Sodium Cyanoborohydride Reduction of (Benzyloxycarbonyl)- and (*tert*-Butoxycarbonyl)hydrazones

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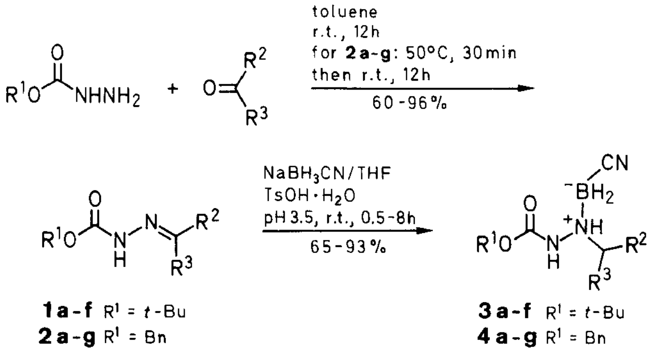
(Benzyloxycarbonyl)- and (*tert*-butoxycarbonyl)hydrazones are easily reduced by sodium cyanoborohydride in acidic medium. The method is an alternative to catalytic hydrogenation and allows ready access to both *N*-benzyloxycarbonyl and *N*-*tert*-butoxycarbonyl protected *N*′-alkyl- and *N*′-arylmethylhydrazines. The products can be isolated as the solid, stable cyanoborane adducts.

N-Benzyloxycarbonyl and *N*-*tert*-butoxycarbonyl substituted hydrazines are important building blocks for the incorporation of α-azaamino acids into azapeptides[1] and construction of protease inhibitors. *N*-*tert*-butoxycarbonyl derivatives have been used preferentially since a general method of preparation requiring catalytic hydrogenation of the parent hydrazones (1, R^1 = *tert*-butyl) has been described.[2] As pointed out by the Authors, when arylaldehyde hydrazones are involved, hydrogenation is very fast, but care must be taken to avoid hydrogenolysis of the benzyl C–N bond. Analogous difficulty was observed by Kurtz[3] previously. The presence of halogens on the aromatic ring or other easily reduced groups may enhance the risk of over-reduction. On the other hand, hydrogenation proceeds very slowly for alkylidene derivatives (40–60 hours) and requires more severe conditions in extreme cases. A more serious disadvantage of the catalytic hydrogenation method is that (benzyloxycarbonyl)hydrazines are not accessible by this route. In fact, only the corresponding derivative of methylhydrazine has previously been prepared by a different method[2] and used in the synthesis of peptides containing α-azaalanine and α-azasarcosine. Successful reduction of the benzylidenehydrazine derived from *N*-acetyl-L-alanyl hydrazide with sodium borohydride in ethanol has been reported by Powers.[4] When the same reaction conditions[5] (borohydride excess, room temperature, 24 hours) were applied to the benzaldehyde (*tert*-butoxycarbonyl)- and (benzyloxycarbonyl)hydrazones (**1c**) and (**2c**) only trace amounts (TLC) of the reduction products, undetectable by ^{1}H-NMR spectroscopy, were obtained.

In view of the importance of the benzyloxycarbonyl and *tert*-butoxycarbonyl protecting groups in peptide synthesis, we wish to report that the corresponding readily accessible hydrazones **1** and **2** are easily reduced by sodium cyanoborohydride in tetrahydrofuran at pH 3.5. Similar conditions were applied by Rosini[6] to the reduction of alkylidenehydrazines.

(*tert*-Butoxycarbonyl)hydrazones **1a–f** and (benzyloxycarbonyl)hydrazones **2a–g** were prepared according to Morley[2] with minor modifications (Table 1). Reductions were performed by adding a solution of *p*-toluenesulfonic acid monohydrate to a solution of the hydrazone derivatives and sodium cyanoborohydride (one molar equivalent) at room temperature, under efficient magnetic stirring.



