Selective N-Benzylation of Amino Acids under Homogeneously Catalyzed Hydrogenation Conditions

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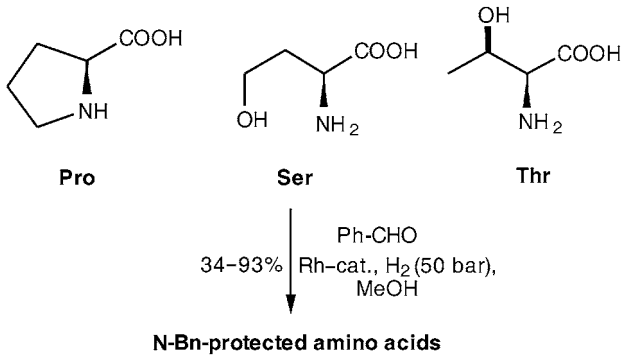
Abstract: The chemoselective N-benzylation of the α-amino acids L-proline, L-serine and L-threonine is described using a reductive amination procedure with benzaldehyde catalyzed by homogeneous Rh-complexes affording N-benzyl protected amino acids.

Key words: hydrogenation, transition metals, catalysis, amino acids

N-Benzyl amino acids find applications in peptide synthesis and are valuable building blocks for the synthesis of chiral compounds.[1] Commonly, they are prepared by N-alkylation of amino acids with benzyl halogenides.[2] However, this method may fail when additional functional groups like HO-functionalities are present in the molecule. As an alternative, the reductive amination with benzaldehyde employing complex borohydrides as hydrogen source was suggested.[3] This method does not match the demand for atom economy. More appealing seems to be the use of molecular hydrogen. Indeed heterogeneously catalyzed reductive N-benzylation of amino acids was suggested some times ago.[4] But the use of 5% Pd/C, as required for sufficient conversion, is not optimal. Moreover, under these conditions, reductive debenzylation may occur to a large extent. In this respect homogeneous catalysis seems to be the method of choice.

Herein we report on a highly chemoselective N-benzylation procedure of selected α-amino acids with PhCHO under Rh(I)-catalyzed hydrogenation conditions (Scheme 1). As amino acids, we have chosen L-proline (Pro), L-serine (Ser) and L-threonin (Thr). Usually, benzylation of these particular amino acids is always associated with serious problems. Thus, N-benzylation of Pro with BnCl has been reported in the literature but the isolation procedure detailed is rather tedious.[5] To the best of our knowledge, it is not possible to alkylate Ser and Thr chemoselectively with benzyl halides.

In preliminary investigations[6] we tested commercially available metal complexes $(Ph_3P)_3RhCl$, $(Ph_3P)_3RuCl_2$ or complexes which are easily prepared using other *P*-ligands like [Rh(dppp)(COD)]BF_4 [dppp = 1,3-bis(diphenylphosphino)propane, COD = 1,5-cyclooctadiene], [Rh(dppb)(COD)]BF_4 [dppb = 1,4-bis(diphenylphosphinobutane] and [Rh(dpoe)(COD)]BF_4 [dpoe = *O*-1,2-bis(diphenylphosphinoxy)ethane]. These five precatalysts were employed in a 25 mL autoclave using 5 mmol of amino acid, 5 mmol of PhCHO, 10 mL of MeOH at r.t. and 50 bar H_2 initial pressure. The reaction mixtures were analyzed by NMR. Neither racemization in case of BnPro nor dehydration or retroaldol products in case of Ser and Thr were found in the reaction mixtures.



Scheme 1

Obviously, the productivity of the catalysts is strongly dependent on the amino acid used. In the production of *N*-BnPro, the following order was found: $(Ph_3P)_3RhCl$ > [Rh(dppp)(COD)]BF_4 > [Rh(dppb)(COD)]BF_4 >>>> [Rh(dpoe)(COD)]BF_4, $(Ph_3P)_3RuCl_2$. In the case of Ser the order was [Rh(dppp)(COD)]BF_4 > [Rh(dppb)(COD)]BF_4 >> [Rh(dpoe)(COD)]BF_4 >>>> $(Ph_3P)_3RhCl$, $(Ph_3P)_3RuCl_2$ and with Thr, [Rh(dppp)(COD)]BF_4 >>> [Rh(dppb)(COD)]BF_4, [Rh(dpoe)(COD)]BF_4. The most efficient catalysts were employed on a preparative scale in a 50-mL autoclave. The products were isolated by simply washing with appropriate solvents (Table 1).[7]

Some further improvements were made during the scale-up. Thus, the yield of *N*-BnPro could be enhanced in comparison with the preliminary experiments by dissolving Pro in MeOH prior to the hydrogenation and usage of a 1.5 molar excess of PhCHO. With a 1000:1 ratio of Pro to $(Ph_3P)_3RhCl$ complete conversion of amino acid was achieved. After evaporation of the solvent and washing, the analytically pure compound was isolated in 93.2% yield. Its optical purity was confirmed by HPLC on a chiral column. When Ser was used as a substrate, the

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Table 1 N-Benzylation of Amino Acids with Benzaldehyde Applying Homogeneous Rh-Catalysts[a]

