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Alkylation and Condensation Reactions of *N,N*-Dibenzylglycine Esters: Synthesis of α-Amino Acid Derivatives

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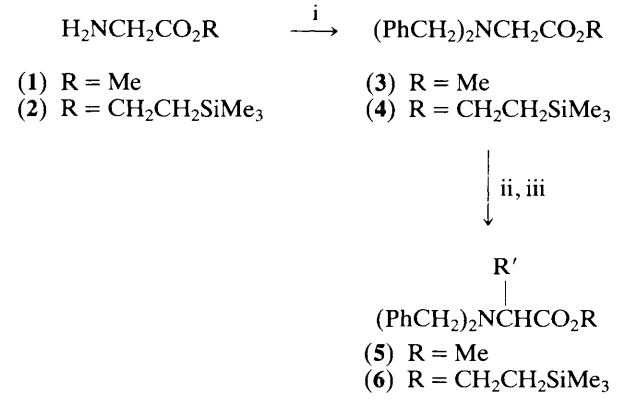
Upon deprotonation *N,N*-dibenzylglycine esters undergo alkylation and condensation reactions at the α-carbon atom with various electrophiles.

Various amino acid derivatives have been developed to allow alkylation[1] and condensation with carbonyl compounds[2] at the α-carbon atom. However, most of the amine protecting/activating groups used are either labile, and thus not compatible with multistep synthetic transformations, or difficult to remove selectively under mild conditions. During studies aimed at the synthesis of the biphenomycin class of antibiotics,[3] we required a glycine anion equivalent which could be selectively alkylated at the α-position and that had an amine protecting group stable to a range of synthetic transformations but removable selectively. We have found that the *N,N*-dibenzyl derivative (**3**) of glycine methyl ester (**1**), upon treatment with lithium di-isopropylamide, can be alkylated selectively or condensed with various electrophiles, according to Scheme 1.

N,N-Dibenzylglycine esters (**3**) and (**4**) were prepared from glycine methyl ester (**1**) and glycine 2-trimethylsilylethyl ester (**2**), respectively, by treatment with benzyl bromide (4 equiv.) and triethylamine (8 equiv.) in acetonitrile. The ester (**2**) was obtained by hydrogenation (10% palladium on carbon) of *N*-benzyloxycarbonyl-glycine trimethylsilylethyl ester[4] in methanol.

The alkylation or condensation reaction proceeds by deprotonation of (**3**) with lithium di-isopropylamide (1.2 equiv.) in tetrahydrofuran at −78 °C, followed by the sequential addition of hexamethylphosphoramide (2 equiv.) and the electrophile (1 equiv.). Reaction times at −78 °C were 2—5 h and the products were obtained pure† by work-up involving quenching with ammonium chloride, extraction (Et_2O), and chromatography (silica gel). Yields are given in Table 1.

The reaction of (**3**) or (**4**) with 1 equiv. of a primary alkyl bromide or iodide gave high yields of monoalkylated products. Dialkylated products were either minor or not detected. The low yield of (**5e**) from the alkylation of (**3**) with 2-iodopropane is attributed to the fact that a secondary iodide reacts sluggishly at −78 °C; therefore the mixture was allowed to warm to 0 °C in this case. An ester functionality may also be



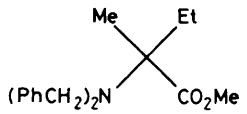
Scheme 1. *Reagents:* i, $PhCH_2Br$, Et_3N, ii, $LiNPr^i_2$, $PO(NMe_2)_3$, iii, electrophile R'^+.

Table 1. Products from reaction of *N,N*-dibenzylglycine ester enolates with electrophiles.

Electrophile	Glycine ester	Product	Yield (%)
$PhCH_2Br$	(**3**)	(**5a**) R′ = CH_2Ph	86
$H_2C{=}CHCH_2Br$	(**3**)	(**5b**) R′ = $CH_2CH{=}CH_2$	77
MeI	(**3**)	(**5c**) R′ = Me	80
$PhCH_2Br$	(**4**)	(**6a**) R′ = CH_2Ph	82
$HC{\equiv}CCH_2Br$	(**4**)	(**6b**) R′ = $CH_2C{\equiv}CH$	77
$BrCH_2CO_2Me$	(**3**)	(**5d**) R′ = CH_2CO_2Me	50
Pr^iI	(**3**)	(**5e**) R′ = Pr^i	40
PhCHO	(**3**)	(**5f**) R′ = CH(OH)Ph	87[a]
$[CH_2]_5CO$	(**3**)	(**5g**) R′ = $C(OH)[CH_2]_5$	85

[a] A 60 : 40 ratio of diastereoisomers.

