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Synthesis, Application and Scope of a New Protected Hydrazine Reagent

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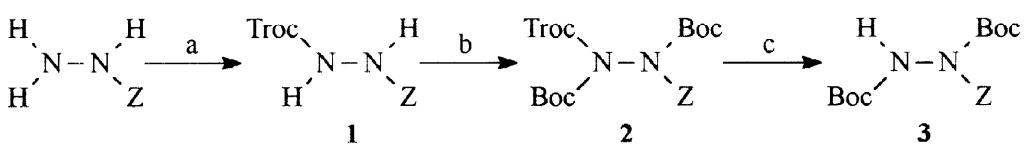
Abstract: A novel triprotected hydrazine reagent, 1,2-Boc_2-2-Z-hydrazine (**3**), has been made and investigated with respect to stepwise alkylation/acylation and intermediary deprotection in order to prepare multisubstituted hydrazine derivatives. Alkylation of **3** requires particularly mild basic conditions. Regiospecific cleavage of one Boc-group with acid in monoalkylated product **4** is difficult but can be accomplished with catalytic amounts of $Mg(ClO_4)_2$ in MeCN at 50 °C in 15 min, furnishing **5** which can easily be alkylated to **6**. This product has recently been converted to fully substituted derivatives **7**.

We recently prepared Boc_3-hydrazine (Boc=*tert*-butoxycarbonyl) and used it in a feasibility study aiming at unsymmetrical, multisubstituted derivatives by a stepwise approach, involving alkylation/acylation and intermediary deprotection.[3] Its alkylation with halides could be accomplished under phase-transfer catalysis (PTC) conditions in excellent yields and from the various products one Boc-group on the diprotected nitrogen atoms could be cleaved off selectively, as a result of which another substitution site became available. After a second alkylation under PTC conditions the two remaining Boc-groups, one on each nitrogen, no longer differed significantly, so in order to proceed by stepwise cleavage and substitution another reagent was required with two *orthogonal* protecting groups. Since we had previously prepared Boc(Z)N-N(Z)Boc (Z=benzyloxycarbonyl) as well as elaborated Boc(Z)-protection of amino groups in the polyamine field,[4,5] we immediately decided to undertake the synthesis and exploration of the alternative reagent **3**, the synthesis of which is outlined in Scheme 1. In the present work commercially available Z-hydrazine was converted to the solid intermediate **1** (Troc=trichloroethoxycarbonyl), from which crude **2** was obtained as an oil after reaction with Boc_2O catalyzed by 4-dimethylaminopyridine (DMAP).[6,7] After a simple extraction procedure, Troc was reductively cleaved off, furnishing the new protected hydrazine reagent **3** as a solid, suitable as starting material in alkylation experiments.[8]



1 **2** **3**

Scheme 1. Reagents/yields: a) Troc-Cl/90%; b) Boc_2O, DMAP and c) Zn, HOAc/86% over two steps.

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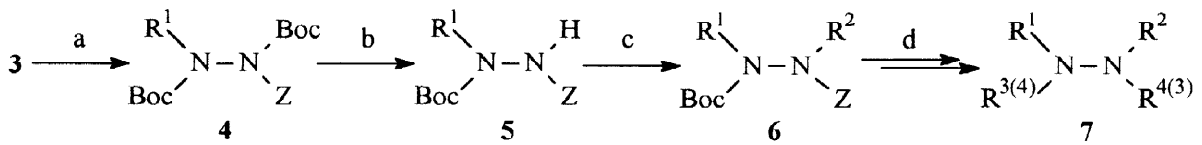
To derivatize reagent **3** as outlined in Scheme 2, it was first alkylated with methyl iodide, benzyl bromide, ethyl bromoacetate and allyl bromide under mildest possible, liquid-liquid PTC conditions (10-20% aq. NaOH, catalytic amounts of n-Bu_4NHSO_4, benzene or toluene, room temperature) to give **4a-d** as oils in very high yield. In BocZ-protected amines, the functionality Z exhibits increased sensitivity to strong base, a fact which could be exploited to cleave off Z selectively on a preparative scale.[5] In the present environment, owing to the additional electron-withdrawing effects of the vicinal nitrogen and its Boc-group in the reagent as well as the products, Z becomes even more sensitive to base, which is normally not a problem with this well established protective group.[9]