1-4	R^2	R^3	1-4	R^2	R^3
a	Me	Me	**e**	H	3-ClC_6H_4
b	H	*i*-Pr	**f**	H	4-ClC_6H_4
c	H	Ph	**g**	H	4-$O_2NC_6H_4$
d	H	2-ClC_6H_4			

Reductions of hydrazones **1a,b** and **2a,b** derived from aliphatic aldehydes or ketones were complete in 30 minutes thus showing this reduction to be much faster than catalytic hydrogenation. On the contrary, hydrazones derived from arylaldehydes were more resistant to reduction, and addition of the acid must be carefully controlled to avoid excess, causing destruction of the reducing agent. Under these conditions, addition of *p*-toluenesulfonic acid for a complete reduction required 7–8 hours and the reaction was slower than catalytic hydrogenation. In all cases, work-up of the reaction mixtures involved simple solvent extraction after dilution with ethyl acetate and addition of saturated aqueous sodium hydrogen carbonate and gave the resulting reduction products as the cyanoborane adducts **3a–f** and **4a–g**. Contrary to the free bases that frequently are liquids, these salts are white solids that could be easily purified by crystallization after flash chromatography on a short pad of silica gel. The results for reductions are reported in Table 2. The free bases could be readily obtained from the reaction mixture or from the purified adducts by rapid hydrolysis[7] of the hydrazine–cyanoborane complexes in the presence of a small excess of 1 N sodium hydroxide and solvent extraction. The identity of the free hydrazine extracted from the adduct **3c** was verified by comparison with an authentic sample obtained by catalytic hydrogenation.[2] Conversely, the adduct **3c** could be obtained by direct addition of cyanoborane to the corresponding hydrazine free base in dimethyl sulfide, according to the method of Györy for the preparation of amine–cyanoborane adducts.[8] Correct elemental microanalyses for C, H, N (combustion in the presence of vanadium (V)oxide) and B were obtained for all compounds except **4h** (B – 0.66%).

Table 1. (*tert*-Butoxycarbonyl)- and (Benzyloxycarbonyl)hydrazones **1**, **2** Prepared

