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Synthesis of α-Substituted and α,α-Disubstituted α-Amino acids by Controlled Mono- and Dialkylation of Ethyl N-Diphenylmethyleneglycinate

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Abstract: Ethyl N-diphenylmethyleneglycinate reacts with one equivalent of alkylating agents in the presence of powdered potassium carbonate to afford, after hydrolysis, monoalkylated glycine esters. A similar process using two equivalents of alkylating agents in the presence of powdered potassium hydroxide and a phase transfer catalysts gives, after hydrolysis, dialkylated glycine esters.

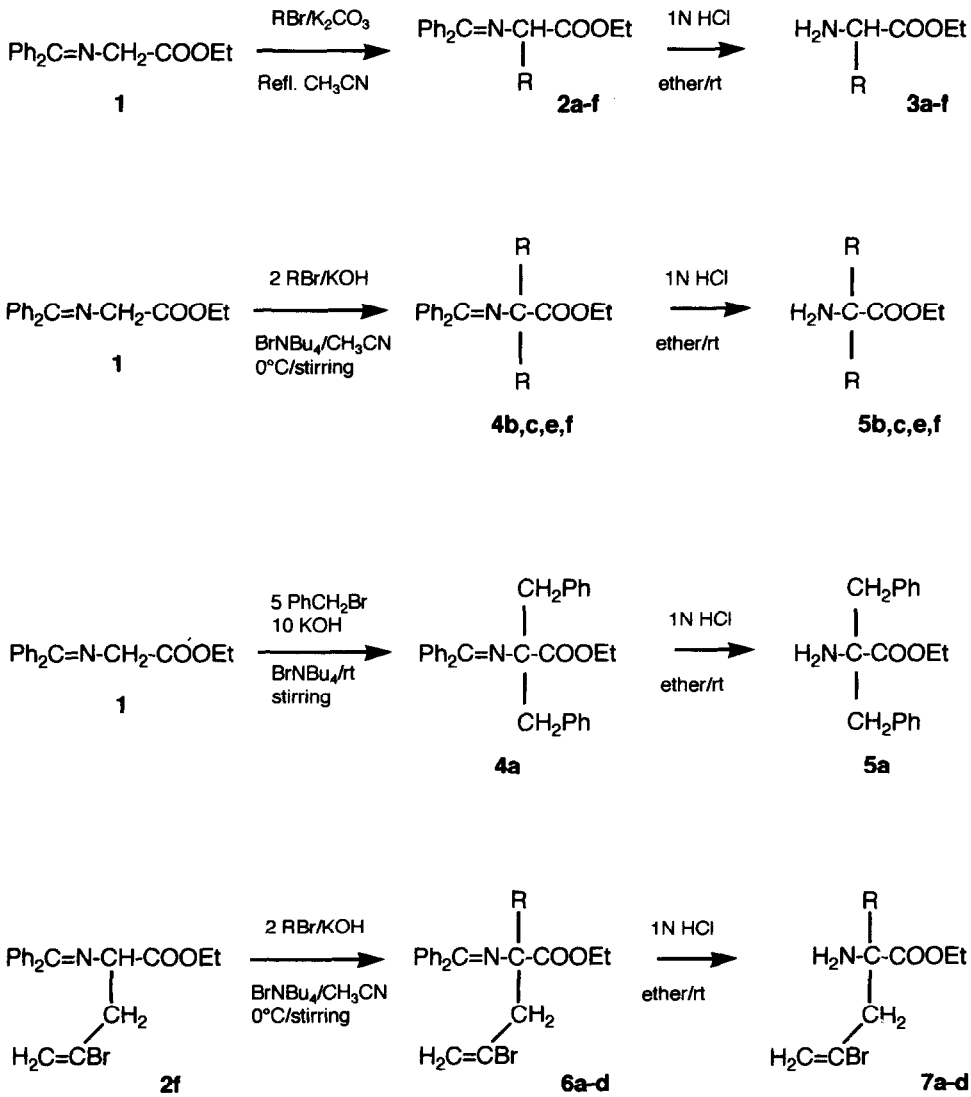
Aldimines of glycine esters are useful anionic synthons for the preparation of amino acids.[1] Their conjugate bases were initially formed by the action of strong bases such as LDA or t-BuOK.[2] Later, it was found that ketimines such as ethyl N-diphenylmethyleneglycinate, **1**, offer advantages due to its superior stability when compared with aldimines and that phase transfer catalysis proved very convenient for the monoalkylation of ketimine **1**.[3] The method has been extended and enantiomeric excesses have been obtained when using phase transfer catalysts based on enantiomerically pure natural alkaloids.[4]

From the work of O'Donnell and associates the view has emerged that useful dialkylations can only be achieved by using aldimines, mainly that from 4-chlorobenzaldehyde and alkyl glycinates. The more stable Schiff base, **1**, formed from benzophenone and ethyl glycinate is the reagent of choice for monoalkylation. This differential reactivity has been attributed to the decreased acidity of the monoalkylated ketimines **2**, thus preventing the required second ionization step.[5] These studies were based on benzyl bromide as alkylating agent

We now wish to report that it is possible to obtain useful yields of dialkylated products from ketimines.

