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Combination of *tert*-Butoxycarbonyl and Triphenylphosphonium Protecting Groups in the Synthesis of Substituted Hydrazines

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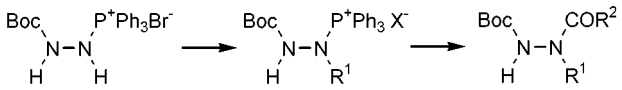
ABSTRACT

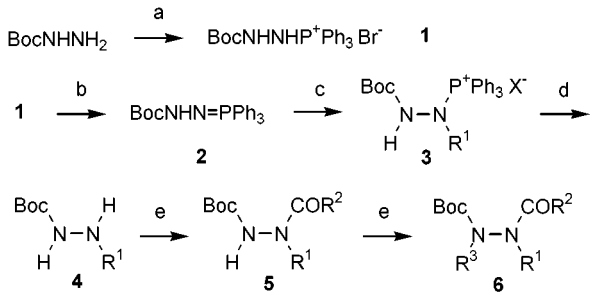


A new reagent for the systematic synthesis of substituted hydrazines is reported. Unlike previously developed reagents, this one contains only two protecting groups, thus providing a faster approach to multisubstituted derivatives. The selective introduction of alkyl and acyl groups is illustrated by a few examples. Also a new fast method for the deprotection of the triphenylphosphonium group is presented.

For the synthesis of multisubstituted hydrazines, various triprotected precursors $P^1P^2N-NP^3H$ have recently been developed.[1] These reagents contain alkyloxycarbonyl- or sulfonyl-based protecting groups, leaving only one hydrogen available for substitution. The triphenylphosphonium moiety was found to be useful for derivatization of some amines[2] and hydrazines.[3] It fulfils simultaneously two different functions, first serving as a protecting group and also enabling the formation of the nucleophilic phosphinimine. To the best of our knowledge, there are no reports on the simultaneous use of triphenylphosphonium and another protecting group for the systematic synthesis of multisubstituted hydrazines. It should be pointed out that only some examples of the synthesis of substances with the general formula $RCONHNHPPh_3\ X^-$ are known.[4]

Thus, we have developed a new reagent, **1**, containing a combination of Boc and Ph_3P groups (Boc = *tert*-butyloxycarbonyl). This reagent can be easily synthesized (Scheme 1) from commercially available *tert*-butyl carbazate and

Scheme 1[a]



[a] (a) Ph_3PBr_2, Et_3N, toluene, rt; (b) BuLi, THF, 0 °C; (c) R^1X; (d) $NaOH/H_2O/CH_2Cl_2$, rt; (e) R^2COX, Py, rt; (f) R^3X, NaOH/K_2CO_3, TBAHS, toluene, rt.

(1) (a) Mäeorg, U.; Grehn, L.; Ragnarsson, U. *Angew. Chem.* **1996**, *108*, 2802−2803; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2626−2627. (b) Mäeorg, U.; Ragnarsson, U. *Tetrahedron Lett.* **1998**, *39*, 681−684. (c) Mäeorg, U.; Pehk, T.; Ragnarsson, U. *Acta Chem. Scand.* **1999**, *53*, 1127−1133. (d) Grehn, L.; Lönn, H.; Ragnarsson, U. *Chem. Commun.* **1997**, 1381−1382. (e) Grehn, L.; Nyasse, B.; Ragnarsson, U. *Synthesis* **1997**, 1429−1432. (f) Brosse, N.; Pinto, M.-F.; Jamart-Gregoire, B. *Tetrahedron Lett.* **2000**, *41*, 205−207. (g) Brosse, N.; Pinto, M.-F.; Jamart-Gregoire, B. *J. Org. Chem.* **2000**, *65*, 4370−4374. (h) Brosse, N.; Pinto, M.-F.; Bodiguel, J.; Jamart-Gregoire, B. *J. Org. Chem.* **2001**, *66*, 2869−2873.

(2) (a) Zimmer, H.; Singh, G. *J. Org. Chem.* **1963**, *28*, 483−486. (b) Zimmer, H.; Jayawant, M.; Gutsch, P. *J. Org. Chem.* **1970**, *35*, 2826−2828. (c) Cristau, H. J.; Garcia, C.; Kadoura, J.; Torreilles, E. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1990**, *49/50*, 151−154.

