Tetrahedron Letters,Vol.31,No.1,pp 23-26,1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

AN IMPROVED METHOD FOR THE PREPARATION OF DESOXOPEPTIDES— REDUCTIONS OF ENDOTHIOPEPTIDES†

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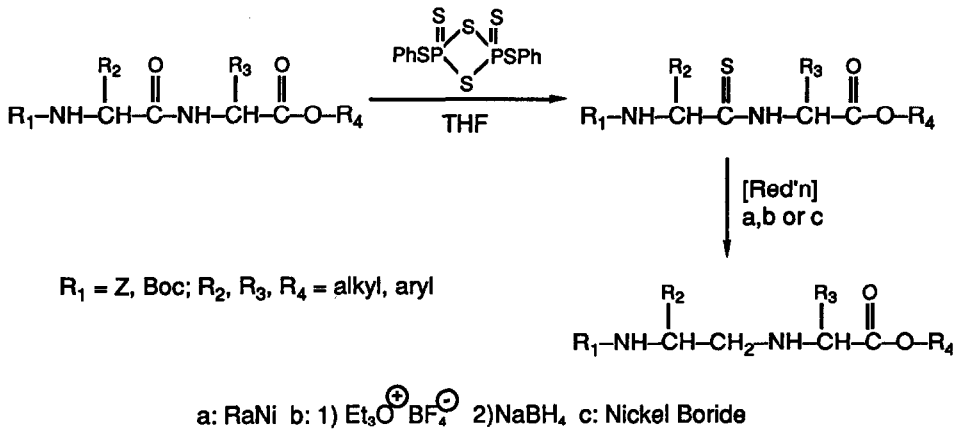
Abstract: Three new procedures for the synthesis of desoxopeptides from endothiopeptides are reported: 1) Raney nickel desulfurization, 2) alkylation with triethyloxonium tetrafluoroborate followed by sodium borohydride reduction, and 3) nickel boride reduction. Of these three, reduction with nickel boride was found to be superior due to high yields, reproducibility and convenience.

Recently, methods for the modification of peptide bonds have been sought in connection with the development of new enzyme inhibitors. One such modification, the desoxopeptide moiety $\psi(CH_2NH)$, involves the replacement of the peptide bond with an aminomethylene moiety. Since the C–N bond of a desoxopeptide is not hydrolyzable, desoxopeptides may prove to be useful inhibitors of proteolytic enzymes.[1,2] Desoxopeptides have been prepared by stepwise routes which utilized synthetic intermediates such as N-2-aminoethylglycine (AEG), the desoxo analogue of glycylglycine,[1] or the desoxo analogues of leucylvaline and phenylalanylphenylalanine which were obtained by the reductive alkylation of the appropriate aminoesters with N-protected aminoaldehydes in the presence of sodium cyanoborohydride.[2] Using these routes it was necessary to protect the secondary amine functions throughout the rest of the peptide synthesis. Desoxopeptides have also been prepared by the direct reduction of a dipeptide with diborane.[3] Diborane, however, is not entirely selective for the amide bond and problems were encountered with reduction occurring at the ester function as well.

We and others have recently reported procedures to prepare endothiopeptides directly from protected dipeptides.[4-9] Treatment of protected dipeptides with dimeric phenylthionophosphine sulfide cleanly afforded the endothiopeptides in good yields (Scheme 1).[4] We now wish to describe convenient reductive procedures which allow for the selective conversion of endothiopeptides into desoxopeptides. Three methods were investigated: (1) direct reduction using Raney nickel, (2) alkylation with triethyloxonium tetrafluoroborate followed by sodium borohydride reduction, and (3) direct reduction with nickel boride (Scheme 1).

†Presented in part at the 196th American Chemical Society National Meeting, Los Angeles, CA, September 1988; ORG 048.



Scheme 1

Raney nickel (RaNi) has been widely used in desulfurization reactions, including conversion of a thiocarbonyl group into a methylene group.[10] Neutral Raney nickel in alcohol solvent gave relatively good desulfurization yields as shown in Table 1, however, a number of disadvantages were noted using this procedure. One major disadvantage was that removal of the carbobenzoxy groups occurred concurrently with thioamide reduction. Carbobenzoxy groups are readily removed by catalytic hydrogenation; Raney nickel also facilitates this hydrogenation.[11] Transesterification under normal reaction conditions was also noted. Finally, the preparation and use of neutral Raney Nickel was time-consuming and tedious. Often different batches of identically prepared reagent would show significantly different reactivities as demonstrated by variation in reaction time and yields. These problems and the potential hazards associated with the pyrophoric nature of Raney Nickel led us to seek other reductive procedures.

