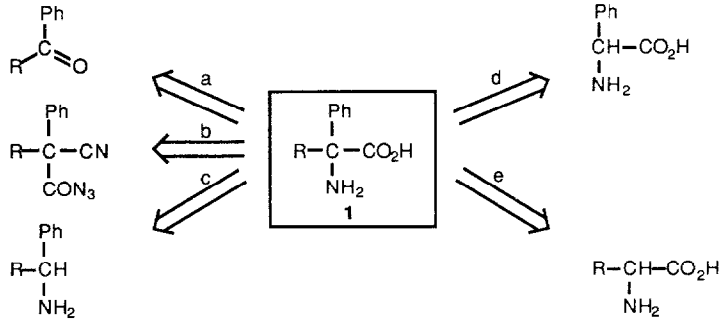
Tetrahedron Letters,Vol.30,No.30,pp 3913-3914,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

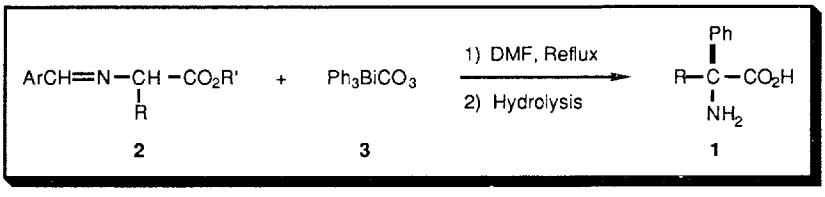
PHENYLATION OF AMINO ACID DERIVATIVES: A NEW ROUTE TO α-PHENYL-α-SUBSTITUTED AMINO ACIDS

Martin J. O'Donnell,* William D. Bennett , William N. Jacobsen and You-an Ma
Department of Chemistry
Indiana-Purdue University at Indianapolis
Indianapolis, IN 46223 USA

α-Phenyl-α-alkyl amino acids **1**, which have been used for a variety of chemical and biological purposes, have been prepared by several different routes: (a) Strecker or Bucherer-Berg syntheses from the ketone;[1] (b) construction of the C_α-NH_2 bond by rearrangement;[2] (c) formation of the C_α-CO_2H bond;[3] and (d) C_α-C_β bond formation by alkylation or carbonyl addition to the anion of a protected phenylglycine.[4] Construction of the C_α-$C_{\beta(phenyl)}$ bond by phenylation of the anion of a protected α-alkyl amino acid (route e, nucleophilic aromatic substitution) has not been reported.[5]



The preceding paper[6] describes the selective monophenylation of a glycine derivative protected as its benzophenone imine using Barton's phenylating reagent, triphenylbismuth carbonate (**3**).[7] Extension of this methodology to phenylation of an arylidene imine derivative of a monoalkyl amino acid **2** should allow *selective introduction of a phenyl group into such active methine compounds to yield the disubstituted product*, thereby providing a general synthesis of the α-phenyl α-substituted amino acids (**1**). Phenylation (route e) is accomplished by reacting **2** with an excess of triphenylbismuth carbonate in refluxing dimethylformamide.[8] As in the related



2 **3** **1**

alkylation chemistry of compounds **2**,[9] the intermediate disubstituted Schiff base esters are generally not isolated, but are hydrolyzed directly to the amino acid products **1**, which are obtained in 21-54% overall yield (see Table).

Table: α-Phenyl-α-Substituted Amino Acids Prepared by Phenylation of Imine **2**

	Imine **2**[a,b]			Product Amino Acid **1**[a,c]	
Entry	Ar	R	R'	R	Overall Yield
a	$4\text{-ClC}_6\text{H}_4$	Me	Et	Me	54%
b	Ph	"	"	"	46%
c	$4\text{-ClC}_6\text{H}_4$	$4\text{-ClC}_6\text{H}_4\text{CH}_2$	"	$4\text{-ClC}_6\text{H}_4\text{CH}_2$	28%
d	"	$n\text{C}_8\text{H}_{17}$	Me	$n\text{C}_8\text{H}_{17}$	21%
e	"	Ph	Et	Ph	32%
f	"	$\text{CH}_2\text{=CHCH}_2$	"	$\text{CH}_2\text{=CHCH}_2$	37%
g	"	PhCH_2	"	PhCH_2	36%
h	"	Et	"	Et	36%
i	"	MeO_2CCH_2	Me	HO_2CCH_2	33%
j	"	$\text{EtO}_2\text{CCH}_2\text{CH}_2$	Et	$\text{HO}_2\text{CCH}_2\text{CH}_2$	45%

[a] All new starting materials **2** and amino acid products **1** gave satisfactory elemental or high resolution mass spectral analyses as well as ^{1}H NMR spectra consistent with the assigned structures. [b] Imines **2** are oils except **2i**, mp 56-8 °C. [c] New amino acids: **1d**, mp 237-8 °C; **1f**, mp 245-6 °C.

