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SYNTHESIS OF DIPHENYL THIOETHER DERIVATIVES OF PEPTIDES AND AMINOACIDS

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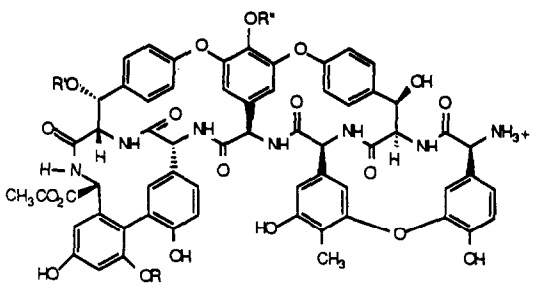
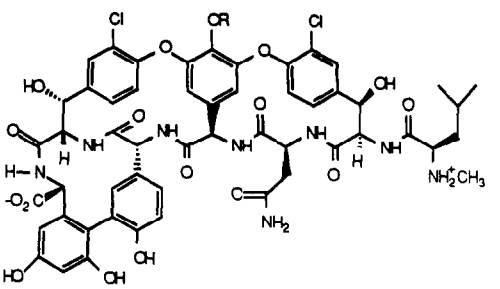
Summary: Derivatives of p-mercaptophenylalanine and iodotyrosine or iodohydroxyphenylglycine are efficiently converted to thioethers by $S_{RN}1$ reaction in ammonia.

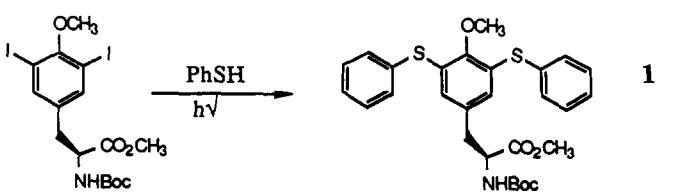
Diphenyl ethers are common substructures in a number of naturally occurring macrocyclic peptides and arise from oxidative coupling of the phenolic sidechains of tyrosine or hydroxyphenylglycine. In some natural products such as the antibiotics ristocetin and vancomycin (below),[1] several such substructures are found and rigidify the otherwise conformationally flexible peptide backbone and thus help define the walls of the crevice into which certain C-terminal peptides bind.





While a number of methods for diphenyl ether synthesis have been reported,[2] none proved suitable for construction of the aminoacid-based diphenyl ethers we required. We therefore turned to the structurally similar but synthetically more accessible diphenyl thioethers.[3] These materials primarily differ from the oxygen analogs by their longer bonds (1.72 C-S vs. 1.36 angstroms C-O) and their lowered barriers to rotation (ca 1 vs. 5 kcal/mole - thioanisole vs. anisole).[4]

In this note, we describe the photoinitiated $S_{RN}1$ coupling of certain iodoanisoles and thiophenols to yield peptidic diphenylthioethers. To find the best method for



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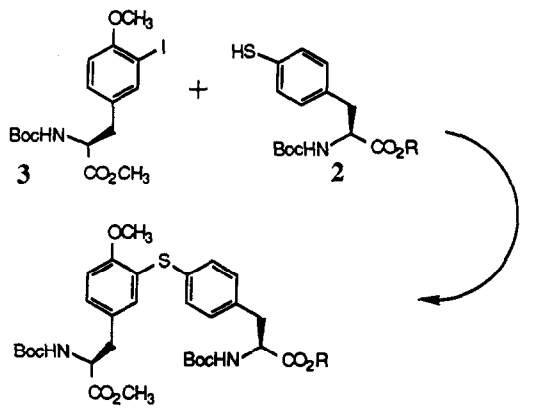
coupling, we investigated the simple system shown below under a variety of conditions including CuO/C_6H_5N and photolysis/NH_3(liq) or THF or CH_3CN.[3] These and other studies indicated that photochemically initiated $S_{RN}1$ reactions in liquid ammonia provided the mildest, most general method and, using this approach, **1** could be prepared in >90% from thiophenol and the diodotyrosine derivative shown above. Racemization was found to be <5% as shown by coupling of the product with each enantiomer of BOC-alanine dinitrophenyl ester.

