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A One-Pot N-Protection of L-Arginine.

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Abstract· *A facile, one-pot synthesis of N^{α}-t-Butyloxycarbonyl,N^{δ},N^{ϖ}-di-benzyloxycarbonyl-L-Arginine (**3a**) and N^{α},N^{δ},N^{ϖ}-tri-benzyloxycarbonyl-L-Arginine (**3b**) is reported N^{α}-t-Butyloxycarbonyl-L-Arginine (**1b**) is treated with trimethylsilylchloride and the tri-silylated intermediate **2c** is subsequently allowed to react with benzyloxycarbonyl chloroformate to give **3a** in 50% overall yield Starting from **1a** or **1c**, **3b** was prepared according to the same procedure in 72% and 60-85% yield, respectively*

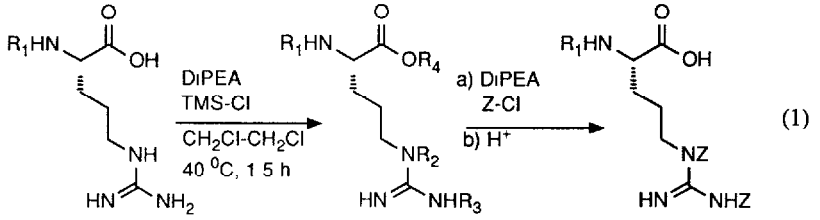
In the framework of our research on natural products and enzyme inhibitors we searched for a facile synthesis of fully protected arginine derivatives We focussed on N^{α}-t-Butyloxycarbonyl-N^{δ},N^{ϖ}-di-benzyloxycarbonyl-Arginine (**3a**) and the tri-benzyloxycarbonyl derivative **3b** Compound **3a** can be used in peptide coupling and selectivly deprotected at the α-nitrogen whereas compound **3b** is a useful derivative for the addition of an arginine residue to the amino terminal of a peptide residue

The available syntheses of suitably protected arginine derivatives have serious drawbacks When the classical Schotten-Baumann conditions are employed [1-3], L-Arginine (**1a**) and its derivatives **1b** or **1c** are converted into the corresponding derivatives **3a** or **3b** in low yields only (15 - 32%) The synthesis of **3a** reported by R Schwyzer et al [4] is a cumbersome one as it involves the intermediacy of N^{δ},N^{ϖ}-di-benzyloxycarbonyl-Arginine, prepared in low yield from **3b**

When Schotten-Baumann conditions for the preparation of **3b** were employed, we observed that the main product was the di-benzyloxycarbonyl derivative **2a**, presumably formed from **3b** by base-catalyzed N^{δ} deprotection It had been shown earlier[5] that **1a** can be converted into **3b** in acceptable yield (56%) when the employment of base is avoided indeed The procedure used involved the preparation of benzyl pentachlorophenylcarbonate and its subsequent reaction with **1a** in the presence of N-trimethylacetamide However, this procedure has as drawback that the working-up conditions are very laborious

For the development of a more simple, one-pot procedure it was realized that (i) employment of benzyloxycarbonyl chloroformate instead of benzyl pentachlorophenyl carbonate should be strived after and (ii) that N-urethane formation can be facilitated by utilizing O,N-trimethylsilyl amino acids as intermediates These considerations are based on the previously mentioned procedure [5] employing N-trimethylacetamide and on a report by Meienhofer et al [6] who showed that O,N-bis-trimethylsilyl amino acids can be formed in situ by treating an amino acid with trimethylsilyl chloride (TMS-Cl) and a base in an aprotic solvent[6] The resulting intermediate was subsequently reacted with 9-fluorenylmethyloxycarbonyl chloride (Fmoc-Cl) to yield -after aqueous workup- Fmoc protected amino acids[7]

As an extension of this approach we report here a facile, one-pot synthesis of **3a** starting from **1b** , and of **3b** starting from either **1a** or **1c**[8]



1a R_1=H
b R_1=Boc
c R_1=Z

2 a R_1=Z, R_2=H, R_3=Z, R_4=H
b R_1=R_2=R_3=R_4= Si(Me)3
c R_1=Boc, R_2=R_3=R_4=Si(Me)3
d R_1=Z, R_2=R_3=R_4=Si(Me)3

3a R_1=Boc
b R_1=Z

L-Arginine (**1a**), N^{α}-Boc-L-Arginine (**1b**) or N^{α}-Z-L-Arginine (**1c**) were silylated to yield **2b**, **2c** and **2d**, respectively, by treatment with TMS-Cl in the presence of diisopropylethylamine (DiPEA) Subsequent treatment of the reaction mixture containing **2b** or **2d** with benzyloxycarbonyl chloroformate (Z-Cl), again in the presence of DiPEA gave **3b** in overall yields of 72% and 60 - 85 % respectively Using a similar procedure **2c** was converted into **3a** (50% overall yield)