Product	Yield[a] (%)	mp (°C)[b] (solvent)[c]	Molecular Formula[d] or Lit. mp (°C)	IR (KBr)[e] ν_{co}(cm^{-1})	^{1}H-NMR (DMSO-d_6)[f] δ, J (Hz)
1a	89	178 (THF/Hx)	182[2]	1660	1.45 (s, 9H), 6.90 (d, 2H, J= 9), 7.55 (d, 2H, J= 9), 8.02 (s, 1H)
1b	91	103 (Hx)	104[2]	1725	1.43 (s, 9H), 1.86 (d, 6H, J= 7)
1c	89	90 (THF/Hx)	90[2]	1703	1.12 (d, 6H, J= 7.5), 1.55 (s, 9H), 2.40–2.80 (m, 1H), 7.16 (d, 1H, J= 5)
1d	93	186 (THF/Hx)	185[2]	1691	1.55 (s, 9H), 7.32–7.52 (m, 3H), 7.68–7.78 (m, 2H), 8.00 (s, 1H)
1e	96	180 (THF/Hx)	$C_{12}H_{15}ClN_2O_2$ (254.7)	1705	1.50 (s, 9H), 7.40–7.62 (m, 3H), 7.90–8.10 (m, 1H), 8.55 (s, 1H)
1f	86	131 (THF/Hx)	$C_{12}H_{15}ClN_2O_2$ (254.7)	1693	1.50 (s, 9H), 7.43–7.78 (m, 4H), 8.09 (s, 1H)
1g	88	168 (THF/Hx)	170[2]	1692	1.52 (s, 9H), 7.45–7.82 (m, 4H), 8.15 (s, 1H)
2a	94	188 (MeOH)	$C_{15}H_{14}N_2O_3$ (270.3)	1692	5.22 (s, 2H), 6.80–7.00 (m, 2H), 7.38–7.64 (m, 7H), 8.04 (s, 1H)
2b	90	85 (CH_2Cl_2/PE)	$C_{11}H_{14}N_2O_2$ (206.2)	1693	1.87 (d, 6H, J= 6), 5.20 (s, 2H), 7.45 (s, 5H)
2c	90	78 (Hx)	$C_{12}H_{16}N_2O_2$ (220.3)	1712	1.08 (d, 6H, J= 7.5), 2.35–2.75 (m, 1H), 5.25 (s, 2H), 7.11 (d, 1H, J= 6), 7.43 (s, 5H)
2d	93	139 (MeOH)	$C_{15}H_{14}N_2O_2$ (254.3)	1693	5.25 (s, 2H), 7.34–7.86 (m, 10H), 8.20 (brs, 1H)
2e	60	103 (THF/Hx)	$C_{15}H_{13}ClN_2O_2$ (288.7)	1704	5.25 (s, 2H), 7.35–7.65 (m, 8H), 7.90–8.12 (m, 1H), 8.60 (s, 1H)
2f	62	101 (THF/PE)	$C_{15}H_{13}ClN_2O_2$ (288.7)	1711	5.30 (s, 2H), 7.23–7.65 (m, 8H), 7.68 (s, 1H), 7.88 (s, 1H)
2g	94	146 (THF/PE)	$C_{15}H_{13}ClN_2O_2$ (288.7)	1711	5.25 (s, 2H), 7.39–7.81 (m, 9H), 8.12 (s, 1H)
2h	90	149 (MeOH)	$C_{15}H_{13}N_3O_4$ (299.3)	1713	5.29 (s, 2H), 7.49 (s, 5H), 8.00 (d, 2H, J= 9), 8.24 (s, 1H), 8.36 (d, 2H, J= 9)

[a] Yield of isolated, purified products.
[b] Uncorrected, measured with a Büchi oil bath apparatus.
[c] PE = petroleum ether (bp 40–60 °C); Hx = hexane.
[d] Satisfactory microanalyses obtained: C ±0.27, H ±0.09, N ±0.25.
[e] Recorded on a Perkin-Elmer 983 spectrophotometer.
[f] Obtained on a Varian EM 390 spectrometer.

The structure of hydrazine cyanoborane adducts was further supported by the following evidence (Table 2). ^{11}B-NMR spectra of adducts **3a–4g** showed an unresolved multiplet in the range δ = 35.9–39.4 relative to trimethyl borate as external standard. This finding is in accordance with data reported[7] for amine cyanoborane adducts, where triplets due to the B–H coupling or poorly resolved multiplets were obtained. IR spectra of all the obtained adducts showed strong absorptions in the B–H stretching region 2464–2218 cm^{-1} and less intense adsorption bands in the CN stretching region 2200–2218 cm^{-1}. In addition to the signals expected for the hydrazine moiety, ^{13}C-NMR spectra gave low intensity CN peaks in the region δ = 131.3–132.6. Molecular peaks of the hydrazine–cyanoborane adducts could not be observed in the MS spectra of compounds **3a–4g**. Molecular ion of the corresponding hydrazine free base and a peak at m/z = 39, attributable to the cyanoborane moiety, were present instead. ^{1}H-NMR spectra appear also to be in accordance with the proposed structures. In particular, cyanoborane adducts **3c–f** presented nonequivalent hydrazine benzyl methylene protons (H_A and H_B) further coupling with proton H_C of the positive adjacent nitrogen. In the case of the adduct **3c**, for example, the methylene signal appeared as two double doublets at δ = 3.77 (J_{AB} = 14 Hz and J_{AC} = 9 Hz) and δ = 4.25 (J_{AB} = 14 Hz and J_{BC} = 3 Hz) and was converted to two doublets at δ = 3.77 and 4.25 (J_{AB} = 14 Hz) after D_2O exchange. It was further simplified to a narrow singlet at δ = 3.90 in the spectrum of the free base and at δ = 4.23 in the spectrum of the hydrogen chloride salt. Behavior of the other adducts was similar, except that poorer resolution of the signal was achieved with the benzyloxycarbonyl derivatives **4c–4g**.

