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Alkoxycarbonylation and Selective Deprotection of N-Silyl Derivatives of L-Arginine

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Abstract: N^{δ},N^{ω},O-Tris(trialkylsilyl)-N^{α}-carbobenzyloxy-L-arginine can be prepared *in situ* from N^{α}-carbobenzyloxy-L-arginine. Treatment with alkyl chloroformates gives N^{δ},N^{ω}-bis(alkyloxycarbonyl)-N^{α}-carbobenzyloxy-L-arginines, which can be converted into N^{δ},N^{ω}-bis(alkyloxycarbonyl)-L-arginines by hydrogenation.

Guanidino-functionalised arginines are valuable in peptide synthesis[1] and as substrates or inhibitors of nitric oxide synthase (NOS)[2], the enzyme mediating the production of the key secondary messenger nitric oxide from arginine[3]. Selective protection of the guanidino group can be problematic[4] while NOS inhibitors are usually obtained by multi-step synthesis from L-ornithine derivatives[5]. Most reported NOS inhibitors are guanidino-alkylated arginines, e.g., N^{ω}-methyl-[2], N^{ω},N^{ω}-dimethyl-[6], N^{ω},$N^{\omega'}$-dimethyl-[6], and N^{ω}-allyl-L-arginine[7], while some are guanidino-functionalised compounds, such as N^{ω}-amino- and N^{ω}-nitro-L-arginine[8].

Synthetic methods which allow the direct introduction of functionality onto the arginine guanidino group could provide routes to novel, pharmacologically significant compounds. Jetten et. al. have reported a method for the controlled benzyloxycarbonylation of arginine[4] *via* the intermediacy of N^{α}-carbobenzyloxy-N^{δ},N^{ω},O-tris(trimethylsilyl)-L-arginine (1). Reported herein is the application of this methodology to the preparation of orthogonally protected arginine derivatives, and the subsequent selective deprotection of these to give guanidino-alkoxycarbonylated arginines.

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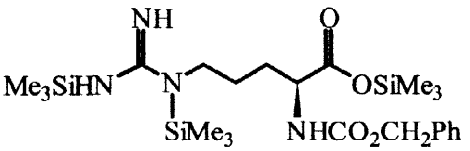
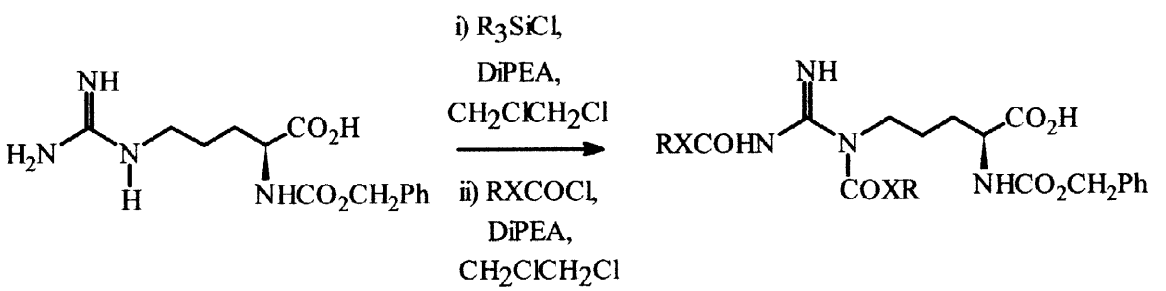


