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IMPROVED SELECTIVE PROTECTIONS OF L-ARGININE

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Abstract: Reliable procedures for the selective introduction of carbobenzyloxy and phthalimido groups onto the α-amino position, and of carboethoxy groups onto the δ- and ω-guanidino positions of L-arginine are described.

The selective N-protection of arginine (1) has been widely investigated in the context of peptide synthesis[1,2]. Discoveries concerning the role of L-arginine as the biochemical precursor to nitric oxide[3] have also increased interest in the preparation of novel arginine derivatives[4,5]. We have found that many of the standard methods for the preparation of N-protected arginines suffer from poor selectivities and herein report procedures for the convenient preparation of some derivatives.

Standard procedures for the N^{α}-carbobenzyloxylation of L-arginine (1), using benzyl chloroformate under basic conditions[6], were found, in our hands, to

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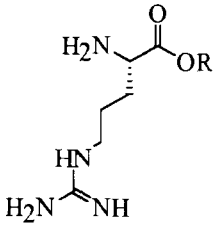
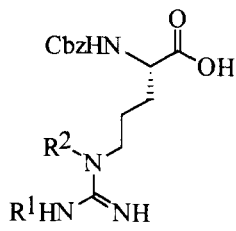
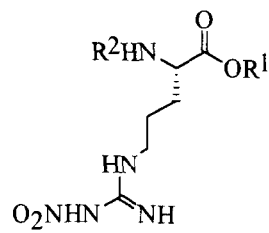
produce quantities of the bis- and tris(carbobenzyloxy) derivatives (4) and (5)[7] in addition to the required product. Crystallization of N^{α}-carbobenzyloxy-L-arginine (3) from the resulting product mixtures was difficult or often impossible. We have found that maintaining the reaction pH within the range 9 to 11 ensures selective carbobenzyloxylation at the N^{α}-amino group, allowing convenient preparation of crystalline N^{α}-carbobenzyloxy-L-arginine (3) in good yield. The necessary buffering can be conveniently achieved using sodium bicarbonate/sodium hydroxide mixtures. These reaction conditions were also found to provide an improved procedure for the preparation of N^{α}-carbobenzyloxy-N^{ω}-nitro-L-arginine (7) from N^{ω}-nitro-L-arginine (6)[8]. Successful crystallization of the product (7) from this reaction was found to require careful control of pH. When L-arginine ethyl ester (2) was subjected to these reaction conditions, N^{α}-carbobenzyloxy-L-arginine (3) was obtained, in 78% yield, as the only product.



(1) R=H
(2) R=C_2H_5



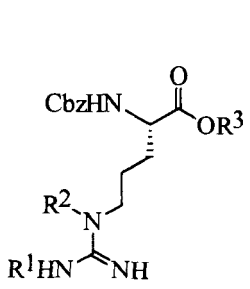
(3) R^1, R^2=H
(4) R^1=Cbz, R^2=H
(5) R^1, R^2=Cbz

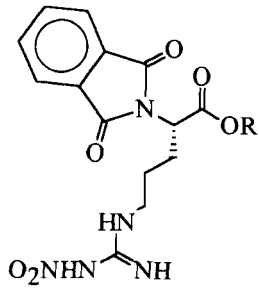


(6) R^1, R^2=H
(7) R^1=H, R^2=Cbz
(8) R^1=CH_3, R^2=H

FIG. 1 [Cbz = $PhCH_2OCO$]

Reported methods for the introduction of carbobenzyloxy groups onto the guanidino nitrogens, using standard benzyl chloroformate/base conditions[7], were also found to be impractical for the preparation of useful quanties of pure material. N^{α}-Carbobenzyloxy-N^{δ},N^{ω},O-tris(trimethylsilyl)-L-arginine (9) has been reported as an intermediate for the preparation of the highly N-protected derivative N^{α},N^{δ},N^{ω}-tris(carbobenzyloxy)-L-arginine (5)[9]. Although this reaction was sucessful in our hands, the yield of tris(carbobenzyloxy) derivative (5) was low and the reaction product was not obtainable by direct recrystallization as reported. Reaction of the *in situ* generated tris(trimethylsilyl) intermediate (9) with ethyl chloroformate provided the highly N-protected derivative N^{δ},N^{ω}-bis(carboethyloxy)-N^{α}-carbobenzyloxy-L-arginine (10) in good yield, although a crystalline product could not be obtained.





