N-Methylation of Secondary Amines

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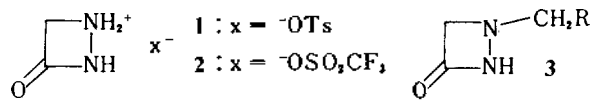
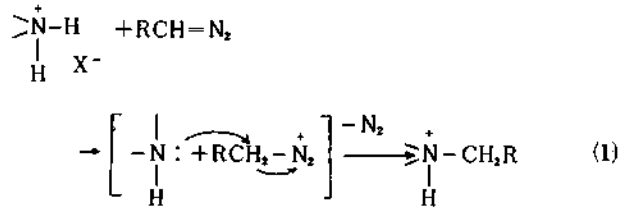
Recently, we were in need of alkylating ammonium salts such as *1*, which and the conjugate base of which are unstable under acidic, basic and/or protic conditions[1]



Thus, due to the imposing restriction, there seemed to exist not many choices by which one could achieve the goal. (*ie. 1→3*) This is also because the positively charged nitrogen in *1* is neither a nucleophile nor a electrophile.

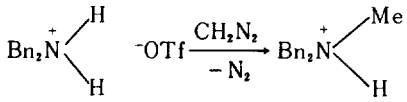
Conceptually, the best candidate would be a pro-alkylating agent (with some proton affinity), which, only upon protonation, would become an alkylating agent. Diazoalkanes seemed to meet this requirements.

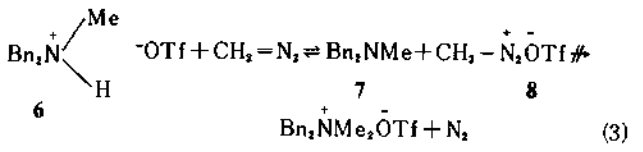


Supporting to this is a report that glycine can be trismethylated by diazomethane in an analogous manner.[7]

Thus, a brief model study was undertaken to examine the possibility.

Initial attempt with preformed dibenzylammonium tosylate with diazomethane was uniformly unsuccessful in ether or CH_2Cl_2. Here, the attendant tosyloxy group was so nucleophilic that methyl tosylate would form. Clearly, a protic acid with a non-nucleophilic anion is preferred. No reaction was observed with BF_3-OEt_2, silica gel, $TsOH \cdot H_2O$, *etc.* However, dibenzylammonium triflate,[2] *in situ* prepared by mixing the corresponding amine with equimolar triflic acid, did provide with excess diazomethane the methylated dibenzylmethylamine albeit in 16% yield with the remainder being dibenzylamine. Presumably, the initially formed trialkylammonium triflate *5* would hesitate protonate diazomethane, or more likely after protonation incipient methyldiazonium ion *8* failed to react with the only nucleophile *2* and thus reverted to *6*. (In fact no quarternary ammonium salt could be visible under the present condition).





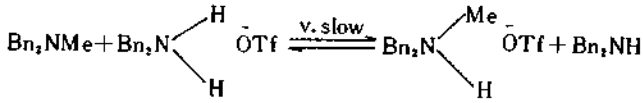
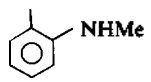
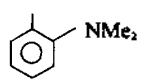
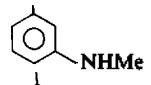
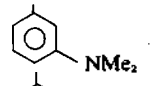
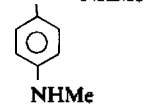
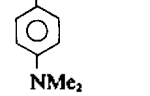


TABLE 1: Methylation of secondary Amines

Amine	Solvent	Rxn	Condition	Product	Yield (%)
$(PhCH_2)_2NH$	ether	0°	0.5 h	$(PhCH_2)_2NMe$	93
c-C_6H_{11}-N(H)-i-Pr	CH_2Cl_2	rt	2 h	c-C_6H_{11}-N(Me)-i-Pr	78
	CH_2Cl_2	rt	20 h		98
	CH_2Cl_2	rt	6 h		92
	CH_2Cl_2	rt	20 h		78
$PhCH_2NHMe$	CH_2Cl_2	rt	20 h	$PhCH_2NMe_2$	68
PhNHMe	CH_2Cl_2	rt	20 h	$PhNMe_2$	74
Ph_2NH	CH_2Cl_2			Ph_2NMe	0

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]

References

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(3) Prepared by an analogous preparation for tosylate 1 (ref. 1) using 1 equiv each of H_2O and triflic acid in ether (mp 82-86°C) IR (thin film) 1820 cm^{-1}.

(4) D.S. Wulfman, G. Linstrumelle and C.F. Cooper in "The Chemistry of Diazonium and Diazo groups", S. Patai ed., Part II, Wiley, p. 821-976 (1978).

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(7) (a) H. Biltz and H. Pacetzold, *Chem. Ber.*, **55**, 1066 (1922); (b) E. Müller, H. Huber-Emden and W. Rundel, Justus Liebigs *Am. Chem.*, **623**, 34 (1959).

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-