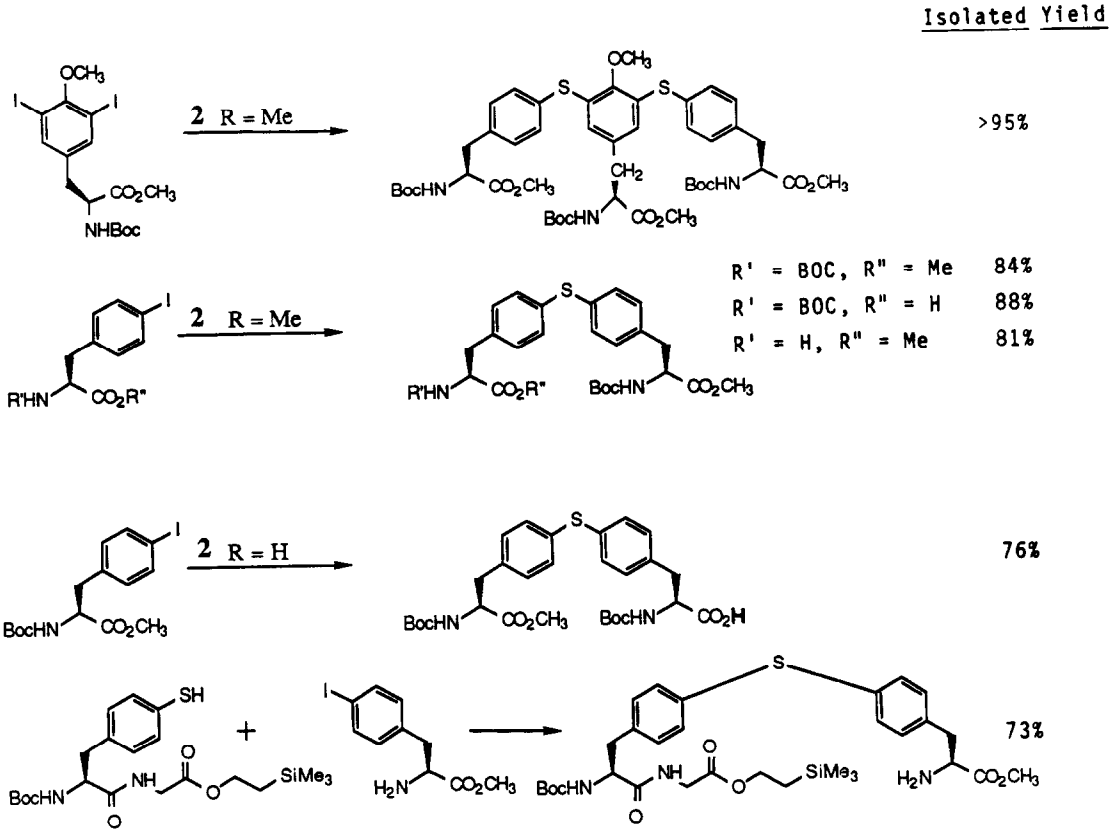
To assess the potential of the reaction as a practical route to more complex, peptidic thiophenyl ethers, BOC-protected p-mercaptophenylalanine methyl ester (**2**, R = Me) and the free acid (**2**, R = H) were prepared by the method of Escher[5] and coupled with a variety of iodinated aryl aminoacid derivatives. Using **2** (R = Me) and monoiodo (O-methyl)BOC-tyrosine methyl ester(**3**, R = BOC) as a representative example, we found that high yields of adducts could be obtained with 1 hour sunlamp irradiation in liquid ammonia (-33° C) using only a 30% excess of the mercaptan and operating at concentrations of as low as 0.01M. All of the following reactions were carried out according to these standard conditions (1 hr sunlamp irradiation, 1.3 equivalents of mercaptan, 0.01M in liquid ammonia).[6] The primary side reaction was simple reduction of the aryl iodide and disulfide formation.