All reagents were of commercial quality from freshly opened containers and were purchased from Fluka, except benzyl carbazate which was prepared according to Boshangen.[9]

(Benzyloxycarbonyl)- and (*tert*-Butoxycarbonyl)hydrazones 1a–f and 2a–g; General Procedure:

A solution of *tert*-butyl carbazate (2.64 g, 20 mmol) and the appropriate carbonyl compound (20 mmol) in toluene (20 mL) is allowed to stand overnight (12 h) at r.t. All (*tert*-butoxycarbonyl[BOC]hydrazones **1a–f** separate as crystalline solids and are collected by filtration of the mixtures. The (benzyloxycarbonyl[Cbz]hydrazones are prepared by a similar procedure from benzyl carbazate. Owing to the poor solubility of this reagent at r.t. mixtures require previous warming at 50 °C for 30 min. After staying overnight (12 h) at r.t., Cbz-hydrazones **2c, f, g** separate as solids while **a, b, d, e** solidify after evaporation of the solvent under reduced pressure. All Boc and Cbz-hydrazones are obtained as pure products by crystallization from solvents indicated in Table 1.

Reduction of (*tert*-Butoxycarbonyl)- and (Benzyloxycarbonyl)-hydrazones 1, 2; General Procedure:

In a N_2 filled round-bottomed flask equipped with serum caps and magnetic stirrer, $NaBH_3CN$ (222 mg, 3 mmol), a Boc or Cbz-hydrazone (3 mmol) and Bromocresol Green (1–2 mg) are dissolved in THF (3 mL). A solution of *p*-toluenesulfonic acid mono-

Table 2. Reduction of (*tert*-Butoxycarbonyl)- and (Benzyloxycarbonyl)hydrazones with Sodium Cyanoborohydride

