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N-Silylation of amines and amino acid esters under neutral conditions employing TMS-Cl in the presence of zinc dust

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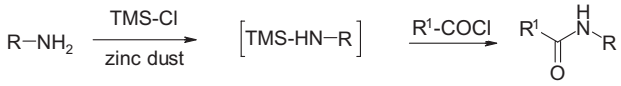
Abstract—An expedient synthetic approach to *N*-silylamines has been developed. The protocol, using TMS-Cl/zinc dust instead of BSA, is useful for the conversion of amines or amino acid esters to the corresponding silyl derivatives, followed by acylation with an acyl chloride or Fmoc-amino acid chloride to give the corresponding amide or peptide. This procedure, affording products in good to excellent yields, is also efficient for the coupling of sterically hindered amino acids like α,α-dialkylamino acids and *N*Me-amino acids. Further, the use of an equimolar quantity of organic base, such as Et_3N/pyridine, is circumvented.

1. Introduction

The synthesis of *N*-silylamines is an important process in organic and biological chemistry.[1–4] It has been found that the nucleophilicity of nitrogen can be increased by silylation.[5] Usually, the *N*-trimethylsilyl-amines or -lactam derivatives have been synthesized by employing trimethylchlorosilane (TMS-Cl) in the presence of an equimolar quantity of an organic base such as Et_3N or pyridine.[6] The base abstracts the HCl liberated and thereby the silylation goes to completion. Other reagents used for *N*-silylation include trimethylsilylalkylamines, hexamethyldisilazane, or a mixture of trimethylsilylamines and TMS-Cl.[7] However, the methods available for silylation of amines are not completely satisfactory.[8] The use of an equimolar quantity of a base results in side reactions including racemization in peptide synthesis.[9] β-Elimination of a Boc group was also observed in the synthesis of microlin lipopeptides when silylation of a lactam nitrogen was carried out in the presence of a base.[10] Whenever the situation requires the use of an organic base to be avoided, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) has been preferred.[11] One such example recently was illustrated by the use of BSA for silylation of amino acid esters and the demonstration of the use of the resulting *N*-trimethylsilyl amino acid esters for the incorporation of sterically hindered amino acids into peptide sequences[12] by Carpino and Bayermann's groups. However, the acetamide that resulted from the reaction was difficult to remove from the reaction medium and BSA is an expensive reagent. A prior demonstration of the use of co-coupling agents such as potassium salts of 1-hydroxybenzotriazole (KOBt) and 7-aza-1-hydroxybenzotriazole (KOAt), zinc dust, etc., with acid chlorides led us to explore *N*-silylation using TMS-Cl and zinc dust under non-Schotten Baumann conditions.[13–15]

2. Results and discussion

Initially, *N*-silylation of aniline was carried out using TMS-Cl and zinc dust to afford TMS-aniline as shown in Scheme 1. This was then allowed to react with benzoyl chloride at room temperature to furnish *N*-phenyl- benzamide. The overall conversion took 10 min



R = C_6H_5, $C_6H_5CH_2$, $O_2NC_6H_4$, $H_3COC_6H_4$; R^1 = C_6H_5.

Scheme 1. Synthesis of amides employing *N*-silylated amines and acid chlorides.

Keywords: *N*-Silylation; TMS-Cl/zinc dust; Acylation; Acid chlorides; Peptides.
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Table 1. Physical constants of amides

Compound	Yield (%)	Melting point (°C)	
		Observed	Reported[17]
N-Phenylbenzamide	94	162–163	162
N-(4-Nitrophenyl)benzamide	90	197–98	199
N-(3-Nitrophenyl)benzamide	88	156–57	157
N-(2-Nitrophenyl)benzamide	85	96–97	98
N-Benzylbenzamide	95	104–106	104–105
N-(4-Methoxyphenyl)benzamide	92	152–53	153–154
N-(3-Methoxyphenyl)benzamide	87	103–104	—
N-(2-Methoxyphenyl)benzamide	89	60–61	60

to complete. This encouraged us to extend the procedure to other substituted anilines and benzylamine. In these cases we observed that the silylation proceeded smoothly and the resulting *N*-silylated derivatives were acylated using benzoyl chloride to afford the corresponding amides in good to excellent yields (Table 1). All the amides prepared were characterized by ^{1}H NMR and mass spectroscopy.