Acknowledgement. We gratefully acknowledge the National Institutes of Health (GM28193) for support of this research. Support for our ongoing collaboration with the laboratory of Prof. L. Ghosez in Belgium by the North Atlantic Treaty Organization is acknowledged. We also thank Dr. W. Motherwell and Prof. M.Makosza for helpful discussions.

REFERENCES

1. a) R.E. Steiger, *Org. Syntheses*, Coll. Vol. 3, 1955, 88; b) Y. Shi, X. Sun, H. Zhu and Y. Jiang, *Gaodeng Xuexiao Huaxue Xuebao*, 1981, **2**, 455 (*Chem. Abstr.*, 1982, **97**: 71906p); c) D.D. Dodsworth, S.V. Pekerar, R. Requiz, P. Fiedler, J.A. Garbarino and M. Piovano, *Rev. Latinoam. Quim.*, 1985, **16**, 37 (*Chem. Abstr.*, 1985, **103**:215748f); d) S.D. Upham and O.C. Dermer, *J. Org. Chem.*, 1957, **22**, 799; e) L.H. Goodson, I.L. Honigberg, J.J. Lehman and W.H. Burton, *J. Org. Chem.*, 1960, **25**, 1920.
2. J. Knabe and C. Urbahn, *Liebigs Ann. Chem.*, 1971, **750**, 21.
3. a) M. Rai, A. Singh and P.S. Kalsi, *Indian J. Chem.*, 1979, **18B**, 273; b) T. Iwasaki and K. Harada, *Bull. Inst. Chem. Res.*, Kyoto Univ., 1983, **61**, 72 (*Chem. Abstr.* 1984, **100**:121561a).
4. a) W. Hartwig and U. Schöllkopf, *Liebigs Ann. Chem.*, 1982, 1952; b) M.J. O'Donnell, W. Bruder, K. Wojciechowski, L. Ghosez, M. Navarro, F. Sainte and J.-P. Antoine, *Peptides: Structure and Function, Proc. 8th Amer. Pept. Symp.*, V.J. Hruby and D.H. Rich, Eds., Pierce Chemical Co., Rockford, IL, 1983, p 151; c) Z.J. Kaminski, M.T. Leplawy and J. Zabrocki, *Synthesis*, 1973, 792; d) A. Calcagni, D. Rossi and G. Lucente, *Synthesis*, 1981, 445.
5. For an electrophilic aromatic substitution involving reaction of an electrophilic α-alkyl amino acid equivalent with Ph^-, see: B.H. Lipshutz, B. Huff and W. Vaccaro, *Tetrahedron Lett.*, 1986, **27**, 4241.
6. M.J. O'Donnell, W.D. Bennett , W.N. Jacobsen, Y.-a. Ma and J.C. Huffman, *Tetrahedron Lett.*, preceeding paper.
7. a) D.H.R. Barton, J.-C. Blazejewski, B. Charpiot, J.-P. Finet, W.B. Motherwell, M.T.B. Papoula and S.P. Stanforth, *J. Chem. Soc. Perkin Trans. 1*, 1985, 2667 and cited references; b) For selective N-phenylation of α-amino acid derivatives, see: D.H.R. Barton, J.-P. Finet and J. Khamsi, *Tetrahedron Lett.*, 1989, **30**, 937.
8. General Experimental Procedure: to an oven dried 50 mL round-bottom flask equipped with a magnetic stirring bar were added amino ester Schiff base **2** (2.0 mmol), triphenylbismuth carbonate **3** (1.0 g, 2 mmol), and DMF (10 mL). A reflux condenser equipped with a CaSO_4 drying tube was attached and the flask was placed in a preheated heating mantle. The mixture was refluxed with stirring for 15 minutes. The mixture was cooled 1-2 minutes and additional triphenylbismuth carbonate (0.5 g, 1 mmol) was added and the mixture was refluxed an additonal 15 minutes. This procedure was repeated until 3-5 equivalents of triphenylbismuth carbonate had been added. The flask was cooled to room temperature and the reaction mixture was worked up to provide the amino ester as before (reference 6). The amino acid ester was dissolved in aqueous HCl (20 mL of 6 N solution, 120 mmol) and the solution was refluxed for one hour. The solution was concentrated *in vacuo* and then lyophilized to yield a white solid, which was dissolved in absolute ethanol (10 mL). Propylene oxide (2 mL) was added and the mixture was refluxed for 15 minutes. The resulting white solid was recrystalized from ethanol/water to yield the amino acid.
9. M.J. O'Donnell, B. LeClef, D.B. Rusterholz, L. Ghosez, J.-P. Antoine and M. Navarro,, *Tetrahedron Lett.*, 1982, **23**, 4259.

(Received in USA 23 February 1989)