1

Solutions of N^{α}-carbobenzyloxy-L-arginine[9] **2** and diisopropylethylamine (DiPEA) were treated with chlorotrimethylsilane, followed by addition of alkyl chloroformates. Use of methyl or isopropyl chloroformate gave the corresponding N^{δ},N^{ω}-bis(alkyloxycarbonyl)-N^{α}-carbobenzyloxy-L-arginines, **3a** and **3b**, in 79% and 45% isolated[10] yields, respectively. The reaction was also successful with methyl chlorothiolformate, giving N^{δ},N^{ω}-bis(methylthiocarbonyl)-N^{α}-carbobenzyloxy-L-arginine **3c**, albeit in poor yield (25%). Use of cyanogen bromide or 3-chloroperoxybenzoic acid as electrophiles in the reaction gave no identifiable products. Use of more sterically demanding chlorotrialkylsilanes did not result in mono-alkoxycarbonylation of the guanidino group, even when only two equivalents of chlorosilane were used. Thus, treatment of **2** with 2.2 equivalents of tert-butylchlorodimethylsilane, followed by addition of benzyl chloroformate, gave N^{α},N^{ω},$N^{\omega'}$-tris(carbobenzyloxy)-L-arginine[4] **3d** as the only product, in 45% yield, while treatment of **2** with 2.0 equivalents of tert-butylchlorodiphenylsilane, followed by methyl chloroformate, gave **3a** as the only product in 68%.



2

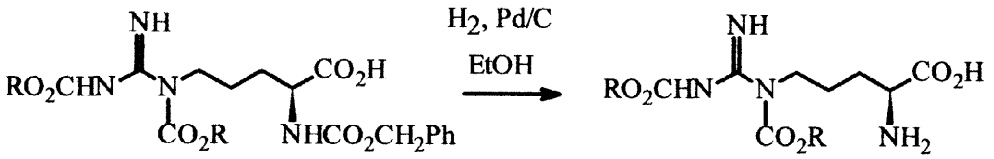
3a RX = MeO

3b RX = iPrO

3c RX = MeS

3d RX = $PhCH_2O$

Compounds **3a**, **3b** and the previously reported derivative N^{δ},N^{ω}-bis(ethoxycarbonyl)-N^{α}-carbobenzyloxy-L-arginine[9] **3e**, were subjected to catalytic hydrogenation[11] to give the N^{δ},N^{ω}-bis(alkyloxycarbonyl)-L-arginines **4a**, **4b** and **4c**, in yields of 56%, 82% and 89% respectively.



3a R = Me
3b R = iPr
3e R = Et

4a R = Me
4b R = iPr
4c R = Et

As guanidino-functionalised derivatives of L-arginine, compounds **4a**, **4b** and **4c** have potential as NOS inhibitors. They could also be metabolised *in vivo* to L-arginine. However, only **4a** showed any observable convertion to arginine during *in vitro* experiments with *porcine pancreatic lipase*. Investigation of the biological activities of compounds **4a**, **4b** and **4c** is in progress.

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10. The following general procedure was used to obtain compounds **3a**,**b**,**c** and **d**. Trialkylchlorosilane (3 eqv.) was added to a suspension of **2** and DiPEA (3 eqv.) in 1,2-dichloroethane under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 30 minutes and then at 40-50°C for 2 to 3 hours, after which it was cooled to 0°C and DiPEA (3 eqv.) added, followed by alkyl chloroformate (3 eqv.). The reaction mixture was stirred for several hours at ambient temperatures, after which it was washed with water, acidified with M hydrochloric acid (pH 2), extracted with

dichloromethane, dried over magnesium sulphate and the solvent evaporated. The product was isolated by silica gel chromatography using dichloromethane:methanol (10:1) as eluent.

3a: white crystalline solid; 135-136°C (MeOH); ν_{max} (KBr)/cm^{-1} 3990, 3328, 3287, 1746, 1731 and 1695; δ_H (200MHz, $CDCl_3$) 1.04 to 1.60 (4H, m, CH_2CH_2), 3.57 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.83 (2H, m, NCH_2), 4.20 (1H, m, C*H*), 4.99 (2H, s, OCH_2Ph), 5.79 (1H, d, N*H*), 7.18 to 7.23 (5H, m, Ar*H*), 9.40 (2H, brs, N*H* x 2), 11.13 (1H, s, O*H*); Found: m/z (CI) $(M + H)^+$ 425.1672. $C_{18}H_{25}N_4O_8$ requires $(M + H)^+$ 425.1672.