Thioamides have been converted by an alkylation-reduction sequence to the corresponding amines.[12] We alkylated several protected endothiopeptides with triethyloxonium tetrafluoroborate and then reduced the S-alkyl derivatives with sodium borohydride. As illustrated in Table 1, the yields were much lower than those obtained by Raney nickel reduction. The majority of material isolated was recovered starting material. It was possible using this method, however, to reduce endothiopeptides which contained carbobenzoxy N-protecting groups without hydrogenolysis.

The third method investigated utilized nickel boride as a reducing agent. Nickel boride has been used in the desulfurisation of heterocyclic thiols[13] and ethylene dithioketals.[14] P-2 nickel boride was prepared by treating nickel chloride • hexahydrate in methanol-tetrahydrofuran with sodium borohydride.[15] The reduction of the thioamide bond in endothiopeptides occurred quite readily with nickel boride. In contrast to the Raney nickel reductions, the carbobenzoxy group was left intact after treatment with the nickel reagent. The yields obtained following the nickel

Table 1: Desoxopeptides Prepared by Reduction of the Corresponding Endothiopeptides

Desoxopeptide	% Yield[a]			
	Raney Nickel	Alkylation/ $NaBH_4$	Nickel Boride	Diborane Red'n[b]
Boc–Gly–ψ(CH_2NH)–Gly–OMe	5	10	41	—
Z–Phe–ψ(CH_2NH)–Gly–OMe	—	15	—	—
Z–Gly–ψ(CH_2NH)–Gly–OEt	—	18	—	—
Boc–Gly–ψ(CH_2NH)–Val–OMe	45	—	45	—
Boc–Ala–ψ(CH_2NH)–Gly–OMe	43[c]	—	—	—
Boc–Ala–ψ(CH_2NH)–Phe–OMe	46[c]	—	66	—
Boc–Leu–ψ(CH_2NH)–Leu–OMe	84[c]	—	52	—
Z–Leu–ψ(CH_2NH)–Leu–OMe	21	5	56	7
Z–Gly–ψ(CH_2NH)–Leu–OMe	6	7	37	26
Boc–Gly–ψ(CH_2NH)–Leu–OMe	53	9	48	30
Boc–Phe–ψ(CH_2NH)–Gly–OMe	—	—	41	—
Z–Gly–ψ(CH_2NH)–Gly–OMe	—	—	18	—

[a] Isolated and purified yields. [b] Prepared by Roeske *et al.* (ref. 3) from the corresponding dipeptides, and isolated as the HCl salts. [c] Crude yield.

boride procedure were higher than those from either the Raney nickel or alkylation/sodium borohydride reduction methods (Table 1). The nickel boride method also gave higher yields than direct reduction of the amide by borane. In addition, another advantage in using nickel boride to reduce endothiopeptides is that the reaction and purification can be completed in one day in contrast to the 2-3 days necessary for the Raney nickel procedure. The yields of desoxopeptides and times required for reaction are also very reproducible and nickel boride is nonpyrophoric.

In a typical procedure, sodium borohydride (240 mmol) was added to a solution of the protected endothiopeptide (10 mmol) and nickel chloride hexahydrate (80 mmol) in tetrahydrofuran/methanol (1:1) in an ice bath. The reaction mixture was stirred at room temperature until no starting endothiopeptide was observed by TLC. After filtering the reaction mixture through Celite and removing the solvent, the crude desoxopeptide was purified by flash chromatography with 10% ethyl acetate/dichloromethane.

In conclusion, we have evaluated procedures for the direct conversion of protected endothiopeptides to desoxopeptides. Of these the nickel boride procedure is superior due to the high yields obtained, reproducibility, and short time necessary for the reaction and purification. Thionation of a protected dipeptide followed by nickel boride reduction appears to be the method of choice for the preparation of desoxopeptides.

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(Received in USA 11 September 1989)