Tetrahedron Letters,Vol.30,No.8,pp 937-940,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

N-PHENYLATION OF AMINO ACID DERIVATIVES

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Abstract *: The selective mono N-phenylation of α-amino acid derivatives has been performed with triphenylbismuth diacetate in the presence of a catalytic amount of copper metal or copper diacylate.*

The synthesis of N-phenyl α-amino acid derivatives can be performed by reaction of aniline with α-haloesters and α-halonitriles[1], or with α-trifluoromethylsulphonyloxy esters[2]. Bis-silyl ketene acetals react with nitrosobenzene to give silylated α-hydroxyamino acid silyl esters, which can be reduced to the amino acids[3]. Direct arylation of α-amino acid derivatives is only possible with aryl halides substituted by strongly electron-withdrawing groups[4], with *ortho* -quinones[5] or with 2-naphthol under the Bucherer reaction conditions[6]. Only a limited range of N-phenyl derivatives of natural α-amino acids is accessible by these procedures.

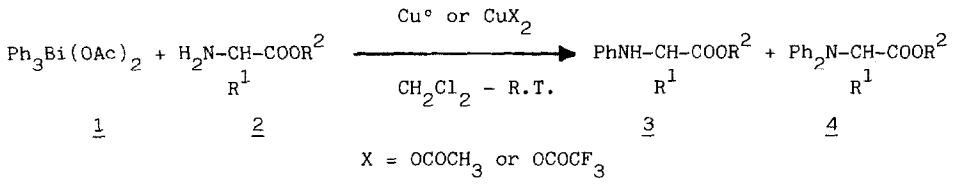
Aliphatic and aromatic primary and secondary amines are mono- or di-N-phenylated by triphenylbismuth diacylate under copper catalysis in a mild, selective and high-yielding reaction[7].

$$R\text{-}NH_2 + Ph_3Bi(OCOR)_2 \xrightarrow[CH_2Cl_2 - R.T.]{Cu^\circ \text{ or } CuX_n} R\text{-}NHPh + R\text{-}NPh_2$$

Mechanistic studies have shown that these copper catalysed reactions do not involve free radical intermediates. The catalytic species is a Cu(I) derivative which is prone to an oxidative aryl addition. The Cu(III) species then transfers its phenyl group to the nitrogen atom in a reductive fragmentation reaction.

$$Ph_3Bi(OAc)_2 + CuX + R\text{-}NH_2 \longrightarrow Ph\text{-}\underset{\uparrow}{Cu}(X)OAc \longrightarrow R\text{-}NHPh + CuX$$
$$R\text{-}NH_2$$

The efficiency and mildness of this procedure led us to apply it to the phenylation of α-amino acids and their derivatives. In preliminary experiments, the reaction of free amino acids with $Ph_3Bi(OAc)_2$ met with complete failure. But when the acid function was protected as an ester, N-phenylation occurred smoothly and efficiently.



The phenylation reaction can be performed with 1 in the presence of metallic copper directly on the salts of the amino-esters. The yields are modest to moderate (Table 1).

Table 1 - Phenylation of Amino Ester Salts 2 with 1 and Cu°

R^1	R^2	Acid	3 (%)
H	Et	HCl	16
$Ph-CH_2$	Bzl	p-TsOH	60
$BzlO_2C-CH_2$	Bzl	p-TsOH	45
$BzlO_2C-(CH_2)_2$	Bzl	p-TsOH	22

Reaction Conditions : 1 (1 eq.), Cu metal (0.1 eq.), CH_2Cl_2, R.T., 20 h

However, when the reactions were performed with the free amino esters, the yields of N-phenylated derivatives were greatly increased (Table 2).