Product	Precatalyst	Yield (%)
N-BnPro	$(Ph_3P)_3RhCl$[b]	93.2
N-BnSer	$[Rh(dppp)(COD)]BF_4$[c]	60.0
N-BnThr	$[Rh(dppp)(COD)]BF_4$[c]	34.0

[a] Conditions: MeOH, r.t., 50 bar H_2 initial pressure.
[b] Molar ratio precatalyst:substrate = 1:1000.
[c] Molar ratio precatalyst:substrate = 1:500.

product could be also isolated by simple filtration. Washing of the solid afforded the analytically pure product. The yield of *N*-BnSer increased from 42.8% to 60.0% when the molar ratio of PhCHO:Ser employed was enhanced from 1.2 to 2.0. The benzylation of Thr was carried out with a molar ratio of PhCHO:Thr of 2.0 using the same conditions as described for Ser. After the washing procedure, analytically pure *N*-BnThr was isolated in 34% yield.

In conclusion, we have found a very mild and highly chemoselective catalytic N-benzylation of those amino acids that cannot be subjected to the usual alkylation procedure. Moreover, this reaction represents a useful alternative to the traditional alkylation of amino acids with alkyl halides since no over-alkylation is observed.

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(7) **(*S*)-*N*-Benzylproline**. In a typical run, a 50-mL Parr autoclave was charged with 32 mg (0.0345 mmol) of commercial $(Ph_3P)_3RhCl$ complex. Air was evacuated by three vacuum–Ar cycles. A solution of 4.00 g (34.7 mmol) of (*S*)-Pro in 30.0 mL MeOH (prepared in an Ar atmosphere) was introduced into the autoclave with a needle followed by addition of 5.3 mL (5.57 g, 52.4 mmol) of PhCHO. The autoclave was pressurized with 50 bar of H_2. The reaction mixture was stirred at r.t. for 3 d until uptake of H_2 ceased. The autoclave was opened and the resulted solution evaporated. The residue was triturated under acetone and the solid was filtered and washed twice with acetone. The product was dried on air. Mp 178–179 °C (Lit.[5] mp 174–175 °C). $[\alpha]_D^{24} = -27.9$ (*c* 1 in EtOH) [Lit.[5] $[\alpha]_D^{20} = -25.8$ (*c* 1 in EtOH)]. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.12; H, 7.34; N, 6.79. ^{1}H NMR (CD_3OD–$CDCl_3$): δ = 1.89–2.12 (m, 2 H), 2.13–2.28 (m, 1 H), 2.33–2.49 (m, 1 H), 3.57–3.69 (m, 1 H), 3.89 (dd, 1 H, *J* = 9.1, 6.6 Hz, α-CH), 4.26 (d, 1 H, *J* = 12.8 Hz, CH_aH_bPh), 4.45 (d, 1 H, *J* = 12.8 Hz, CH_aH_bPh), 7.38–7.54 (m, 5 H, ArH).
(*S*)-*N*-Benzylserine. Mp 214–216 °C (decomp.) (Lit.[8] mp 235–236 °C). $[\alpha]_D^{24} = 5.6$ (*c* 1 in 6 N HCl)[Lit.[8] *S*-isomer $[\alpha]_D^{22} = 4.9$ (*c* 1 in 6 N HCl), *R*-isomer $[\alpha]_D^{22} = -5.5$ (*c* 1 in 6 N HCl)]. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.42; H, 6.43; N, 7.16. ^{1}H NMR (CD_3OD–DCl conc.): δ = 4.05–4.26 (m, 3 H, α-H and β-H_2-Ser), 4.38 (d, 1 H, *J* = 13.0 Hz, $PhCH_aH_b$), 4.42 (d, 1 H, *J* = 13.0 Hz, $PhCH_aH_b$), 7.44–7.52 (m, 3 H, ArH), 7.55–7.63 (m, 2 H, ArH). ^{13}C NMR (CD_3OD– DCl conc.): δ = 51.78 (CH_2), 60.42 (CH_2), 62.35 (CH), 131.04 (CH), 131.61 (CH), 132.08 (CH), 132.23 (C), 170.54 (COO).
(*S*)-*N*-Benzylthreonine. Mp 237–238 °C. $[\alpha]_D^{24} = -15.1$ (*c* 1 in 6 N HCl). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.15; H, 7.07; N, 6.67. ^{1}H NMR (CD_3OD– DCl conc.): δ = 1.35 (d, 3 H, *J* = 6.5 Hz, Me), 3.72 (d, 1 H, *J* = 6.5 Hz, α-H), 4.24 (dq, 1 H, *J* = 6.5, 6.5 Hz, β-H), 4.36 (d, 1 H, *J* = 13.0 Hz, $PhCH_aH_b$), 4.42 (d, 1 H, *J* = 13.0 Hz, $PhCH_aH_b$), 7.44–7.52 (m, 3 H, ArH), 7.53–7.60 (m, 2 H, ArH). ^{13}C NMR (CD_3OD–DCl conc.): δ = 21.48 (CH_3), 52.32 (CH_2), 66.40 (CH), 67.50 (CH), 131.09 (CH), 131.74 (CH), 131.96 (C), 132.28 (CH), 170.40 (COO).
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