(3) (a) Zimmer, H.; Singh, G. *J. Org. Chem.* **1964**, *29*, 1579−1581. (b) Barluenga, J.; Merino, I.; Viña, S.; Palacios, F. *Synthesis* **1990**, 398−400. (c) Bestmann, H. J.; Göthlich, L. *Liebigs Ann. Chem.* **1962**, *655*, 1−19.

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triphenylphosphine dibromide. Unlike the preparation of other hydrazine reagents,[1] only one step is required here to obtain the starting material in a yield of 78−87%.[5]

Because of the great difference in acidities of the NH hydrogens in **1**, the phosphinimine **2** is readily and selectively obtained by the action of 1 equiv of BuLi. The following alkylation is carried out as a one-pot synthesis without isolation of the phosphinimine. During the reaction the resulting phosphonium salts **3** precipitate from the reaction mixture and thus can be easily isolated in good yield, pure by TLC and NMR spectra. Also, an additional amount of product can be precipitated by adding ether to the solution.[6] However, in the case of **3c** and **3f** this fraction was contaminated and therefore not included in the overall yield given in Table 1. Probably the lower steric hindrance of the methyl group enables the formation of the 1:1 THF solvate (calculated by intensities of signals of NMR spectra) in the case of **3a**, since it was not observed in the case of other salts **3**. We failed to introduce the *sec*-butyl group using the same procedure. The phosphinimine **2** does not react with *sec*-BuBr and causes extensive elimination of the corresponding *sec*-BuI, resulting in the starting material **1** as a 1:1 THF solvate.

Table 1. The Synthesis of Phosphonium Salts **3**

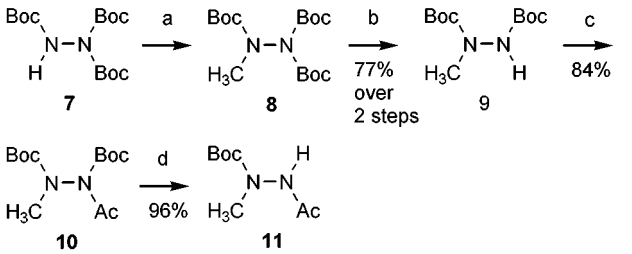
compound no.	R^1	reaction time, h	yield, %
3a	methyl	4	75
3b	benzyl	5	76
3c	4-nitrobenzyl	22	62
3d	*n*-butyl[a]	50	72
3e	propargyl	7	68
3f	ethoxycarbonylmethyl	20	67
3g	allyl	7	71

[a] 10 equiv of RX was used.

In the earlier studies,[2a,b,3] the removal of the triphenylphosphonium moiety required several hours of heating with a strong base. We have found that corresponding salts **3** can be easily deprotected within 2−3 min at rt in the system dichloromethane/2 M NaOH. Probably, phase transfer catalysis takes place here and the starting phosphonium salt serves as a catalyst, so the equimolar mixture of deprotected hydrazine **4** and triphenylphosphine oxide is obtained. Further, this mixture can be brought to acylation without separation into components. Amide nitrogen is not acylated under typical conditions (1.1 equiv of RCOCl or maleic anhydride in pyridine solution, 10−15 min). Also, reaction of the mixture of **4** and triphenylphosphine oxide in acetic anhydride is a very effective (95%), clean, and fast method for acetylation. After column chromatography the corresponding hydrazines **5** were obtained in yields of 70−86% over two steps (R^2CO = PhCO, CH_3CO, COCH=CHCOOH). These substances can be further used for introduction of additional alkyl and acyl substituents using the previously illustrated methodology.[1a,b] For example, the compound **6** where R^3 = allyl was readily synthesized (97%) by our standard PTC alkylation procedure.[1a]