Table 2 - Phenylation of Free Amino Esters 2 with 1 and Cu°

R^1	R^2	1 (eq.)	Reaction Time (h)	3 (%)	4 (%)
H	Et	1	20	81	4
H	Et	2.2	20	0	85
$PhCH_2$	Bzl	1	48	80	0
$PhCH_2$	Bzl	2.2	48	90	8
$BzlO_2C-CH_2$	Bzl	1	24	50	0
$BzlO_2C-CH_2$	Bzl	2.2	24	92	0
$BzlO_2C-(CH_2)_2$	Bzl	1	48	58	0
$BzlO_2C-(CH_2)_2$	Bzl	2.2	48	75	9

Reaction Conditions : Cu metal (0.1 eq.), CH_2Cl_2, R.T.

The mono-N-phenylation generally occurred, although with glycine ethyl ester, the mono- and the di-N-phenylation were selectively obtained, depending on the amount of 1. In other cases, use of an excess of phenylating agent 1 led only to increased yields of the

mono-N-phenyl derivatives. Bibasic amino acid ester, such as histidine or arginine methyl ester were not phenylated.

The nature of the copper derivative used as catalyst does not modify the yield of N-phenylamino esters. Thus, reaction of α-amino esters with $Ph_3Bi(OAc)_2$ 1 and copper diacetate 5 or copper bis-trifluoroacetate 6 gave similar results (Table 3).

Table 3 - Phenylation of Free Amino Esters 2 with 1 in the Presence of Copper Salt 5 or 6

R^1	R^2	1 (eq.)	Copper Salt	Reaction Time (h)	3 (%)	4 (%)
$PhCH_2$	Bzl	1	5	24	80	
$PhCH_2$	Bzl	1	6	24	84	2
$BzlO_2C-CH_2$	Bzl	1	5	22	52	
$BzlO_2C-CH_2$	Bzl	2.2	5	22	76	20
$BzlO_2C-CH_2$	Bzl	2.2	6	22	77	20

Reaction Conditions : Copper Salt (0.1 eq.), CH_2Cl_2, R.T. ; 5 = $Cu(OAc)_2$; 6 = $Cu(OCOCF_3)_2$

The synthesis of the bis-N-phenyl derivatives 4 was more difficult. Reaction of 1 (1.5 eq.) and 6 (0.1 eq.) with the mono-N-phenyl derivatives 3 of phenylalanine, aspartic acid and glutamic acid for 20 h. at room temperature led to the corresponding N,N-diphenyl derivatives in yields of 27, 30 and 29% respectively.

These results show that by proper choice of the reaction conditions, good to high yields of the mono-N-phenyl amino esters can be obtained. With the range of available triarylbismuth[8] and the easy synthesis of the pentavalent triarylbismuth diacylates[9], this method provides an easy and mild access to a wide range of N-aryl α-amino esters.

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10 - Physical data of compounds 3 : *a)* R^1=H, R^2=Et : m.p. 56-57°C, lit.[12] 57°C. *b)* R^1=$C_6H_5CH_2$, R^2=$C_6H_5CH_2$: m.p. 60-62°C ; IR ($CHCl_3$) cm^{-1} : 3400, 1730, 1600. NMR ($CDCl_3$) δ : 7.5-6.55(15H, m, ArH), 5.09(2H, s, OCH_2), 4.23(1H, t, N-CH), and 3.13(2H, d, CH-CH_2). $[\alpha]_D$ + 16.5° (c 0.034, $CHCl_3$). MS m/z : 331(M^+). $C_{22}H_{21}NO_2$ calculated C, 79.75 ; H, 6.34 ; N, 4.22 ; O, 9.66. Found C, 79.90 ; H, 6.19 ; N, 4.22 ; O, 9.53%. *c)* R^1=$C_6H_5CH_2O_2C$-CH_2, R^2=$C_6H_5CH_2$: m.p. 91-93°C. IR ($CHCl_3$) cm^{-1} : 3390, 1720, 1600. NMR ($CDCl_3$) δ : 7.54-6.5(15H, m, ArH), 5.18 and 5.14(2x2H, 2s, $OCH_2C_6H_5$), 4.58(1H, t, N-CH, and 2.95(2H, d, CH-CH_2). $[\alpha]_D$ + 4.9° (c 0.029, $CHCl_3$). MS m/z : 389(M^+). $C_{24}H_{23}NO_4$ calculated C, 74.03 ; H, 5.91 ; N, 3.59 ; O, 16.45. Found C, 73.88 ; H, 5.85 ; N, 3.39 ; O, 16.34%. *d)* R^1 = $C_6H_5CH_2O_2C$-$(CH_2)_2$, R^2 = $C_6H_5CH_2$: oil. IR : ($CHCl_3$) cm^{-1} : 3400, 1720, 1600. NMR ($CDCl_3$) δ : 7.5-6.5(15H, m, ArH), 5.16 and 5.13(2x2H, 2s, O-$CH_2C_6H_5$), 4.2(1H, t, CH-CH_2), and 2.66-2.06(4H, m, CH_2-CH_2). $[\alpha]_D$ + 15.53°(c 0.030, $CHCl_3$). MS m/z : 403(M^+). $C_{25}H_{25}NO_4$ calculated C, 74.44 ; H, 6.2 ; N, 3.47 ; O, 15.88. Found C, 74.68 ; H, 6.13 ; N, 3.30 ; O, 15.64%.