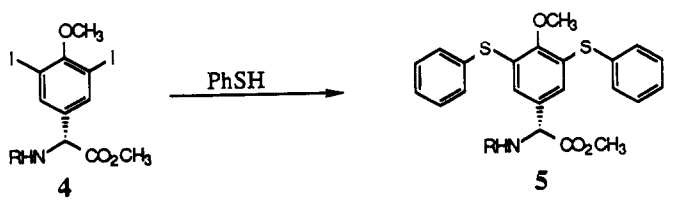
Equivalents of **2** (.01M)	Yield
1.0	56%
1.1	76%
1.3	90%
2.0	91%

Concentration (1.3 equiv **2**)	Yield
0.001 M	36%
0.010 M	90%
0.100 M	90%

With other iodinated derivatives of phenylalanine, we found that iodophenylalanine itself, monoiodotyrosine methyl ether and diiodotyrosine methyl ether all gave high yields of the desired diphenyl thioethers as shown below. Furthermore, either the acid or the amine functionality could be left unprotected without substantially effecting of the product yield. Only the phenolic hydroxyl of iodotyrosine could not go unprotected as noted previously[7] with $S_{RN}1$ coupling studies of iodophenol derivatives.

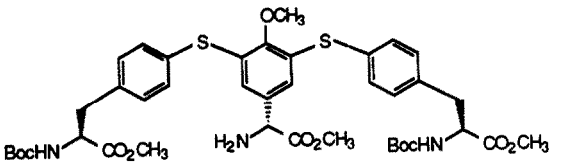


While racemization does not appear to be a problem under the coupling conditions with derivatives of phenylalanine, iodophenylglycine couplings present much more of a problem. For example, when the diiodohydroxyphenylglycine derivative **4** (R = BOC)[8] was coupled with thiophenol under standard conditions in liquid ammonia, the product (**5**, R = BOC) obtained in 81% yield was completely racemized. This finding could be a serious problem for synthetic efforts using phenylglycine derivatives since examination of the system revealed that both the starting material and the product were rapidly racemized in liquid ammonia at -33° C. It is known, however, that the rate of racemization of



4 **5**

aminoacid derivatives is highly dependent on the nature of the nitrogen protecting group and is highest when the protected nitrogen is least basic. We therefore coupled the free base (**4**, R = H) with thiophenol and obtained a 96% yield of **5** ($[\alpha]_D$ (0.7M, MeOH) = -71^0) which was shown to be at least 95% enantiomerically pure. Similar results were obtained with **2** (R = Me) which led in >95% yield to the structure below which shows remarkable similarity to the bisdiphenyl ether substructure of ristocetin.[9]



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5. E. Escher, M. Bernier and P. Parent, Helv. Chim. Acta, 1355 (1983). The p-mercaptophenylalanine thus prepared was shown to be formed with less than 5% racemization by coupling the N,S-diBOC derivative with both D and L alanine t-butyl ester to yield two diastereomeric dipeptides. For $S_{RN}1$ coupling, the free thiol was prepared from the disulfide by reduction (Ph_3P, H_2O).

6. General Procedure: A 1:1.3 molar ratio of iodide and mercaptan was dissolved in liquid ammonia to give a 10mM solution. After stirring for 1 hr at -33^0 C with continuous irradiation from a 275 watt sunlamp, the ammonia was allowed to evaporate and the residue chromatographed on silica gel.

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8. Compound **4** (R = BOC, $[\alpha]_D$ (1M, CH_2Cl_2) = -95^0) was prepared with less than 5% racemization (by alanine diastereomer test) from D-hydroxyphenylglycine by iodination (ICl, HOAc; 78%) and protection (1. BOC_2O, Na_2CO_3; 2. MeI, NaOH, phase transfer catalyst; 64%).

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