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SYNTHESIS OF AMINO ACIDS. ALKYLATION OF ALDIMINE AND KETIMINE DERIVATIVES OF GLYCINE ETHYL ESTER UNDER VARIOUS PHASE-TRANSFER CONDITIONS[1]

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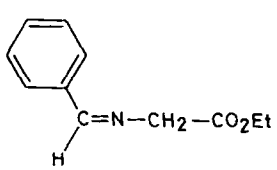
Abstract : The Schiff base derived from glycine ethyl ester and p-chlorobenzaldehyde can be alkylated by the ion-pair extraction method as well as under catalytic liquid-liquid or solid-liquid phase-transfer conditions. This imine is compared with the corresponding benzophenone Schiff base.

Alkylation of glycine synthons represents an attractive route for the synthesis of structurally diversified amino acids, especially when both L- and D- isomers are needed. Recently several examples of the direct alkylation of activated glycine esters have been described.[2] Initial studies have shown that the Schiff base 1 derived from benzaldehyde and glycine ethyl ester can be alkylated in the presence of strong bases under anhydrous condtions.[2a] A more practical method involves the alkylation of the very stable Schiff base 2, prepared from benzophenone imine and glycine ethyl ester, under phase-transfer conditions.[3] Although this ketimine is readily available,[4] for practical considerations especially on a large scale, it would be even more convenient to alkylate aldimines derived from glycine esters. However, this could have presented difficulties due to the lower stability and acidity[5] of these Schiff bases.



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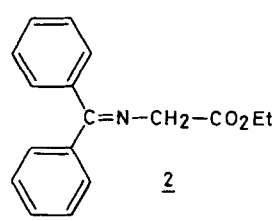

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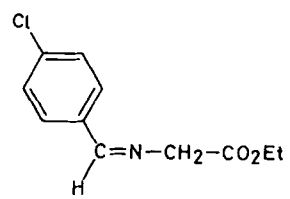

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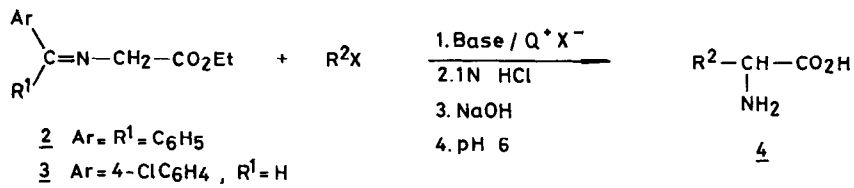
We would like to report our preliminary studies of the alkylation of the Schiff base derived from p-chlorobenzaldehyde and glycine ethyl ester using various phase-transfer techniques. Aldimine 3 has been chosen as the starting glycine synthon because it is a crystalline compound, in contrast to 1 which is an oil.



2 Ar = $R^1 = C_6H_5$

3 Ar = 4-ClC_6H_4 , $R^1 = H$

4

The results are presented in the Table. Three sets of conditions have been used:

1) Examples A to D were conducted under normal ion-pair extraction conditions,[6] which uses a full equivalent of the phase-transfer reagent and dilute aqueous hydroxide. We have previously shown that ketimine 2 can be efficiently alkylated under these conditions.[3] It is demonstrated that the method also applies to the aldimine 3. However, with less sterically demanding (C) or less reactive (D) alkyl halides, yields were slightly lower due to side reactions. The best yields were obtained at 13°C; at lower temperatures the alkylation was too slow.
2) Experiments E-H were done using the *catalytic* liquid-liquid phase-transfer method. Such conditions (50% NaOH, catalytic Q^+X^-) are generally avoided in the presence of unhindered esters which can be readily saponified.[7] As can be seen, both Schiff bases 2 and 3 can be alkylated with active benzylic halides under these conditions, whereas with the less reactive alkyl halides, the yield of product is poor.
3) Examples I-L were conducted under *catalytic* solid-liquid phase-transfer alkylation conditions using solid potassium hydroxide as the base in methylene chloride. Once again both imines are alkylated efficiently with active halides. With less active halides, the benzophenone Schiff base 2 is the preferred starting material.

Although more work will have to be done in order to define the exact scope of this new process for amino acid synthesis, the present data clearly show that it provides an attractive alternative to the classical Sörensen method[8] in terms of simplicity, cost and overall yield. In addition, in several cases we have found that this method can be readily adapted for the larger scale (0.5 molar) preparation of amino acids.

Table : Phase-Transfer Alkylation of Imines 2 and 3[a]

	Imine	R^2X (eq.)	Q^+X^- (eq.)[b]	Base (eq.)	T(°C)	%4
A	3	4-ClC_6H_4-CH_2Br (1.0)	TBA (1.05)	10% NaOH (2.5)	13	94
B	3	1-$C_{10}H_7$-CH_2Br (1.0)	TBA (1.05)	10% NaOH (2.5)	13	91
C	3	CH_2=CH-CH_2Br (1.0)	TBA (1.0)	10% NaOH (2.5)	13	76
D	3	CH_3CH_2I (1.1)	TBA (1.0)	10% NaOH (2.5)	13	76
E	3	4-ClC_6H_4-CH_2Br (1.2)	TEBA (0.1)	50% NaOH (2.5)	13	73
F	3	$CH_3(CH_2)_5I$ (1.4)	TEBA (0.2)	50% NaOH (2.5)	20	18
G	2	4-ClC_6H_4-CH_2Cl (1.2)	TEBA (0.1)	50% NaOH (2.5)	20	86
H	2	$CH_3(CH_2)_7Br$ (4.0)	TEBA (0.1)	50% NaOH (2.5)	20	33
I	3	4-ClC_6H_4-CH_2Br (1.0)	TEBA (0.1)	KOH (2.0)[c]	20	71
J	3	$CH_3(CH_2)_5I$ (1.4)	TEBA (0.1)	KOH (2.0)	20	47
K	2	4-ClC_6H_4-CH_2Cl (1.2)	TEBA (0.1)	KOH (2.0)	20	80
L	2	$CH_3(CH_2)_7Br$ (4.0)	TEBA (0.1)	KOH (2.0)	20	74

[a] All reactions were conducted in CH_2Cl_2 using 3.0 g of starting Schiff base. For I-L, the CH_2Cl_2 was distilled from P_2O_5.

[b] TBA = Tetrabutylammonium hydrogen sulfate, TEBA = Benzyltriethylammonium chloride.

[c] Finely ground KOH pellets.

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