Product	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c]	IR (KBr), (cm^{-1})[d] ν_{BH}	ν_{CN}	ν_{CO}	^{1}H-NMR (DMSO-d_6, TMS)[e] δ, J (Hz)	^{13}C-NMR (DMSO-d_6, TMS)[f] δ	^{11}B-NMR[f,g] δ	MS (70 eV)[h] m/z (%)
3a	66	135	$C_9H_{20}BN_3O_2$ (213.1)	2446 2421	2200	1704	1.08 (d, 6H, J = 7.5), 1.45 (s, 9H), 3.10–3.50 (m, 1H)	15.7, 17.9 ($\underline{\mathrm{Me}}_2$CH), 27.9 ($\underline{\mathrm{Me}}_3$C), 57.0 (CH), 80.8 (Me$_3\underline{\mathrm{C}}$), 132.1 (CN), 154.6 (CO)	−38.9	174 (free base M$^+$, 10), 39 (39)
3b	65	136	$C_{10}H_{22}BN_3O_2$ (227.1)	2459 2429	2210	1704	0.92 (d, 6H, J = 6), 1.49 (s, 9H), 1.70–2.20 (m, 1H), 2.74 (t, 2H, J = 6)	20.4, 20.6 ($\underline{\mathrm{Me}}_2$CH), 24.0 (CH), 27.9 ($\underline{\mathrm{Me}}_3$C), 63.6 (CH$_2$), 80.9 (Me$_3\underline{\mathrm{C}}$)	−37.8	188 (free base M$^+$, 3), 39 (63)
3c	80	152	$C_{13}H_{20}BN_3O_2$ (261.1)	2442 2418	2214	1705	1.25 (s, 9H), 3.77 (dd, 1H, J_{AB} = 14, J_{AC} = 9), 4.20 (dd, 1H, J_{AB} = 14, J_{BC} = 3), 7.28–7.60 (m, 5H)	27.9 ($\underline{\mathrm{Me}}_3$C), 59.8 (CH$_2$), 80.6 (Me$_3\underline{\mathrm{C}}$), 127.9–136.0 (Ar), 131–132 (CN),[i] 153.6 (CO)	−37.1	222 (free base M$^+$, 11), 39 (64)
3d	65	136	$C_{13}H_{19}BClN_3O_2$ (295.5)	2454 2422	2213	1710	1.25 (s, 9H), 4.05 (dd, 1H, J_{AB} = 15, J_{AC} = 8), 4.37 (dd, 1H, J_{AB} = 15, J_{BC} = 3), 7.33–7.55 (m, 3H), 7.60–7.80 (m, 1H)	27.6 ($\underline{\mathrm{Me}}_3$C), 57.6 (CH$_2$), 81.0 (Me$_3\underline{\mathrm{C}}$), 126.8–134.5 (Ar), 131.6 (CN), 153.9 (CO)	−37.0	256 (free base M$^+$, 4), 39 (70)
3e	82	144	$C_{13}H_{19}BClN_3O_2$ (295.5)	2441 2419	2213	1703	1.25 (s, 9H), 3.76 (dd, 1H, J_{AB} = 13.5, J_{AC} = 7), 4.25 (dd, 1H, J_{AB} = 13.5, J_{BC} = 1.5), 7.50 (s, 3H), 7.65 (s, 1H)	27.6 ($\underline{\mathrm{Me}}_3$C), 59.2 (CH$_2$), 80.8 (Me$_3\underline{\mathrm{C}}$), 128.5–134.1 (Ar), 131.7 (CN), 153.6 (CO)	−37.3	256 (free base M$^+$, 1), 39 (12)
3f	66	142	$C_{13}H_{19}BClN_3O_2$ (295.5)	2469 2437	2208	1697	1.25 (s, 9H), 3.65 (dd, 1H, J_{AB} = 12.5, J_{AC} = 8.5), 4.25 (dd, 1H, J_{AB} = 12.5, J_{BC} = 3), 7.40–7.65 (m, 4H)	27.6 ($\underline{\mathrm{Me}}_3$C), 59.0 (CH$_2$), 80.7 (Me$_3\underline{\mathrm{C}}$), 127.8–133.5 (Ar), 131.9 (CN), 153.5 (CO)	−36.7	256 (free base M$^+$, 0.6), 39 (11)
4a	71	119	$C_{12}H_{18}BN_3O_2$ (247.1)	2452 2426	2209	1710	1.10 (d, 6H, J = 6), 3.15–3.50 (m, 1H), 5.25 (s, 2H), 7.46 (s, 5H)	16.7, 17.9 (Me), 57.2 (CH), 67.6 (CH$_2$), 127.2–136.0 (Ar), 132.1 (CN), 155.1 (CO)	−39.4	248 (adduct M + 1$^+$, 6), 247 (M$^+$, 14), 208 (27), 39 (66)
4b	70	132	$C_{13}H_{20}BN_3O_2$ (261.1)	2438 2417	2210	1710	0.92 (d, 6H, J = 6), 1.92 (hept, 1H, J = 6), 2.79 (t, 2H, J = 6), 5.24 (s, 2H), 7.48 (s, 5H)	20.4, 20.6 (Me), 24.0 (CH), 63.8 (NCH$_2$), 66.6 (ArCH$_2$), 127.8–136.0 (Ar), 131.7 (CN), 154.5 (CO)	−36.7	262 (adduct M + 1$^+$, 3), 261 (M$^+$, 14), 222 (27), 39 (40)
4c	80	133	$C_{16}H_{18}BN_3O_2$ (295.1)	2453 2421	2211	1725	3.84–4.04 (m, 1H), 4.18–4.42 (m, 1H), 5.05 (d, 2H, J = 6.6), 7.18–7.64 (m, 10H)	59.7 (NCH$_2$), 66.2 (ArCH$_2$), 126.8–131.7 (Ar), 131.9 (CN), 154.3 (CO)	−38.5	256 (free base M$^+$, 21), 39 (40)
4d	93	134	$C_{16}H_{17}BClN_3O_2$ (329.6)	2465 2415	2213	1712	4.10–4.60 (m, 2H), 5.19 (s, 2H), 7.25–7.67 (m, 8H), 7.72–8.05 (m, 1H)	56.3 (NCH$_2$), 66.4 (ArCH$_2$), 126.7–135.8 (Ar), 131.3 (CN), 154.5 (CO)	−36.6	290 (free base M$^+$, 21), 39 (49)
4e	75	125	$C_{16}H_{17}BClN_3O_2$ (329.6)	2458 2440	2208	1704	3.67–4.02 (m, 1H), 4.12–4.48 (m, 1H), 5.07 (d, 2H, J = 4.5), 7.15–8.05 (m, 9H)	59.0 (NCH$_2$), 66.3 (ArCH$_2$), 126.6–133.9 (Ar), 131.5 (CN), 156.9 (CO)	−36.6	290 (free base M$^+$, 23), 39 (42)
4f	83	144	$C_{16}H_{17}BClN_3O_2$ (329.6)	2434 2414	2216	1705	3.68–4.03 (m, 1H), 4.12–4.46 (m, 1H), 5.10 (s, 2H), 7.15–7.68 (m, 9H)	58.9 (NCH$_2$), 66.2 (ArCH$_2$), 127.4–135.9 (Ar), 131.6 (CN), 154.3 (CO)	−36.7	290 (free base M$^+$, 8), 39 (37)
4g	86	118	$C_{16}H_{17}BN_4O_4$ (340.1)	2443 2413	2218	1703	3.50–3.87 (m, 1H), 4.00–4.40 (m, 1H), 5.07 (m, 2H), 7.15–7.54 (m, 5H), 7.83 (d, 2H, J = 9), 8.27 (d, 2H, J = 9)	58.8 (NCH$_2$), 66.3 (ArCH$_2$), 122.8–147.5 (Ar), 132.6 (CN), 154.3 (CO)	−35.9	290 (free base M$^+$, 7), 39 (42)