Scheme 2. Reagents/yields: a) R^1X, PTC/85-98%; b) $Mg(ClO_4)_2$, MeCN, 50 °C[10]/98-99%; c) R^2X, PTC/91-99%; d) selective cleavage of Boc-(Z)-protective group and subsequent acylation twice in alternative order. Compounds made: **4a-6a** (R^1=Me; R^2=Bn), **4b-6b** (R^1=Bn; R^2=Me), **4c-6c** (R^1=$EtOCOCH_2$, R^2=Bn), **4d-6d** (R^1=allyl; R^2=$EtOCOCH_2$), **6e** (R^1=Bn; R^2=4-$NO_2C_6H_4CH_2$).

Attempted cleavage of **4b** with TFA (2 equiv. in CH_2Cl_2 at room temperature for 24 h) gave rise to a mixture of three components which, after chromatographic workup, yielded 79% of **5b** together with 5% of recovered starting material and 12% of 1-benzyl-2-Z-hydrazine. Similar cleavage experiments with less acid/ longer reaction time or more acid/shorter reaction time also indicated incomplete regiospecificity and for a while then other hydrazine reagents, prepared in parallel with **3** and involving aromatic sulfonyl groups, were pursued.[11,12] Thus in the meantime a few unsymmetrical, tetrasubstituted hydrazines have for the first time been synthesized via intermediate **6**.[11]

We then applied a recently introduced cleavage method for *tert*-butyl imidodicarbonates and *tert*-butyl acylcarbamates, involving catalytic amounts of $Mg(ClO_4)_2$ in MeCN at room temperature or 50 °C.[10] Magnesium ions were postulated to form a chelate with their two carbonyls, favouring facile elimination of isobutylene, as a result of which deprotection can take place. To our satisfaction, we found that this method indeed worked excellently on hydrazine derivatives of type **4** which are presumably further activated for cleavage by the neighbouring nitrogen and the second Boc-group. As a result very fast (5-15 min), completely regiospecific Boc-cleavage from the imidodicarbonate function of **4a-d** was observed. Experimentally the procedure was also simple, involving addition of $Mg(ClO_4)_2$ to a stirred solution of **4** at 50 °C under a stream of nitrogen, quenching with water and extraction of the product. No chromatographic workup of products was required in experiments according to this method so far, allowing therefore convenient isolation of **5** on a gram scale in nearly quantitative yield. Thus, in the hydrazine derivative **4** the two Boc-groups can be considered orthogonal.

Having optimized the first two steps of Scheme 2, the third step involving the alkylation of **5** was performed in the same way as for **3** to give a number of compounds **6a-e**, the structures of which are given in the legend to this scheme, as oils in yields above 91%. Of these compounds, derivatives **6a** and **6c** have previously been made and **6a** also converted to a tetrasubstituted derivative 7 by a stepwise strategy.[11] Their protective groups, Boc and Z, can in principle be cleaved in optional order. Nevertheless, these groups impose some obvious restrictions on the substituents R^n (n=1-3) with respect to sensitivity to acid and/or catalytic hydrogenation/hydrogenolysis.

Whereas compounds **1** and **3** gave simple ^1H and ^{13}C NMR spectra,[8] those of **4** and **6** presented evidence for the existence of two or more conformers, which required strict chromatographic rather than spectroscopic criteria to be used for the evaluation of their purity. This was noticed also in our previous work.[3] With reference to the bulk of the Boc-moieties, additional contribution from the Z- and R-groups and the proximity of the nitrogen atoms this is not unreasonable and therefore it was decided to perform some simple modelling of these compounds by a semi-empirical method (PM3). One view each for **4b** and **6e** is shown in Figure 1. In both derivatives the two nitrogen lobes with their protective groups and substituent(s) are clearly visible and we have neither been able to detect any striking interference between nor within these parts of the molecules. This may be due in part to the absence of branching next to the nitrogens in the benzyl and 4-nitrobenzyl substituents and both moieties seem to orient themselves away from the nitrogens. Repulsion between the free electron pairs on the nitrogens of hydrazine derivatives is known to have a major influence on their overall confor-

