively unreactive amines under mild conditions is required and thereby can compliment the use of **1** for amine guanylation. These derivatives also can serve as versatile synthons in the formulation of schemes for the synthesis of complex guanidine containing compounds.

Appropriate minor modification of the methodology reported here is likely to give rise to the synthesis of other useful bis-protected guanidines.

Because various types of mono, di, and trisubstituted guanidines are of potential pharmacological interest, the synthesis of 1-guanylpyrazole derivatives having various types of substituents is in progress. Studies of such derivatives will also be useful in establishing what factors affect reactivity and should provide additional mechanistic insight.

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5. Abbreviations used: Arg = arginine, Boc = *tert*-butyloxycarbonyl, Cbz = Benzyloxycarbonyl, DIEA = diisopropylethylamine, DMF = dimethylformamide, EDTA = ethylenediaminetetracetic acid, Fmoc = 9-fluorenylmethyloxycarbonyl, MeOH = methanol, OSu = N-oxysuccinimide, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TLC = thin layer chromatography.
6. Authenticity of reported compounds was established by ^{1}H and ^{13}C NMR, mass spectroscopy, and CHN analysis.
7. As evidenced by TLC, **2b** was completely consumed in 2.5 h at room temperature by reaction with aniline in THF. In contrast, about 10% starting **2a** was still present after 5 h under the same conditions.
8. To 1.0 mmole **2a** or **2b** was added 1.1 mmole amine (1.2 mmole in the case of volatile 2,2,2-trifluoroethylamine) followed by 0.3 ml - 0.4 ml dry THF and the resulting mixtures were stirred for the indicated times (Table 1) at room temperature. The reaction mixtures were diluted with hexanes and directly applied to a short silica gel (15g silica) column and the products separated from unreacted **2a** and **2b** by a stepwise gradient elution from 0 to 30% ethyl acetate in hexanes. Drying of the product fractions *in vacuo* generally directly produced crystalline compounds.
9. The only amines thus far examined which have failed to produce the desired guanidines by displacement of pyrazole from **2a** and **2b** were the sterically hindered, secondary, diisopropyl and dicyclohexyl amines.
10. As expected, cleavage of the Boc groups from **3a-c** with excess 4N HCl in p-dioxane was slower than with TFA/CH_2Cl_2 (1:1).
11. The m.p. of **6a** was 98-9 °C and the m.p. of **6b** was 108-9 °C.
12. It was necessary to gradually elevate the temperature of this reaction to 65 °C to achieve complete incorporation of the Boc group. Complete reaction of **6b** with Cbz-OSu occurred at room temperature.
13. The m.p. of **2a** was 84-5 °C (crystallized from MeOH/H_2O) and the m.p. of **2b** was 89-91 °C (crystallized from ether/ethyl acetate/hexanes).
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