The selective substitution of the PNH hydrogen in reagent **1** is evident from an analysis of the NMR spectra of products **3**. The values of $^3J_{PH}$ are in the range of 5.2−6.2 Hz and those of $^2J_{PC}$ in the range of10.8−15.7 Hz, thus being in good agreement with previously reported experimental values.[3b] To further demonstrate the regioselective alkylation of **1**, compound **11**, which is isomeric to **5a** (R^1 = R^2 = CH_3), was synthesized. For this purpose we used our earlier developed strategy[1a] as illustrated in Scheme 2. One Boc-group can be cleaved very selectively in the presence of Mg$(ClO_4)_2$ from *tert*-butyl imidodicarbonate **8** and *tert*-butyl acylcarbamate **10** as well.[1b,7] Under forcing conditions (excess of acetic anhydride and pyridine in the presence of 8% DMAP for ∼5 days) the amide nitrogen of **9** can be successfully acetylated, furnishing pure **10**. A comparison of the ^{1}H NMR spectra of **11** and **5a** enables one to conclude that these compounds are isomers but not identical substances. As the acetyl group is more electronegative than

Scheme 2[a]



[a] (a) CH_3I, NaOH/K_2CO_3, TBAHS, toluene, rt; (b, d) Mg$(ClO_4)_2$, MeCN, 50 °C; (c) Ac_2O, Py, 50 °C.

(4) (a) Walker, C. C.; Shechter, H. *J. Am. Chem. Soc.* **1968**, *90*, 5626−5627. (b) Merrill, G. B.; Shechter, H. *Tetrahedron. Lett.* **1975**, 4527−4530. (c) Frøyen, P. A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1991**, *57*, 11−15.

(5) **Reagent 1**. The experiment and the weighing of dibromotriphenylphosphorane were carried out under argon. To the suspension of Ph_3PBr_2 (4.103 g, 9.72 mmol) in toluene (∼15 mL) was added triethylamine (1.36 mL, 1 equiv), followed by a solution of *tert*-butyl carbazate in toluene (1.284 g, 1 equiv). The reaction was monitored by TLC (EtOAc/chloroform 1:1 as the mobile phase). When the reaction was complete (∼6 h), cold water was added to the reaction mixture. The insoluble product was isolated by suction and carefully washed many times with water and toluene, yielding 4.007 g (87%) of white solid **1**, pure by TLC. The solid was recrystallized from acetonitrile for further use, mp 184−185 °C (dec). ^{1}H NMR (CD_3OD): δ = 1.46 (s, 9H, Boc), 7.9−8.2 (m, 15H, 3 × Ph). ^{13}C NMR (CD_3OD): δ = 28.6 (s, Boc), 83.0 (s, C_q, Boc), 121.1 (d, Ph, J_{PC} = 102.2), 131.4 (d, Ph, J_{PC} = 13.1), 135.7 (d, Ph, J_{PC} = 10.9), 137.0 (s, Ph), 158.2 (CO).

(6) All experiments were carried out in a flask sealed with a septum and under argon. A typical procedure is given below using **3b** as an example: 1.370 g (2.894 mmol) of fine-grained **1** was suspended in THF (17 mL). On ice cooling and stirring, 1.48 mL of 1.96 M BuLi/hexane (1 equiv) was introduced dropwise by syringe within 30 min. After another 30 min, benzyl bromide (0.34 mL, 1 equiv) was added and the ice-bath was removed. After 5 h of stirring, the solid precipitate was isolated by suction and washed with THF. A total of 1.046 g (64%) of **3b** was obtained, pure by TLC (EtOH/CH_2Cl_2 1:7). An additional amount of product (0.191 g, pure by TLC) was precipitated by adding ether to the original THF solution, and thus the overall yield was 76%.

(7) Stafford, J. A.; Brackeen, M. F.; Karanewsky, D. S.; Valvano, N. L. *Tetrahedron Lett.* **1993**, *34*, 7873−7876.

Boc, the NH of **11** should be more acidic than that of **5a,** which seems to be in agreement with the recorded ^{1}H NMR chemical shifts (∼8.5 and ∼ 7.5 ppm for **11** and **5a**, respectively).

In summary, we have presented a new reagent for the synthesis of multisubstituted hydrazines. It contains only two protecting groups, but its NH hydrogens are readily distinguished by base. This selectivity is verified by the analysis of coupling constants of NMR spectra and proved by the independent synthesis of a compound, which is isomeric to **5a**. The phosphinimine enables one to introduce primary alkyl substituents. The triphenylphosphonium moiety can be easily cleaved under PTC conditions, and the obtained hydrazines can be readily acylated. In comparison with previously reported methods, fewer steps are required for the selective introduction of the substituents.

Supporting Information Available: Full experimental procedures for the synthesis of compounds **5**−**11** and corresponding ^{1}H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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