3b: oil; ν_{max}(KBr)/cm^{-1}, 3390 and 1715; δ_H(200MHz, $CDCl_3$), 1.09 to 1.69 (4H, m, CH_2CH_2-), 1.22 to 1.29 (12H, m, $CH_3 \times 4$), 3.92 (2H, m, NCH_2), 4.31 (1H, t, C*H*), 4.85 to 5.03 (2H, septet, $CH(CH_3)_2 \times 2$), 5.08 (2H, s, CH_2Ph), 6.00 (1H, d, N*H*), 7.31 (5H, m, Ar*H*), 9.4 (2H, brs, N*H* x 2); Found: m/z (CI) $(M + H)^+$ 481.2340. $C_{22}H_{33}N_4O_8$ requires $(M + H)^+$ 481.2298.

3c: yellow solid; 142-145°C; ν_{max}(KBr)/cm^{-1}, 3376, 3292, 1730, 1695 and 1659; δ_H(200MHz, $CDCl_3$), 0.92 to 1.84 (4H, m, CH_2CH_2), 2.26 (3H, s, SCH_3), 2.35 (3H, s, SCH_3), 3.98 (2H, m, NCH_2), 4.40 (1H, t, C*H*), 5.16 (2H, s, CH_2Ph), 5.76 (1H, d, N*H*), 7.29-7.39 (5H, m, Ar*H*), 9.42 (2H, brs, N*H* × 2); Found m/z (CI) $(M + H)^+$ 457.1195. $C_{18}H_{25}O_6N_4S_2$ requires $(M + H)^+$ 457.1215.

11. Compounds **4a**, **b** and **c** were obtained by reaction of compounds **3a**, **b** and **e** and 10% palladium on carbon catalyst in ethanol solution under a hydrogen atmosphere.

4a: light yellow solid, 205-207°C; ν_{max}(KBr)/cm^{-1} 3395, 1790, 1725 and 1698; δ_H(200MHz, $CDCl_3$), 1.22 to 1.73 (4H, m, CH_2CH_2), 3.03 to 4.2 (3H, m, C*H* and NCH_2), 3.66 (3H, s, CH_3O), 3.72 (3H, s, CH_3O), 6.20 (2H, brs, NH_2), 8.20 and 9.40 (2H, brs, N*H* x 2); Found m/z (FAB) $(M + H)^+$ 291.1321. $C_{10}H_{19}N_4O_6$ requires $(M + H)^+$ 219.1305.

4b: yellow oil; ν_{max}(KBr)/cm^{-1}, 3406, 1786, 1719 and 1686; δ_H(200MHz, $CDCl_3$), 0.90 to 1.80 (4H, m, CH_2CH_2), 1.23 (12H, m, $CH_3 \times 4$), 3.92 to 4.30 (3H, m, NCH_2 and C*H*), 4.95 (2H, m, $CH(CH_3)_2 \times 2$), 7.05 to 7.24 (2H, m, NH_2), 9.40 (2H, brs, N*H* x 2); Found m/z (FAB) $(M + H)^+$ 347.1966. $C_{14}H_{27}N_4O_6$ requires $(M + H)^+$ 347.1931.

4c: white solid, 173-175°C; ν_{max}(KBr)/cm^{-1} 3394, 1725 and 1608; δ_H (200MHz, $CDCl_3$), 1.28 to 1.32 (6H, t, $CH_3CH_2 \times 2$), 1.00 to 1.84 (4H, m, CH_2CH_2), 3.10 to 4.10 (3H, m, C*H* and NCH_2), 4.13 to 4.28 (4H, m, $CH_3CH_2O \times 2$), 9.43 (2H, brs, N*H* x 2), Found m/z (FAB) $(M + H)^+$ 319.1614. $C_{12}H_{23}N_4O_6$ requires $(M + H)^+$ 319.1617.