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THE SYNTHESIS OF AMINO ACIDS BY PHASE-TRANSFER REACTIONS[1]

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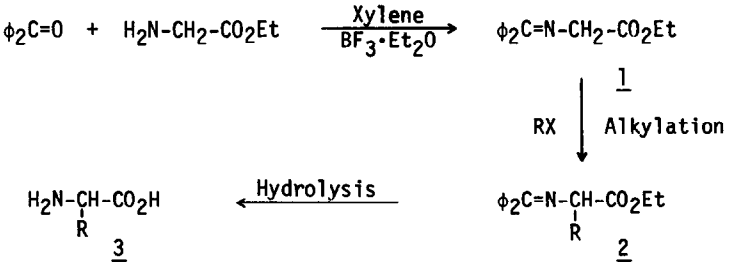
Several Schiff base derivatives of glycine have recently been used to prepare higher amino acids by alkylation routes.[2] A common problem with this procedure is the general instability of the imines derived from amino acid esters and carbonyl compounds, unless the carbonyl component contains an ortho hydroxy group which can stabilize the resultant Schiff base by chelate formation.[3] In addition, strong bases, low temperatures and anhydrous reaction conditions are commonly employed in such alkylations.

We would like to report the preparation and alkylation of a *stable* Schiff base (1) derived from glycine ethyl ester and benzophenone. Alkylation of 1 to form the protected amino acids



(2) is accomplished either by normal anhydrous alkylation procedures or by the novel use of phase-transfer reagents to effect alkylation in a two-phase system.[4,5] The alkylated Schiff bases (2) can then be hydrolyzed to the corresponding amino acids (3).

Schiff base 1 is prepared in 82% isolated yield by refluxing benzophenone with glycine ethyl ester in xylene which contains a trace of boron trifluoride etherate. The crude reaction product is distilled (flame, 185-195°C/2 mm Hg) and then recrystallized (ether/hexane) to give pure 1, mp = 49-50°C.[6] This product is stable in the air at room temperature for extended periods of time.[7]

Alkylation of 1 via anhydrous conditions was accomplished by adding the Schiff base in THF

to a preformed solution of lithium diisopropylamide (LDA) in THF at -78°C, using hexamethylphosphoramide (HMPA) as a cosolvent. The reaction mixture was stirred for one hour at -78°C, followed by addition of the alkyl halide in THF. After a further hour at -78°C, the temperature of the reaction mixture was slowly brought to 0°C and then the reaction mixture was poured into ice water. Normal extractive workup gave the alkylated Schiff bases in good yields (see Table).

In contrast to the anhydrous alkylations of 1, the alkylations using phase-transfer techniques are especially noteworthy because of their simplicity. A two-phase mixture of 1 (1 eq.), tetrabutylammonium hydrogen sulfate (TBAH) (1.2 eq.), alkyl halide (1.2-4 eq.), 10% aqueous sodium hydroxide and methylene chloride was stirred overnight at room temperature. The layers

$$\underset{\underline{1}}{\phi_2C{=}N\text{-}CH_2\text{-}CO_2Et} + RX \xrightarrow[10\%\ NaOH/CH_2Cl_2]{nBu_4\overset{+}{N}\ HSO_4^-} \underset{\underline{2}}{\phi_2C{=}N\text{-}\underset{\displaystyle R}{\underset{|}{C}}H\text{-}CO_2Et}$$

were separated and the organic layer was washed with saturated aqueous NaCl and dried. The solvent was removed and the residue was taken up in ether, filtered to remove the residual quaternary iodide and the solvent was removed to give the crude alkylation product. These products were chromatographed on grade V basic alumina (0.25% ethyl acetate in hexane) to give the pure monoalkylated Schiff bases 2.[6] (See Table) The alkylation products can be hydrolyzed to the corresponding amino acids by refluxing for six hours in concentrated hydrochloric acid.[2c] Alternatively, the imine functionality can be selectively hydrolyzed by stirring overnight with aqueous citric acid.[2b]

The phase-transfer alkylations of Schiff-base 1 provide a particularly attractive approach to the preparation of amino acid derivatives. The protecting and activating groups are easily introduced and removed and the starting substrate is a stable, crystalline compound. The phase-transfer alkylations of 1 involve the use of inexpensive starting materials, reagents and solvents and yield relatively clean reaction products, the major by-product being unreacted starting material when hindered halides are used. In all cases except benzyl, in which trace amounts of dialkylated products were seen, only monoalkylated products were observed. Finally, the simplicity of the reaction procedure combined with the possibility of recycling the phase-transfer

reagent and solvents imply that these reactions could readily be carried out on a large scale.

Further studies of the phase-transfer alkylations of this and related systems are in progress.

TABLE I. SCHIFF BASE ALKYLATIONS VIA ANHYDROUS CONDITIONS AND PHASE-TRANSFER REACTIONS

RX	% 2[a]		Amino Acid
	Anhydrous	Phase-Transfer	
CH_3I	93%	89%	Alanine
CH_3CH_2Br	87%	--	α-Amino Butyric Acid
CH_3CH_2I	--	77%	α-Amino Butyric Acid
ϕCH_2Br	85%	78%	Phenylalanine
$(CH_3)_2CHI$	73%	60%	Valine
$CH_3CH_2(CH_3)CHI$	65%	59%	Isoleucine

[a] Yields are of isolated monoalkylated products and have not been maximized.[6] Reactions were all run on a scale of 1.0 g of starting Schiff base (1). See text for experimental details.

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6 All new compounds gave elemental analyses and integrated NMR spectra in complete agreement with the assigned structures.

7 a) In contrast, the Schiff base formed from glycine ethyl ester and benzaldehyde was "stable in the freezer for several months," Ref 2c; b) We have prepared the Schiff base from glycine ethyl ester and acetophenone. This product can be recrystallized at low temperature (mp = 33-34°C), but as in the above case, it slowly decomposes even if kept at low temperature under argon. M.J. O'Donnell and G. Buchanan, unpublished results.