In fact, addition of equimolar triethylamine to the mixture maintained proper condition of free dialkylamine, thereby affording high yields of dialkylmethylamine. It should be noted that under the present condition quarternary ammonium salt could not be detected.

Following is the representative procedure: To a solution of dibenzylamine (0.20g, 1.01 mmol) and triethylamine (0.14 m*l*, 1.01 mmol) in 1 ml CH_2Cl_2 at 0°C, triflic acid (0.09 m*l*, 1.01 mmol) was added followed by excess alcohol-free diazomethane in ether. After stirring at 0°C for 0.5 hr. 30 m*l* of aqueous sat. sodium bicarbonate was added. After extractive work-up and chromatography, 0.20g (93%) of dibenzylmethylamine was obtained.

As shown in Table 1, the yields are often high except for the case of diphenylamine which itself is a very weak nucleophile. Unfortunately, neither tosylate 1 nor the corresponding triflate 2[3] resisted methylation under present condition. Here, the compounding problem is the poor solubility of ammonium salts 1 and 2 in common organic solvents.

Some further comments on the mechanism of the reaction are warranted. Diazomethane did react with triflic acid in ether to give methyl triflate as judged by NMR (δ 4.15) and GC.[4] Indeed independently prepared methyl triflate[5] (1.1 equiv) reacted with dibenzylamine in CH_2Cl_2 (0°C, 0.5 hr.) to give 75% yield of dibenzylmethylamine. But in the presence of 1 equiv of triethylamine, methyl triflate could not be detected under otherwise identical condition, which would render credence to our original proposition. However it is also recognized that the above experiments completely rule out the formation and reaction of methyl triflate. In conclusion, irrespective of its actual mechanism, the present method would be a mild alternative for methylation of secondary amines, though not general.[6,7]

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A Rapid Synthesis of Met-Enkephalin Derivative by p-Nitrobenzophenone Oxime Resin

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Fragment condensation approach is ideal strategy in solid-phase peptide synthesis when a large peptide molecule has to be constructed on a solid support.[1] Such an approach gives an opportunity for the purification and characterization of peptide intermediates and can minimize the problems of purification after removing final peptides from the polymer supports. To make this strategy useful, a convenient method for preparing protected peptide acids must be generalized. Several methods have been reported to obtain protected peptide acid from resin supports, such as photolysis,[2] hydrogenolysis,[3] and nucleophilic cleavage.[4] All of these methods depend upon the property of functional groups on the resin supports, and have some disadvantages.

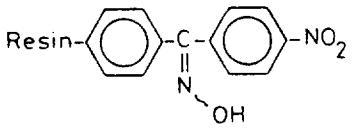
Recently, p-nitrobenzophenone oxime resin (2) has been proved as a good polymer support for the synthesis of peptide fragments.[5] Fully protected peptides are usually recovered from 2 by nucleophilic displacement with amino acid esters,[6] or 1-hydroxypiperidine.[7] But there are few choices to obtain free acid from fully protected peptide fragment. Hydrolytic cleavage of peptide alkyl ester without any side reactions is difficult procedure.[8] Reductive cleavage of 1-piperidyl ester with zinc in acetic acid[7] may be useful, but it is difficult to obtain 1-piperidyl ester in pure form from 2.

In this communication, we now report an improved and efficient way for the synthesis of protected peptide acid which has the sequence of Met-Enkephalin (1c) from 2. The oxime resin (2) which had been derived[6] from polystyrene-1%-divinylbenzene co-polymer was coupled with Boc-L-Phe by DCC. After blocking unreacted oxime group by acetylation, Boc group was removed from the resin by 25% TFA/CH_2Cl_2 for 30 minutes. Then, Boc-Gly (twice) and Z-L-Tyr (OBzl) were coupled to the resin successively by the usual procedure of solid-phase peptide synthetic method.[6] Each amino acid derivatives was introduced as symmetric anhydride form, and each coupling steps proceeded nearly 100% within 2 hours as determined by ninhydrin color test.[9] The resulting fully pro-

Z-Tyr(OBzl)-Gly-Gly-Phe-X

1a X=2, 1b X=3

1c X=Met-OH



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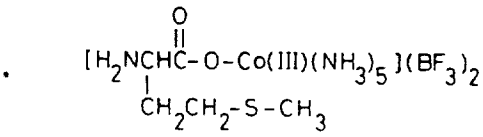

3

tected peptide resin (**Ia**) was reacted with L-Met-Co (III) complex (**3**)[10] in the presence of acetic acid as catalyst. After 19 hours, IR spectrum of the resin showed the disappearance of the oxime ester peak at 1775 cm^{-1}, which indicates the cleavage of the peptide from the resin and the formation of **Ib**. The pentapeptide-Co (III) complex (**Ib**) was recovered as pink solids after filtration and evaporation of the solvent in vacuo (70% yield based on Boc-L-Phe-oxime resin). The unreacted **3** was easily removed from the reaction mixture by washing with methanol.

As previously reported, Co (III) group was selectively removed from **Ib** by briefly treating with sodium borohyride.[10] Gel filtration and crystallization of the crude product in methanol afforded **1c** in white crystals.[11] One of the advantages of this reaction scheme is that both conditions employed for the recovery of the peptide from the resin and for the removal of Co (III) complex are very mild and there is no danger of racemization during these steps.[6,10] Furthermore, simple purification without any complicate chromatographic work has ensured high yield.

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(11) Yield, 50% from Boc-Phe-oxime resin; M.P. 178-180°C; TLC, R_f 0.75 (silica gel; n-butanol-acetic acid-H_2O, 40:4:12); Amino acid anal., Gly 2.19, Tyr 0.78, Phe 1.10 (Met could not be detected because of oxidation during hydrolysis); ^1H NMR (DMSO-d_6) δ: 2.04 (3H, *s*, S-CH_3), 2.40-4.90 (19H, *m*, 5 methines and 6 methylenes), 5.08 and 5.20 (4H, *s*, 2-OCH_2Ph), 6.90-7.80 (21H, *m*, 4 aromatics and 2 amides), 7.80-8.90 (3H, *m*, 3 amides).

Unusually Stable Thiolsulfinate: *o*-Hydroxyphenyl-*o*-hydroxybenzene-thiolsulfinate

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Considerable interest has focused on thiolsulfinates, **2**[1] which are unstable, but an important precursor of unstable intermediate, α-disulfoxides, **3**[2] thiolsulfonates, **4**[1b,3] being well used for the synthetic utility for organosulfur compounds. Although thiolsulfinates are known to be unstable, only a few exceptionally stable thiolsulfinates such as *trans*- and *cis*-1,2-dithiane-4,5-dioldiacetate[4] and 2,4,6-triisopropylphenyl-2,4,6-triisopropylbenzene thiolsulfinate[5] have been reported without any detailed evidence or suitable explanation for their stability. During the course of our studies on the oxidations of disufide reated compounds we have found that *o*-hydroxyphenyl-*o*-hydroxybenzene disulfide[6] was readily monooxidized with equimolar amount of m-chloroperbenzoic acid at −45°C to give the corresponding unusually stable thiolsulfinate which showed no change after more than two years at room temperature.[7]