Monoalkylation reactions of ketimine **1** were achieved in refluxing acetonitrile in the presence of powdered potassium carbonate as indicated in Table 1 and in Scheme 1. Potassium carbonate has been used in the past for ketimine **1** monoalkylation but in the presence of a phase transfer catalysts.[3f] However, we found the catalyst is not required and useful synthetic yields of monoalkylated ketimines **2** were obtained. Hydrolysis of products **2** gave amino esters **3**.

To our surprise, treatment of **1** with two equivalents of 2,3-dibromopropene in acetonitrile in the presence of powdered (a simple coffee-mill was used) potassium hydroxide at 0°C afforded the dialkylated ketimine **4f**, that upon hydrolysis gave the amino ester **5f** in 72% overall yield. Then, we decided to explore the scope of this reaction. Ketimines **4b,c** and **4e** were prepared and converted into amino esters **5b,c** and **5e**, thus indicating that dialkylations are in fact more general than initially expected. In complete agreement with


Ph2C=N-CH2-COOEt
1
RBr/K2CO3
Refl. CH3CN
Ph2C=N-CH-COOEt
R
2a-f
1N HCl
ether/rt
H2N-CH-COOEt
R
3a-f
2 RBr/KOH
BrNBu4/CH3CN
0°C/stirring
Ph2C=N-C-COOEt
4b,c,e,f
H2N-C-COOEt
5b,c,e,f
5 PhCH2Br
10 KOH
BrNBu4/rt
stirring
CH2Ph
4a
5a
H2C=CBr
2f
6a-d
7a-d

SCHEME I

O'Donnell's findings our initial attempts to dialkylkate **1** with two equivalents of benzyl bromide failed, only the monoalkylated ketimine **2a** being formed. However, after some experimentation we found that treatment of **1** with 5 equivalents of benzyl bromide and 10 equivalents of powdered potassium hydroxide at room temperature in the absence of any solvent afforded **4a** which was hydrolyzed to **5a** (24% overall yield). Product **5a** was contaminated with the corresponding benzyl ester. The rest of benzyl bromide had been transformed into dibenzyl ether. Therefore, it seems that the decreased acidity of **2a** is not the only factor that prevents double alkylations. The excess benzyl bromide reacts with sodium hydroxide to give benzyl alcohol, which as its alkoxide consumes more benzyl bromide to give dibenzyl ether. This alkoxide probably also causes transesterification. Transesterification was also observed in the formation of the diallyl derivative **5c**.

Table 1.- Alkylation of ketimines **1** and **2f**.

Ketimine	R	Amino ester (%)[a]	Mp or bp[b]	Lit. bp or analysis
1	$PhCH_2$-	**3a** (52)	150°C/3mm Hg	117-8°C/4mmHg[6]
1	$PhCH{=}CHCH_2$-	**3b** (59)	200-10°C/0.6mmHg	e
1	$CH_2{=}CHCH_2$-	**3c** (33)	110-5°C/16mmHg	80-5°C/10mmHg[7]
1	$HC{\equiv}CCH_2$-	**3d** (46)	125-30°C/16mmHg	90-100°C/13mmHg[8]
1	4-O_2NPhCH_2-	**3e** (92)	225-30°C/1.5mmHg	185-7°C/2.5mmHg[9]
1	$CH_2{=}CBrCH_2$-	**3f** (51)	155-60°C/13mmHg	e
1	$PhCH_2$-	**5a** (24)[c]	220-30°C/0.5mmHg	e
1	$PhCH{=}CHCH_2$-	**5b** (34)	oil (chromatography)	e
1	$CH_2{=}CHCH_2$-	**5c** (37)[d]	75-7°C/14mmHg	
1	4-O_2NPhCH_2-	**5e** (19)	Mp 154-5°C	e
1	$CH_2{=}CBrCH_2$-	**5f** (72)	140-50°C/0.6mmHg	e
2f	$PhCH_2$-	**7a** (33)	150-70°C/0.4mmHg	e
2f	$PhCH{=}CHCH_2$-	**7b** (25)	210-20°C/0.5mmHg	e
2f	$CH_2{=}CHCH_2$-	**7c** (23)	100°C/0.3mmHg	e
2f	$HC{\equiv}CCH_2$-	**7d** (40)	95-105°C/0.5mmHg	e

a) Overall yields from **1** or **2f** refer to isolated pure products. All compounds **3-7** showed spectrocopic behaviour as expected. b) oven temperature. c) Benzyl 2-benzylphenylalaninate[e] (mp 93-4°C, 9%), analogous to **5a**, was isolated. Dibenzyl ether was characterized by MS. d) GC-MS characterization in a mixture containing allyl 2-allyl-2-amino-4-pentenoate (5%). e) Correct elemental analysis for at least two elements and spectroscopic behaviour as expected.

We speculated that still another factor could be responsible for the reduced activity in dialkylation reactions. In fact the alkylation of **1** in the presence of potassium hydroxide requires the transfer of unsolvated (or nearly unsolvated) hydroxide anion to the organic phase; however when the first alkylation has occurred one equivalent of water has been formed that contributes to the solvation of the second equivalent of hydroxide anion. An excess of potassium hydroxide can help to overcome this effect provided that parallel reactions are maintained at an acceptable level. For these reasons we chose the particular conditions described in the Scheme for the preparation of **4a**.

Finally, we studied the possibility of introducing two different chains. Thus the monoalkylated ketimine **2f** was treated with a second alkylating agent under the same conditions as for the direct dialkylations. Dialkylated ketimines **6a-d** and from them dialkylated amino esters **7a-d** were obtained.

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