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PREPARATION OF AN ELECTROPHILIC GLYCINE CATION EQUIVALENT AND ITS REACTION WITH HETEROATOM NUCLEOPHILES

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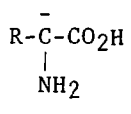
Abstract: A variety of heteroatom substituted Schiff base amino esters 4 - 7 are prepared either from the benzophenone imine of glycine ethyl ester (3) or by reaction of acetate 4 with heteroatom nucleophiles.

The development and application of new and practical methods for the preparation of structurally diversified amino acid derivatives is of fundamental importance because of the widespread use of these compounds in practically all areas of the physical and life sciences. During the past several years major synthetic efforts have focused on the reactions of various nucleophilic amino acid synthons 1 with electrophilic reagents.[1]



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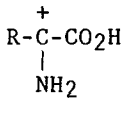
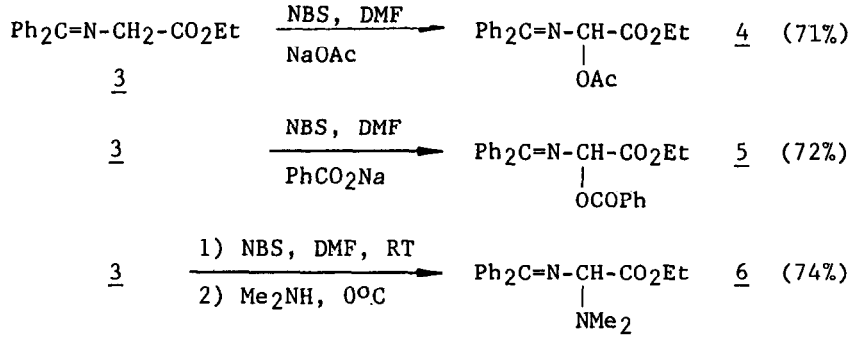


2

In comparison, there are considerably fewer general routes for the preparation of amino acid derivatives which involve the reaction of nucleophiles with cationic amino acid synthons 2.[2] Such methods would provide direct access to structural types of amino acid derivatives which cannot be directly prepared via 1. We would like to report the preparation and initial reaction studies of such a system.

The stable electrophilic glycine synthon 4 is prepared directly from the benzophenone imine of glycine ethyl ester 3[3] by bromination in the presence of

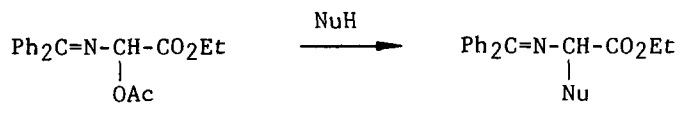


acetate.[4] Other α-heteroatom-substituted derivatives prepared similarly include the benzoate 5 and the dimethylamino derivative 6.[5,6]

A study of the reactions of the stable acetate 4 with various heteroatom nucleophiles was undertaken to better understand the chemistry of this multifunctional compound (Table). Alkoxy groups can be readily introduced (entries 1,2,4) by reaction with the neutral alcohol. Use of the stronger nucleophile ethoxide ion results in attack at the imine carbon (entry 3) which gives hydrolysis products. Phenoxy groups are not easily introduced (entries 6 and 7) although the thiophenoxy derivative is readily prepared by reaction with thiophenol (entry 8).[7] Primary alkyl amines yield the transimination product (entry 9) resulting from attack at the imine carbon while secondary amines do not react (entry 10). These results show that the acetate 4 is a sterically demanding electrophile with multiple potential sites for reaction.

The complimentary routes described from either the imine 3 or the acetate 4 provide ready access to several oxygen-, nitrogen- and sulfur-heteroatom substituted amino acid derivatives. We are currently exploring the further reactions and synthetic utility of the compounds reported here.[8]

TABLE. Reactions of the Acetate 4 with Heteroatom Nucleophiles.



