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THE SYNTHESIS OF AMINO ACID DERIVATIVES BY CATALYTIC PHASE-TRANSFER ALKYLATIONS[1]

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The current widespread interest in the preparation and utilization of amino acids,[2] "the building blocks of life," is based on their use in many diversified areas. For example, amino acids are employed as protein dietary supplements,[3] as drugs[4] and as starting materials for the synthesis of biologically active natural products.[5] New and general synthetic routes to the amino acids are, therefore, of interest for both the large-scale production of known amino acids as well as the preparation of rare and/or unknown amino acids.

Phase-transfer reactions[6] provide a potentially attractive synthetic route for the preparation of higher amino acids from derivatives of the simplest amino acid, glycine. We recently reported[7] the first general synthesis of amino acid derivatives using phase-transfer alkylations.[8,9] The Schiff base 1[7] is an active methylene compound in which both the carboxylate and

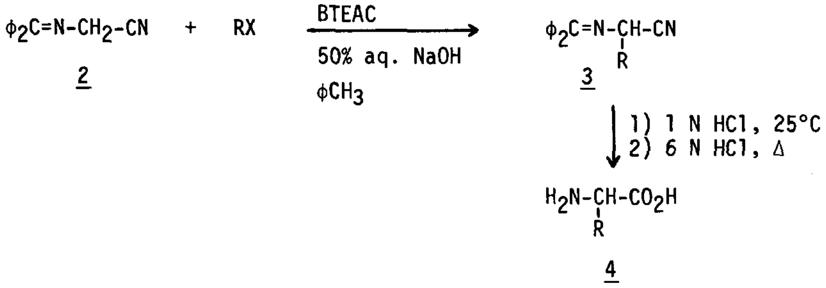
$\phi_2C=N-CH_2-CO_2Et$ 1

$\phi_2C=N-CH_2-CN$ 2

the amino group of glycine have been protected towards proton abstraction by groups which will stabilize an adjacent carbanion. Compound 1 can be alkylated using either conventional anhydrous conditions or by the novel use of phase-transfer alkylations.[7] The major restriction with this route is the need to use dilute aqueous hydroxide (10% aqueous NaOH) in order to avoid saponification of the ethyl ester. This, in turn, requires the use of a full equivalent of the phase-transfer reagent (Brändström's ion-pair extraction method[10]).

We would now like to report the preparation and *catalytic* phase-transfer alkylations of the protected glycine derivative $\underline{2}$. The Schiff base $\underline{2}$ is readily prepared by the condensation of benzophenone and aminoacetonitrile. Thus, a solution of benzophenone (2.0 eq.), aminoacetonitrile (1.0 eq.) (prepared from the hydrochloride), boron trifluoride etherate (0.05 eq.) and toluene is refluxed overnight with azeotropic removal of water. Extractive workup followed by distillation and recrystallization (carbon tetrachloride) yields the pure Schiff base $\underline{2}$ in 70% yield, mp = 83-4°C.[11]

The catalytic phase-transfer alkylations of $\underline{2}$ are carried out with benzyltriethylammonium chloride (BTEAC) as the phase-transfer catalyst and 50% aqueous sodium hydroxide as the aqueous phase (Makosza's phase-transfer catalytic method[12]):



$$\underset{\underline{2}}{\phi_2C{=}N{-}CH_2{-}CN} + RX \xrightarrow[\substack{50\%\ aq.\ NaOH \\ \phi CH_3}]{BTEAC} \underset{\underline{3}}{\phi_2C{=}N{-}\underset{R}{CH}{-}CN} \xrightarrow[2)\ 6\ N\ HCl,\ \Delta]{1)\ 1\ N\ HCl,\ 25^\circ C} \underset{\underline{4}}{H_2N{-}\underset{R}{CH}{-}CO_2H}$$

Only monoalkylated products (Table I) are obtained if an equivalent of the alkylating agent is added slowly to the ice-cooled reaction mixture. In general, the yields of alkylated products are higher by the catalytic phase-transfer method than with the ion-pair extraction method[7] (Table I). The corresponding amino acids ($\underline{4}$) can be obtained by hydrolysis of the alkylated products ($\underline{3}$) with hydrochloric acid.[13] A typical alkylation procedure follows:

Catalytic Phase-Transfer Alkylation of $\underline{2}$

Schiff base $\underline{2}$ (1.0 g, 4.5 mmoles), BTEAC (0.1 g, 0.4 mmoles), 50% aqueous NaOH (1.1 g, 14 mmoles) and toluene (1 ml) are placed in a round-bottom flask which contains a magnetic stirrer. The flask is stoppered and immersed in an ice-water bath. Ethyl bromide (0.4 ml, 5.4 mmoles) is added dropwise from a syringe over one to two hours to the above stirred solution. The reaction mixture is stirred for an additional two hours at 0°C and is then brought to room temperature and the reaction is continued for an additional twenty-four hours. The reaction mixture is poured into a separatory funnel which contains 20 ml of CH_2Cl_2 and 40 ml of H_2O. The layers are separated and the aqueous layers are washed with 3 x 10 ml CH_2Cl_2. The combined organic layers are washed with 3 x 10 ml H_2O and 1 x 10 ml saturated aqueous NaCl, dried ($MgSO_4$), filtered and the solvent is removed to yield 1.08 g (96%) of a yellow oil which is essentially pure alkylated product by NMR. Further purification by column chromatography using grade V basic alumina (hexane) gave 1.02 g (90%) of pure $\underline{3}$ ($R{=}CH_2CH_3$) as a colorless oil.

TABLE I. CATALYTIC PHASE-TRANSFER ALKYLATIONS OF SCHIFF BASE 2

RX	% 3[a,b]
$(CH_3)_2SO_4$	95% (89%)
CH_3CH_2Br	90% (77%)
$(CH_3)_2CHBr$	79% (60%)
$(CH_3)_2CHCH_2Br$	76% (65%)
$CH_3CH_2(CH_3)CHBr$	82% (59%)
ϕCH_2Cl[c]	75% (78%)

[a] Yields are isolated monoalkylated products.[11] See text for experimental details.

[b] Yields in parentheses are those obtained using the ion-pair extraction method with the Schiff base derived from benzophenone and glycine ethyl ester.[7]

[c] 30% aqueous NaOH.[14]

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13. We have found that the stepwise hydrolysis of the alkylated Schiff bases (*3*) gives better yields of the amino acids (*4*) than does the direct hydrolysis in refluxing 6 N hydrochloric acid. Thus, for example, the alkylated product (*3*, R = Et) was stirred at room temperature overnight in a two-phase mixture of aqueous hydrochloric acid (1 N) and pentane. The layers were separated and the aqueous layer was washed twice with pentane. The concentration of the aqueous solution was then adjusted to 6 N by adding concentrated hydrochloric acid and the resulting solution was refluxed for twelve hours. Workup and recrystallization gave pure α-aminobutyric acid (90% from *3*).

14. Alkylation with benzyl chloride and 50% aqueous NaOH gave *3* (R = ϕCH_2) in 60% isolated yield.

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