For the conversion of **1c** to **3b** via **2d** the reaction has been carried out several times at a 1 to 25 gram scale with yields ranging from 60 - 85% In a typical, large scale experiment **1c**[1] (15 0 g, 48 7 mmol) was suspended in 1,2-dichloroethane (125 ml) and three equivalents of DiPEA (146 1 mmol, 25 5 ml) were added The mixture was kept under dry nitrogen After slowly having added TMS-Cl (146 1 mmol, 18 7 ml) to the solution the reaction mixture was kept at 40 ° C for 1 5 h

After having cooled the solution to 0° C another three equivalents of DiPEA (146 1 mmol, 25 5 ml) were added followed by Z-Cl (146 1 mmol, 21 8 ml, added in one portion) The solution was stirred in an ice bath for 20 minutes, after which the reaction mixture was allowed to warm up to room temperature Stirring was continued for 4 h Acidification with aqueous 1N HCl until the organic layer was approximately pH 2 was followed by extraction with dichloromethane (3 x 100 ml), the combined organic layers were concentrated and the residue was crystallized from methanol/water (4/1, v/v) to yield a first crop of 30 4 grams of **3b** (64% based on **1c**) TLC of the mother liquor indicated the presence of some more of the desired product in it

When **1a** was used as starting compound the same procedure was followed The only difference in the procedure was the amount of TMS-Cl and of DiPEA used, eight equivalents of each were added to compound **1a** to obtain **2b** and subsequently, after adding four equivalents of DiPEA and Z-Cl, **3b** was obtained after work-up in high overall yield (72%)

The conversion of **1b**[9] to **3a** via **2c** followed the same procedure as described above for the synthesis of **3b** Compound **3a** was crystallised from ethanol/water, 1/1, v/v, resulting in a first crop of 20% The motherliquor was evaporated to dryness,resolved in dichloromethane and stirred with Montmorillonite K-10 After filtration and evaporation another crop of 30% of **3a** was obtained

The proton NMR spectra of **3a** and **3b** indicate that the N^{δ} atom is protected (for the chemical shift value see physical constants) The chemical shift value of the $C^{\delta}H_2$ protons in the unprotected side chain of **1a**, **1b** and **1c** is 3 2 ppm In the spectrum of **3a** and **3b** the signal of the $C^{\delta}H_2$ protons is at 3 75 - 4 05 ppm (broad signals) NMR analysis also indicated that N^{α} was monosubstituted At δ= 6 85 ppm (**3a**) and at δ=7 6 ppm (**3b**) a doublet is present representing the coupling $N^{\alpha}H$ - $C^{\alpha}H$

Physical constants of 3a and **3b**

3a Melting Point 133-135°C (Lit [1] 141-142°C), $[\alpha]^{25}_{D}$= + 18° (c=1, $CHCl_3$, lit[3] +13° c=1, $CHCl_3$), TLC (Merck Fertig Platten 60 F_{254}, solvent system toluene/ethanol, 8/2, v/v), R_f(**3a**)= 0 65 (detection UV and Reindel-Hoppe)
^{1}H-NMR data (200 MHz, DMSO-d6, tetramethylsilane as internal standard) δ 1 40 (9H, Boc), 1 50 - 1 80 (m 4H β-CH_2,χ-CH_2), 3 75 - 4 05 (m 3H δ-CH_2, α-CH), 5 08 (s 2H $C\underline{H}_2$-C_6H_5), 5 25 (s 2H $C\underline{H}_2$-C_6H_5), 6 85 (d 1H $N^{\alpha}H$) 7 20 - 7 50 (m 10H CH_2-$C_6\underline{H}_5$), 9 15 (s 2H (broad signal) HN=C-NHZ)

3b Melting Point 138 9 °C (lit [1] 138-139°C), $[\alpha]^{25}_{D}$= + 17 1° c=1, chloroform (lit [1] + 16 8°, c=1 chloroform), TLC (Merck Fertig Platten 60 F_{254}, solvent system toluene/ethanol, 8/2, v/v), R_f(**3b**)= 0 7 (detection UV and Reindel-Hoppe)
^{1}H-NMR data (200 MHz, DMSO-d6, tetramethylsilane as internal standard) δ 1 50 - 1 80 (m 4H β-CH_2, χ-CH_2), 3 75 - 4 05 (m 3H δ-CH_2, α-CH), 5 02 (s 2H $C\underline{H}_2$-C_6H_5), 5 08 (s 2H $C\underline{H}_2$-C_6H_5), 5 25 (s 2H $C\underline{H}_2$-C_6H_5), 7 20 - 7 50 (m 15H CH_2-$C_6\underline{H}_5$), 7 60 (d 1H N^{α}-H), 9 15 (s 2H (broad signal) HN=C-NHZ)

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(7) Tri-N-protected L-Arginine was not included in the list of derivatives reported in ref 6 and 8

(8) During the preparation of this manuscript a similar strategy was reported for the N-protection of amino acids mediated through previous silylation Becu, Chr , Reymers, M F , Anteunis, M F , Callens, R , *Bull Soc Chim* , **1990**, *10*, 779-782 These authors employed trimethylsilyl cyanide instead of TMS-Cl/base See also ref 7

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