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A Surprising Observation about Mitsunobu Reactions in Solid Phase Synthesis

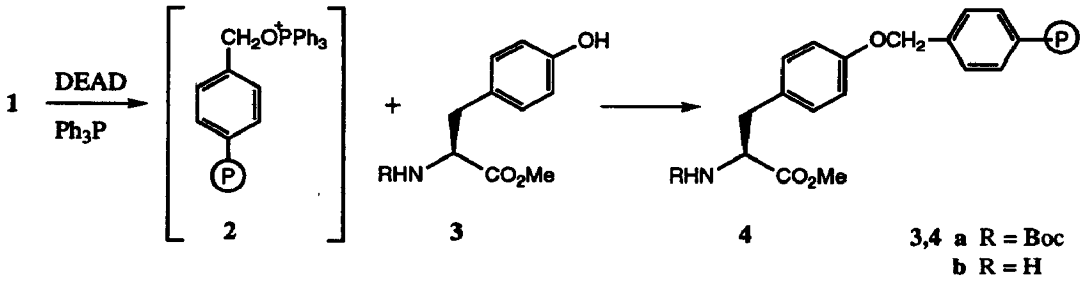
Lutz S. Richter[*‡] **and Thomas R. Gadek**
Department of Bioorganic Chemistry
Genentech, Inc.
390 Point San Bruno Boulevard
South San Francisco, CA 94080

Abstract: The Mitsunobu reaction of N-Boc-L-Tyrosine methyl ester with hydroxymethyl polystyrene resin proceeds in practically quantitative yield in the presence of a tertiary amine. Coupling yields in the absence of an amine are significantly lower.

Attachments of the side chains of amino acids (e.g. of Asp and Glu with suitably protected α-carboxylate) have been used for head-to-tail cyclizations of peptides on solid support.[1] For similar reasons, we were interested in the attachment of the phenolic side-chain of derivatives of L-tyrosine. Since all our attempts to couple N-Boc-L-tyrosine methyl ester **3a** to chloromethyl polystyrene resin via S_N2-reaction went unsatisfactory,[2] we focussed our attention on the Mitsunobu reaction of the phenol group with hydroxymethyl polystyrene resin **1** (Scheme 1).

Although the racemization-free attachment of the α-carboxylate of N-Boc-protected cysteines and methionines to hydroxymethyl polystyrene resin **1** has been reported,[3a] our initial attempts to couple the phenolic side-chain of **3a** or L-tyrosine methyl ester **3b** to **1** were unsatisfactory (entries 1, 2; Table 1).[3b]

Scheme 1



We were surprised to find that L-tyrosine methyl ester **3b**, despite the poor solubility of this compound in THF, gave better coupling yields than its N-Boc-derivative **3a**. Further investigations whether the free amino terminus accelerates the reaction confirmed that the yield of this Mitsunobu reaction is significantly higher in the presence of an amine, preferably a tertiary amine. The highest level of resin substitution was obtained when N-methylmorpholine was used as the solvent and the more soluble N-Boc-L-tyrosine methyl ester **3a** as the phenolic component. Under these conditions, we observed substitution levels of 0.90 meq/g[4] (Table 1).

Table 1

entry	solvent	R	substitution level
1	THF	Boc (**3a**)	0.16 meq/g
2	THF	H (**3b**)	0.28 meq/g
3	CH_2Cl_2	H	0.03 meq/g
4	Benzene	H	0.20 meq/g
5	THF / 0.1 Eq. DIEA	H	0.41 meq/g
6	NMM	H	0.68 meq/g
7	NMM	Boc	0.90 meq/g

The rate-determining steps of Mitsunobu esterifications have been shown to be either the alcohol activation or the S_N2-attack of the incoming nucleophile.[5] In our case, a tertiary amine should both facilitate the deprotonation of the alcohol prior to the PPh_3-transfer[6] and catalyze the formation of the phenolate thereby enhancing its nucleophilicity. Consequently, the overall rate of the reaction should be increased.

References and Notes:

‡Current address: Chiron Corporation, 4560 Horton Street, Emeryville, CA 94080

Abbreviations: Asp, aspartic acid: Boc, *tert.* butoxycarbonyl: DEAD, diethyl azodicarboxylate; DIEA, diissopropylethylamine; DMF, dimethyl formamide; Glu, glutamic acid:; NMM. N-methylmorpholine; PPh_3, triphenylphosphine; THF, tetrahydrofurane.

1. a) Trzeciak, A.; Bannwarth, W. *Tetrahedron Lett.* **1992**, *33*, 4557; b) Kates, S.A.; Solé, N.A.; Johnson, C.R.; Hudson, D.; Barany, G.; Albericio, F. *Tetrahedron Lett.* **1993**, *34*, 1549 and references cited therein.

2. Reactions of N-Boc-L-tyrosine methyl ester with chloromethyl polystyrene resin were performed with KF or $CsCO_3$ in DMF at 25°C, 40°C or 80°C or with potassium *tert.* butoxide in THF at 0°C or 25°C. All reactions that gave coupling yields of ≥25% lead to at least partial racemization of the starting material.

3. a) Stanley, M.: Tom, J.Y.K.; Burdick, D.J.; Struble, M.; Burnier, J.P., Poster presentation at the 12th American Peptide Symposium 1991, Cambridge, Massachusetts. b) Under otherwise identical conditions, the reaction of **3a** with benzyl alcohol instead of **1** goes to completion.

4. Diethylazodicarboxylate (3.0 equivalents) was added dropwise to a mixture of N-Boc-L-tyrosine methyl ester (3.0 eq.), triphenylphosphine (3.0 eq.) and hydroxymethyl polystyrene resin (1.0 eq., subst. level 1.08 meq/g) in 10 ml NMM/ g resin, and the mixture was shaken at 25°C for 16 h. The crude resin was washed with THF, methanol and dried. The reaction works equally fine for 1 mmol and 30 mmol of resin (cooling during DEAD-addition!) and proceedes without racemization of the starting material. The Boc-group was cleaved (45% trifluoroacetic acid, 45% dichloromethane, 5% thiocresol, 5% ethanedithiol), the resin was washed with 10% DIEA in CH_2Cl_2, and the substitution level was determined by picrate titration (Gisin, B. *Anal. Chim. Acta* **1972**, *58*, 248). Due to the increase in weight, a substitution level of 0.90 meq/g (for **4b**) corresponds to a coupling yield of 100%.

5. a) Hughes, D.L.; Reamer, R.A.; Bergan, J.J.; Grabowski, E.J.J. *J. Am. Chem. Soc.* **1988**, *110*, 6487; b) Hughes, D.L. *Org. Reactions* **1992**, *42*, 335.

6. For Mitsunobu esterifications, the rate of the formation of the triphenylphphosphine-adduct (**2**) increases significantly with the basicity of the carboxylate (see ref. 5a). The authors conclude that the rate of the formation of this intermediate is controlled by the basicity and the solvation of the acidic component.

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