† All new compounds exhibited satisfactory spectroscopic and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogenous materials.



(7)

present in the alkylating agent; thus reaction of (**3**) with methyl bromoacetate gave (**5d**), albeit in modest yield. The *N*,*N*-dibenzyl derivative of alanine methyl ester (**5c**) may also be used in alkylation reactions. For instance, alkylation of (**5c**) with ethyl iodide gave the α,α-dialkylated product (**7**) in 86% yield. α,α-Disubstituted α-amino acids are of interest because of their activity as specific enzyme inhibitors.[5] The anion of (**3**) was also condensed in separate reactions with benzaldehyde and cyclohexanone. These results parallel the work of Touzin[2d] who used *N*,*N*-dimethylglycine t-butyl ester in similar condensation reactions.

The *N*-benzyl groups can be removed by catalytic transfer hydrogenation using formic acid as the hydrogen donor.[6] Thus treatment of (**5a**) with an equal weight of palladium black (Aldrich) (under argon) in 4.4% formic acid/methanol over 2 h at room temperature gave a 90% yield of phenylalanine methyl ester hydrochloride (after neutralization and HCl work-up).

The use of the *N*,*N*-dibenzyl protecting group in the synthesis of α-amino acid derivatives complements other procedures in that the group is stable (thus enabling further synthetic transformations on the protected α-amino acids) and can be removed selectively by hydrogenation.

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References

1 (a) *via* α-isocyano esters: U. Schollkopf, D. Hoppe, and R. Jentsch, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 331; (b) benzylideneglycine esters: G. Stork, A-Y. W. Leong, and A. Touzin, *J. Org. Chem.*, 1976, **41**, 3491; (c) *N*-benzoylglycine (ester) *via* di- or tri-anion: A. P. Krapcho and E. A. Dundulis, *Tetrahedron Lett.*, 1976, **26**, 2205; (d) *via* α-[bis(alkylthio)methyleneamino] acid esters: D. Hoppe, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 426; (e) *via* tetramethyldisilylazacyclopentane adducts: S. Dijuric, J. Venit, and P. Magnus, *Tetrahedron Lett.*, 1981, **22**, 1787; (f) *via* amidine esters: J. J. Fitt and H. W. Gschwend, *J. Org. Chem.*, 1977, **42**, 2639; (g) *via* bis-lactim ethers: U. Schollkopf, U. Busse, R. Kilger, and P. Lehr, *Synthesis*, 1984, 271.

2 (a) *via* *N*,*N*-bis(trimethylsilyl)glycine trimethylsilyl ester: A. Shanzer, L. Somekh, and D. Butina, *J. Org. Chem.*, 1979, **44**, 3967; (b) *via* *N*-benzoylglycine ester: D. A. Evans and P. J. Sidebottom, *J. Chem. Soc., Chem. Commun.*, 1978, 753; (c) *via* benzylideneglycine ester: A. Calcagni, D. Rossi, and G. Lucente, *Synthesis*, 1981, 445; (d) *via* *N*,*N*-dimethylglycine ester: A. M. Touzin, *Tetrahedron Lett.*, 1975, **18**, 1477.

3 I. Uchida, N. Shigematsu, M. Ezaki, M. Hashimoto, H. Aoki, and H. Imanaka, *J. Antibiotics*, 1985, 1462.

4 P. Sieber, *Helv. Chim. Acta*, 1977, 2711.

5 T. L. Sourkes and A. D'Iorio, 'Metabolic Inhibitors,' ed. K. M. Hochster and J. H. Quastel, Academic Press, New York, vol. II, 1963, p. 79: W. G. Clark, *idem*, vol. I, 1963, p. 315.

6 B. ElAmin, G. M. Anantharamaiah, G. P. Royer, and G. E. Means, *J. Org. Chem.*, 1979, **44**, 3442.