4 7

Entry	NuH	Conditions[a]	Product (Yield)[b]
1	MeOH	R,1h	7a (91%)
2	EtOH	R,24h	7b (87%)
3	NaOEt	EtOH,RT,2h	$Ph_2C=O$
4	iPrOH	HOAc(1eq),R,96h	7c (65%)
5	tBuOH	HOAc(1eq),R,48h	$Ph_2C=O$
6	PhOH	iPrOH,HOAc(1eq),R,24h	$Ph_2C=O$+4
7	NaOPh	EtOH,RT,24h	$Ph_2C=O$
8	PhSH	Et_2O,RT,1h	7d (95%)
9	$nPrNH_2$	EtOH,RT,72h	$Ph_2C=NnPr$
10	Me_2NH	EtOH,0°C.,24h	$Ph_2C=O$

a R = reflux, RT = room temperature.
b Yield of isolated Schiff base derivative 7. All new compounds gave elemental analyses and proton NMR spectra consistent with the assigned structures.

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References and Notes

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2. Lead references involving electrophilic amino acid synthons: a) T. Shono, Tetrahedron, 40, 811 (1984); b) D. Ben-Ishai and S. Hirsch, Tetrahedron Lett., 24, 955 (1983); c) R. Kober, W. Hammes and W. Steglich, Angew. Chem., Int. Ed. Engl., 21, 203 (1982); d) C.H. Stammer, Chem. Biochem. Amino Acids, Pept., Proteins, 6, 33 (1982); e) C.G. Shin, Y. Sato, H. Ohmatsu and J. Yoshimuura, Bull. Chem. Soc. Jpn., 54, 1137 (1981); f) J.D.M. Herscheid, R.J.F. Nivard, M.W. Tijhuis, H.P.H. Scholten; and H.C.J. Ottenheijm, J. Org. Chem., 45, 1880 (1980); g) Y. Ozaki et al, J. Org. Chem., 44, 391 (1979).

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4. Preparation of ethyl-N-(diphenylmethylene)-2-acetoxyglycinate: a solution of N-bromosuccinimide (13.9 g, 78 mmol) dissolved in dry DMF (40 ml) was added dropwise at room temperature with stirring over three hours to a mixture of Schiff base 3 (16.05 g, 60 mmol), anhydrous sodium acetate (16.5 g, 201 mmol) and N,N-dimethylformamide (60 ml, distilled from calcium hydride) in a 500 ml round-bottom flask equipped with a magnetic stirrerand a dropping funnel ($CaCl_2$ tube). The mixture was stirred at room temperature overnight, poured into 100 ml of water, extracted with ether (3 X 75 ml), the ether extracts were washed with water (2 X 75 ml), dried ($MgSO_4$), filtered through a 3 cm pad of silica gel (Aldrich, grade 60, 22,719-6) and the solvent was removed in vacuo. The resulting yellow oil was recrystallized from ether/ligroin (bp 35-60°C.) to yield 4 (13.7 g, 71%), mp: 62-5°C. This product can be stored in the freezer under argon for several months.

5. In addition to being of interest as potential intermediates for the preparation of higher amino acids and amino acid derivatives, α-heteroatom-substituted amino acid derivatives are also structural elements of several naturally occuring compounds: a) peptide ergot alkaloids - H.G. Floss, Tetrahedron, 32, 873 (1976); b) β-lactam antibiotics - "Chemistry and Biology of β-Lactam Antibiotics," Vol. 1-3, R.B. Morin and M. Gorman, Eds., Academic Press, N.Y., 1982. c) mould metabolites - U. Schmidt, Pure Appl. Chem., 49, 163 (1977); d) bicyclomycin - R.M. Williams, J.S. Dung, J. Josey, R.W. Armstrong and H. Meyers, J. Am. Chem. Soc., 105, 3214 (1983)

6. For similar reactions with amides and related compounds, see: a) H. Böhme and M. Haake in "Iminium Salts in Organic Chemistry," Advances in Organic Chemistry, Vol. 9, Part 1, E.C. Taylor, Series Ed., H. Böhme and H.G. Viehe, Eds., Wiley, N.Y., 1976, pp. 173-5; b) H.E. Zaugg, Synthesis, 85, 181 (1984).

7. Attempted preparation of the thiophenoxy compound via the anion of 3 (LDA, THF, -78 C. then addition of PhSSPh) resulted in mixtures of products and starting material although the corresponding pyridyl thioether (7, Nu = -S-2-Pyr) was prepared in 40% yield from the anion and 2,2'-dipyridyl disulfide.

8. M.J. O'Donnell and J.B. Falmagne, Tetrahedron Lett., following paper.

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