Furthermore, the protocol for *N*-silylation of amino acid esters was explored, which were to be used for peptide coupling employing Fmoc-amino acid chlorides. The amino acid methyl ester hydrochloride salt was initially deprotonated by stirring in dry $CHCl_3$ for 10 min in the presence of an equimolar quantity of zinc dust.[16] The resulting free amino acid ester was converted to its *N*-silylated derivative by treatment with TMS-Cl mediated by zinc dust (Scheme 2). The silylation was found to be complete within 5 min as was confirmed by ^{1}H NMR. The reaction mixture was filtered under an N_2 atmosphere, to give the resulting *N*-silylated amino acid esters. Fmoc-amino acid chloride in $CHCl_3$ was added and stirring continued at room temperature. The acylation, as monitored by TLC and IR, was complete in about 5–10 min. This was confirmed by the absence of the characteristic stretching frequency for an acid chloride at around 1780 cm^{-1}.

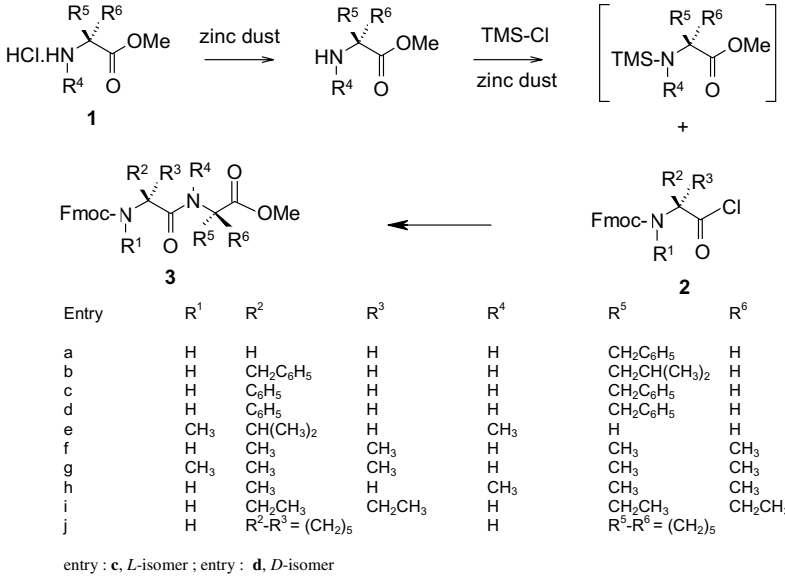
Since the addition of base is avoided, neither oxazol-5-(4*H*)-one formation nor the premature deblocking of the Fmoc group was observed during coupling. The coupling, as monitored by ^{1}H NMR, was free from racemization. Furthermore, the coupling of hindered amino acids, such as α,α-dialkylamino acids and *N*Me-amino acids, was also accomplished. The resulting peptide esters were isolated and characterized as white solids in good yields (Table 2). A comparison of the yields obtained using different methods employing amino acid chlorides and amino acid ester derivatives are given in Figure 1.

In conclusion, an expedient approach for *N*-silylation of both amines and amino acid esters by using TMS-Cl and zinc dust instead of BSA has been demonstrated. The resulting silylated derivatives were acylated using acid chlorides under non-Schotten Baumann conditions.