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[a] Yield of isolated, purified products.

[b] Uncorrected, measured with a Büchi oil bath apparatus.

[c] Satisfactory analyses obtained: C ± 0.40, H ± 0.39, N ± 0.3% (combustion with V_2O_5) and B ± 0.24, except **4h**: B − 0.66%.

[d] Recorded on a Perkin-Elmer 983 spectrophotometer.

[e] Recorded on a Varian EM-390 spectrometer.

[f] Recorded on a Varian XL 300 spectrometer.

[g] DMSO-d_6, $(MeO)_3B$ as external standard.

[h] Obtained on a V.G. Micromass 7070 F spectrometer.

[i] Obscured by an aromatic signal.

hydrate (576 mg, 3 mmol) in THF (3 mL) is slowly added via syringe, under efficient stirring, at r.t.: any new addition is performed after indicator toning. Completion of the addition, under these conditions, requires 0.5 h for alkylidenehydrazines and 8 h for arylmethylenehydrazines. The mixture is diluted with EtOAc (15 mL) 0.5 h after the last addition and the suspension extracted with brine (10 mL), aq NaHCO (10 mL) and brine (10 mL). The organic phase is separated, dried (Na_2SO_4) and the solvents evaporated at reduced pressure. The crude product is purified by flash chromatography on silica gel (20 g) using benzene/THF (9:1) as eluant. All *tert*-butoxycarbonyl- or benzyloxycarbonylhydrazines **3a–3f**, **4b–4g**, obtained as BH_2CN adducts, are further purified by crystallization from THF/hexane.

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