Tetrahedron Letters,Vol.30,No.33,pp 4411-4412,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

FACILE REDUCTION OF METHIONINE SULFOXIDE WITH SULFUR TRIOXIDE/THIOL SYSTEM

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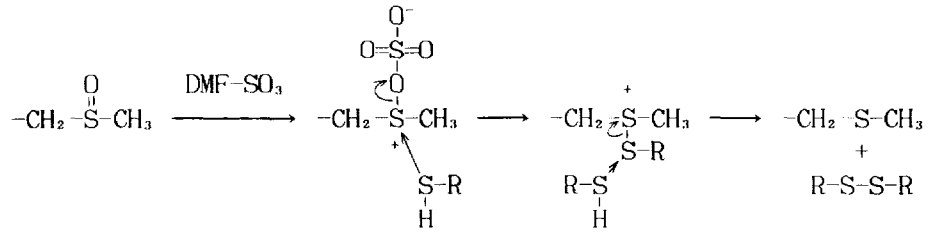
Summary: A new condition for effective reduction of methionine sulfoxide (sulfur trioxide/thiol) was developed and the usefulness of this reduction was demonstrated in the synthesis of methionine-enkephalin.[1]

To avoid S-alkylation during the N^{α}-deprotection and partial sulfoxide-formation on manipulation in the synthesis of methionine(Met)-containing peptide,[2] an approach in which Met is protected in the form of sulfoxide (Met(O))[3] has been developed. When this approach is adopted, it becomes necessary to reduce Met(O) back to Met at the final stage of the synthesis. The most popular method now used is to reduce Met(O)-peptide by incubation with thiol after deprotection.[4] However, this method is often time-consuming and, furthermore, sometimes reduction is incomplete. To overcome the defects of this method, Yajima et. al.,[5] developed a new approach in which Met(O) was reduced to Met by treatment with phenylthiotrimethylsilane[6] before deprotection.

We now wish to report another novel system to reduce Met(O) before deprotection. This system consists of sulfur trioxide, conveniently in the form of dimethylformamide(DMF) complex,[7] and thiol in the presence of pyridine. The reduction seems to proceed with the initial formation of a sulfonium and subsequent nucleophilic attack of thiol. The reduction is very rapid at room temperature and completes within an hour.



In general, the reduction is conveniently carried out by addition of DMF-SO_3 complex and ethanedithiol to a solution of Met(O)-containing protected peptide in DMF-pyridine(4:1). The solution is maintained at

room temperature during the addition and the subsequent reduction period. After evaporation of the solvent, the residue is washed with water, followed by recrystallization from appropriate solvents.

Following this procedure, Z(OMe)-Phe-Met(O)-OMe[8] was reduced within 30 min in 85% isolated yield.[9] Protected methionine-enkephalin, Boc-Tyr(Cl_2Bzl)-Gly-Gly-Phe-Met(O)-OBzl[10] was reduced within an hour in 90% isolated yield,[11] followed by deprotection with 1M CF_3SO_3H-thioanisole/CF_3COOH[12] in the presence of ethanedithiol and m-cresol (0℃, 90 min). Subsequent purification with DEAE-Sephadex A-25® (1% pyridine-0.04% AcOH) and Diaion HP-20® (CH_3CN-0.1N AcOH) afforded methionine-enkephalin, H-Tyr-Gly-Gly-Phe-Met-OH, in 49% yield.[13]

This new method should be applicable not only to the Met(O)-reduction in peptide synthesis but also to reduction of various sulfoxides.

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9) DMF-SO_3 complex (5eq) and ethanedithiol (5eq) were used. The ^{1}H-NMR spectrum ($CDCl_3$, δ 2.04 (3H, s, SCH_3), 2.38 (2H, t, J=7, CH_2S)), mp (118-120℃) and $[\alpha]_D^{20}$ (-16.6°, c=1.0, DMF) of the reduced product are identical with those of the authentic Z(OMe)-Phe-Met-OMe.
10) This protected peptide was prepared stepwisely by the conventional solution method.
11) DMF-SO_3 complex (10eq) and ethanedithiol (10eq) were used. The molecular weight of the reduced protected peptide was ascertained by fast atom bombardment mass spectrometry: m/z 946.5 $(M+Na)^+$.
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13) Amino acid ratios after enzymatic digestion: Tyr 0.96, Gly 2.00, Phe 1.08, Met 0.93. Retention time in HPLC (14.9 min, on YMC-AM312 column by gradient elution with CH_3CN(20-35%, 30 min)in 0.1% CF_3COOH at a flow rate of 1 ml/min) was identical with that of the authentic sample (purchased from Peptide Institute, Inc., Osaka, Japan).

(Received in Japan 7 June 1989)