3. Experimental

3.1. Synthesis of amides employing *N*-silylated amines and acid chlorides

To an amine (1 mmol) in dry $CHCl_3$ (5 mL), zinc dust (0.070 g, 1 mmol) and TMS-Cl (0.1086 g, 1 mmol) were added and mixture was stirred for 5 min. The reaction mixture was filtered under an N_2 atmosphere, benzoyl chloride (1 mmol) added the filtrate and the stirring continued. After completion of the reaction (as monitored by TLC), the mixture was diluted by adding $CHCl_3$ (20 mL) and washed with 5% HCl, 5% $NaHCO_3$ and water and then dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo and recrystallization of the resulting residue from $CHCl_3$/*n*-hexane (3:7) gave the amide as a solid.



Entry	R^1	R^2	R^3	R^4	R^5	R^6
a	H	H	H	H	$CH_2C_6H_5$	H
b	H	$CH_2C_6H_5$	H	H	$CH_2CH(CH_3)_2$	H
c	H	C_6H_5	H	H	$CH_2C_6H_5$	H
d	H	C_6H_5	H	H	$CH_2C_6H_5$	H
e	CH_3	$CH(CH_3)_2$	H	CH_3	H	H
f	H	CH_3	CH_3	H	CH_3	CH_3
g	CH_3	CH_3	CH_3	H	CH_3	CH_3
h	H	CH_3	H	CH_3	CH_3	CH_3
i	H	CH_2CH_3	CH_2CH_3	H	CH_2CH_3	CH_2CH_3
j	H	R^2-R^3 = $(CH_2)_5$		H	R^5-R^6 = $(CH_2)_5$	

entry : **c**, *L*-isomer ; entry : **d**, *D*-isomer

Scheme 2. Synthesis of peptides employing *N*-silylated amino acid esters and Fmoc-amino acid chlorides.

Table 2. Physical constants of N^{α}-Fmoc-protected dipeptide esters

Peptide	Yield (%)	Mp (°C)	$[\alpha]_D^{25}$ (lit.)	^{1}H NMR (400 MHz, $CDCl_3$)
Fmoc-Gly-Phe-OMe[18a]	84	136	+16.12 (+16.0) (c = 1, $CHCl_3$)	δ 2.11 (2H, s), 2.72 (2H, J = 6.4, d), 4.25 (1H, J = 6.8, t), 4.50 (2H, J = 6.8, d), 5.00 (1H, s), 5.51 (1H, br), 7.32–7.80 (13H, m)
Fmoc-Phe-Leu-OMe[18b]	90	156–57	−21.6 (−21.6) (c = 1, $CHCl_3$)	δ 0.85 (6H, J = 7.32, d), 1.50–1.62 (3H, m), 3.04 (1H, q), 3.20 (1H, q), 3.68 (3H, s), 4.22 (2H, J = 6.8, d), 4.33 (1H, J = 6.8, d), 4.40 (2H, J = 6.6, d), 4.68 (1H, J = 6.6, d), 6.41 (1H, br s), 6.90 (1H, br s), and 7.12–7.70 (13H, m)
Fmoc-L-Phg-Phe-OMe[18c]	93	191–92	+22.6 (+22.6) (c = 0.5, DMF)	δ 2.92 (2H, J = 6.6, t), 3.16 (1H, J = 6.6, t), 3.64 (3H, s), 4.25 (1H, J = 6.8, t), 4.52 (2H, J = 6.8, d), 5.22 (1H, J = 6.6, d), 6.20 (1H, br s), 6.95 (1H, br s), and 7.30–7.90 (18H, m)
Fmoc-D-Phg-Phe-OMe[18c]	92	192–93	+22.6 (+22.6) (c = 0.5, DMF)	δ 2.92 (2H, J = 6.6, t), 3.18 (1H, J = 6.6, t), 3.73 (3H, s), 4.25 (1H, J = 6.8, t), 4.52 (2H, J = 6.8, d), 5.23 (1H, J = 6.6, d), 6.20 (1H, br s), 6.95 (1H, br s), and 7.3–7.9 (18H, m)
Fmoc-*N*MeVal-Sar-OMe[13b]	83	80–82	+168.08 (c = 1, $CHCl_3$)	δ 0.80 (6H, J = 7.4, d), 1.32 (3H, J = 7.4, d), 1.50 (2H, J = 6.6, t), 2.42 (4H, m), 3.61 (3H, s), 4.12 (1H, J = 6.8, d), 4.30 (2H, J = 6.8, t), 7.30–7.80 (8H, m)
Fmoc-Aib-Aib-OMe[15]	88	70–71	—	δ 0.92–2.10 (12H, m), 3.80 (3H, s), 4.1 (1H, J = 6.8, d), 4.21 (2H, J = 6.8, t), 6.82 (1H, br s), and 7.22–7.80 (9H, m)
Fmoc-*N*MeAib-Aib-OMe[12]	88	70–71	—	δ 0.92–2.11 (12H, m), 3.62 (3H, s), 3.80 (3H, s), 4.10 (1H, J = 6.8, d), 4.21 (2H, J = 6.8, t), 6.82 (1H, br s), and 7.22–7.80 (9H, m)
Fmoc-Ala-*N*MeAib-OMe[12]	88	70–71	—	δ 0.92–2.10 (9H, m), 3.65 (3H, s), 3.82 (3H, s), 4.10 (1H, J = 6.8, d), 4.21 (2H, J = 6.8, t), 6.80 (1H, br s), and 7.20–7.80 (9H, m)
Fmoc-Deg-Deg-OMe[18d]	82	122–24	—	δ 0.82–2.00 (20H, m), 3.70 (3H, s), 4.21 (1H, J = 6.8, d), 4.32 (2H, J = 6.8, t), 6.60 (1H, br s), 7.02 (1H, br s), and 7.20–7.80 (8H, m)
Fmoc-Ac_6c-Ac_6c-OMe[18d]	86	164–66	—	δ 0.80–2.10 (20H, m), 3.72 (3H, s), 4.20 (2H, J = 6.8, t), 4.51 (1H, J = 6.8, d), 5.93 (1H, s), 6.80 (1H, s), and 7.30–7.80 (8H, m)