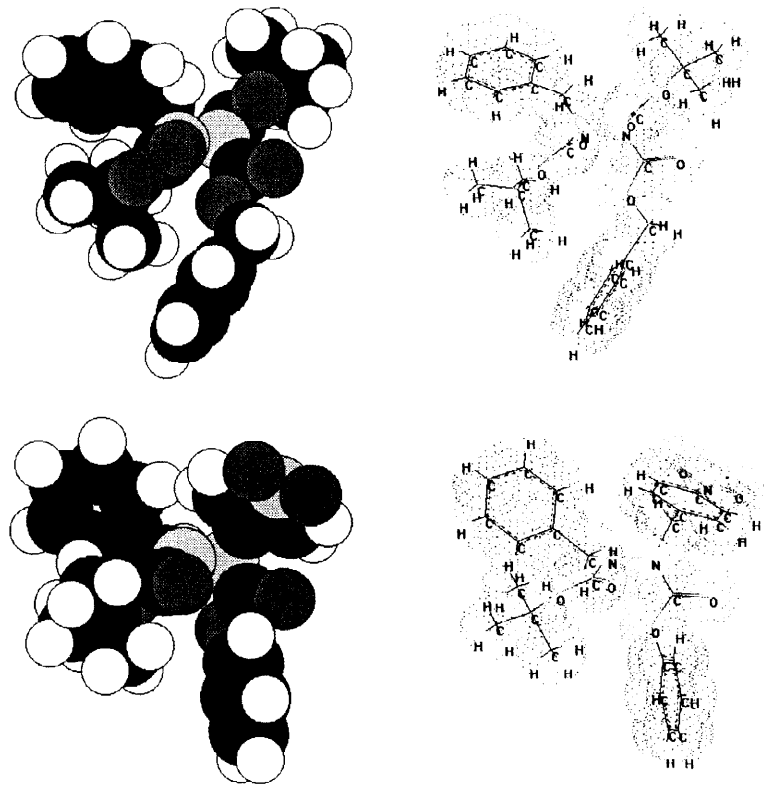


Figure 1. Modelling of compounds **4b** and **6e**. Molecules are oriented with the N-N bonds horizontally and the Z-groups in the lower, right corner.

mation. E,Z-isomerism around CO-N bonds can be envisaged to occur and give rise to multiple conformations, although their relative populations may occasionally be low.

Returning to the synthetic aspects of the present work, it should be pointed out that the method does not involve intermediary N-nitroso amines.[13] Steric hindrance has not been a problem so far in the alkylation steps and yields have been invariably high. In cases with extreme bulk of R^1 and/or R^2 some relief will generally be provided in the subsequent deprotection step(s), for which reason this repetitive approach is believed to have a fairly wide scope. Due to the commercial availability of alkyl and other reactive halides as well as acyl derivatives, the reagent should be an attractive one for application in combinatorial chemistry.

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References and Notes

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8. Data on compound **1**: Mp. 132.5-134 °C (from Et_2O/light petroleum); ^1H NMR (270 MHz, $CDCl_3$): δ_H=4.78 (s, 2H, Troc), 5.19 (s, 2H, Z), 6.68 (s, 1H, NH-Z), 6.90 (s, 1H, NH-Troc), 7.36 (s, 5H, Ph); ^{13}C NMR (67.8 MHz, DMSO-d_6): δ_C= 66.8 (Bn), 73.8 (CH_2-Troc), 95.7 (CCl_3), 127.9, 128.0, 128.4, 136.4 (Ph), 155.0, 156.2 (CO). Found: C, 38.7; H, 3.2; Cl, 31.2; N, 8.2. $C_{11}H_{11}Cl_3N_2O_4$ (341.56) requires: C, 38.68; H, 3.25; Cl, 31.14; N, 8.20. Data on compound **3**: Mp. 82-83 °C (from Et_2O/light petroleum); ^1H NMR (270 MHz, $CDCl_3$): δ_H=1.37, 1.46, 1.49 (3s, 18H, Boc), 5.24 (s, 2H, CH_2), 6.60 (s, 1H, NH), 7.28-7.42 (m, 5H, Ph); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ_C=27.8 and 28.1 (Boc), 69.0 (Bn), 81.9 and 84.3 (C_q, Boc), 128.2, 128.4, 128.5, 135.1 (Ph), 150.4, 152.5, 154.0 (CO). Found: C, 58.9; H, 7.2; N, 7.6. $C_{18}H_{26}N_2O_6$ (366.38) requires: C, 59.01; H, 7.15; N, 7.68.
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