11 - Physical data of compounds 4 : *a)* R^1=H, R^2=Et : oil. IR ($CHCl_3$) cm^{-1} : 1740, 1600. NMR ($CDCl_3$) δ : 7.46-6.86 (10 H, m, ArH), 4.43 (2H, s, N-CH_2), 4.16 (2H, q, CH_2-CH_3), 1.2 (3H, t, CH_2-CH_3). MS m/z : 255 (M^+). $C_{16}H_{17}NO_2$ calculated C, 75.29 ; H, 6.66 ; N, 5.49 ; O, 12.55. Found C, 74.98 ; H, 6.54 ; N, 5.33 ; O, 12.51%. *b)* R^1=C_6H_5-CH_2, R^2=$C_6H_5CH_2$: oil. IR ($CHCl_3$) cm^{-1} : 1725, 1600. NMR ($CDCl_3$) : 7.4-6.7 (20H, m, ArH), 5.14 (2H, s, OCH_2), 4.83 (1H, t, N-CH-CH_2), 3.26 (2H, d, CH-CH_2). MS m/z : 407 (M^+). $C_{28}H_{25}NO_2$ calculated C, 82.85 ; H, 6.14 ; N, 3.44 ; O, 7.86. Found C, 82.45 ; H, 6.14 ; N, 3.33 ; O, 7.71%. *c)* R^1=$C_6H_5CH_2O_2CCH_2$, R^2=$C_6H_5CH_2$: oil. IR ($CHCl_3$) cm^{-1} : 1735, 1590. NMR ($CDCl_3$) δ : 7.3-6.7 (20H, m, ArH), 5.25 (1H, t, CH-CH_2), 5.08 and 5.02 (2x2H, 2s, $OCH_2C_6H_5$), 3.08 (2H, d, CH-CH_2). MS m/z : 465 (M^+). $C_{30}H_{24}NO_4$ calculated C, 77.42 ; H, 5.80 ; N, 3.01 ; O, 13.76. Found C, 77.42 ; H, 5.87 ; N, 2.97 ; O, 13.52%. *d)* R^1=$C_6H_5CH_2O_2C$-$(CH_2)_2$, R^2=$C_6H_5CH_2$: oil. IR ($CHCl_3$) cm^{-1} : 1730, 1600. NMR ($CDCl_3$) δ : 7.46-6.7 (20H, m, ArH), 5.13 and 5.06 (2x2H, 2s, O-$CH_2C_6H_5$), 4.76 (1H, t, N-CH), 2.56-2.16 (4H, m, CH_2-CH_2). $[\alpha]_D$ + 32.57° (c 0.016, $CHCl_3$). MS m/z : 479 (M^+). $C_{31}H_{29}NO_4$ calculated C, 77.66 ; H, 6.05 ; N, 2.92 ; O, 13.36. Found C, 77.40 ; H, 6.22 ; N, 2.75 ; O, 13.30%.

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(Received in France 30 November 1988)