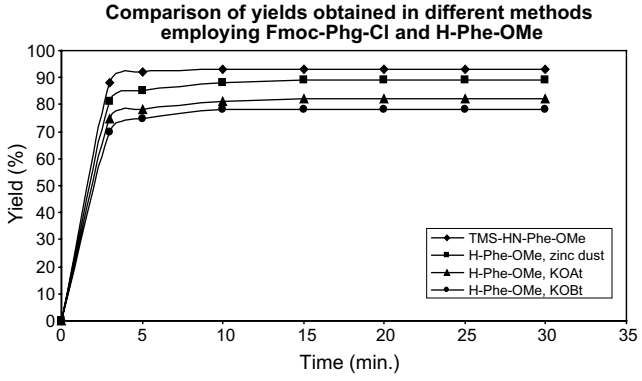


Figure 1. Comparison of yields obtained using different methods employing Fmoc-Phg-Cl and H-Phe-OMe.

3.2. Synthesis of peptides employing *N*-silylated amino acid esters and Fmoc-amino acid chlorides

The amino acid methyl ester hydrochloride salt (1 mmol) was deprotonated by stirring in dry $CHCl_3$ (5 mL) with zinc dust (0.140 g, 2 mmol) for 10 min. TMS-Cl (0.1086 g, 1 mmol) was added and stirring was continued for another 5 min. The reaction mixture was filtered under an N_2 atmosphere, the Fmoc-amino acid chloride (1 mmol) in $CHCl_3$ was added to the filtrate and the stirring was continued. After completion of the reaction (as monitored by TLC), the mixture was diluted by adding $CHCl_3$ (20 mL) and washed with 5% HCl, 5% $NaHCO_3$ and water and then dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo and recrystallization of the resulting residue from $CHCl_3$/*n*-hexane (3:7) gave the peptide as a solid.

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