(9) R^1, R^2, R^3=$Si(CH_3)_3$ (11) R=H

(10) R^1, R^2=$C_2H_5O_2C$, R^3=H (12) R=CH_3

FIG. 2 [Cbz = $PhCH_2OCO$]

An attempt to introduce selectivity for the N^{ω}- over the N^{δ}-guanidino site, by the use of *tert*-butyl(dimethyl)silyl chloride as the silylating agent, produced mixtures of the bis- and tris(carbobenyloxy) derivatives (4) and (5) after the addition of benzyl chloroformate.

N^{ω}-Nitro-N^{α}-phthalimido-L-arginine (11) can be prepared in poor yield by direct fusion of N^{ω}-nitro-L-arginine (6) and phthalic anydride[10]. The yield and convenience of this preparation can be considerably improved by the use of 1,4-dioxane as solvent. The same reaction conditions were used to prepare N^{ω}-nitro-N^{α}-phthalimido-L-arginine methyl ester (12) from N^{ω}-nitro-L-arginine methyl ester (8) in good yield.

Experimental

N^{α}-Carbobenzyloxy -L-arginine (3)

L-Arginine (1) (3.5g, 0.02mol) was added to a mixture of 15ml of 1M aqueous sodium bicarbonate and 5ml of 4N aqueous sodium hydroxide. The mixture was stirred vigorously at room temperature and benzyl chloroformate (3.7g, 0.022mol) was added slowly over a period of 30 minutes. The stirring was continued for a further 1 hour. After the reaction was complete, a crystalline precipitate of the desired product (3) was collected by filtration, washed with cold water, and finally recrystalized from boiling water and dried in air. The mother liquor was

concentrated *in vacuo* to yield a second crop, 5.0g (80%); m.p., 172-173°C (lit.[7] 175 °C).

N^{ω}-Nitro-N^{α}-carbobenzyloxy-L-arginine (7)

N^{ω}-Nitro-L-arginine (6) (439mg, 2mmol) was added to a mixture of 1ml 4N aqueous sodium hydroxide and 1.5ml 1N aqueous sodium bicarbonate. The mixture was stirred at room temperature until the starting material had dissolved. A solution of benzyl chloroformate (370mg, 2.2mmol in 1.2ml dioxane) was added to the reaction mixture slowly over a period of 30 minutes. Stirring was continued for 2 hours. The resulting mixture was then washed with ethyl acetate (3×5ml) and the pH of the solution was adjusted to 3 by addition of 2N hydrochloric acid. The clear solution was poured to another container and refrigerated for a week. The desired product (7) was collected by filtration, washed with water and dried in air to give a crystalline solid, 370mg, (53%); m.p., 132-134°C (lit[10]. 132-134 °C).

N^{α}-Carbobenzyloxy-N^{δ},N^{ω}-bis(carboethyloxy)-L-arginine (10)

Chlorotrimethylsilane (1.1g, 10 mmol.) was added slowly to a suspension of N^{α}-carbobenzyloxy-L-arginine (3) (1.1g, 3.5 mmol.) and di(isopropyl)ethylamine (1.3g, 10 mmol.) in 1,2-dichloroethane (11 ml.) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 30 minutes and at 40°C for 2 hours. The reaction mixture was then allowed to cool and was further cooled to 0°C, after which di(isopropyl)ethylamine (1.3g, 10 mmol.) was added, followed by ethyl chloroformate (1.1g, 10 mmol.). The reaction mixture was stirred overnight

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at room temperature, after which it was acidified to pH 1 by addition of M hydrochloric acid, extracted with dichloromethane (3 x 10 ml), dried over magnesium sulphate and the solvent evaporated to give a brown oil. Silica gel chromatography, using dichloromethane:methanol (10:1) as eluent, gave the product (10) as a yellow oil (1.3g, 80%), ν_{max} (KBr)/cm^{-1} 3389, 3036, 2982, 1718, 1610, 1516, 1456, 1369, 1258, 1099, 1030, 808, 778 and 698; δ_H ($CDCl_3$) 1.30 (6H, t, CH_3CH_2 x 2), 1.10 to 2.05 (4H, m, CH_2CH_2), 3.80 (3H, brs, 3 x NH), 3.80 to 4.50 (6H, m, CH_2N and 2 x CH_2O), 5.10 (2H, s, OCH_2Ph), 5.85 (1H, t, α-CH), 7.30 to 7.45 (5H, m, ArH), 9.40 (1H, brs, OH); [Found: m/z (CI) $(M + H)^+$, 453.1985. $C_{20}H_{29}O_8N_4$ requires $(M + H)^+$, 453.1986].

N^{ω}-Nitro-N^{α}-phthalimido-L-arginine (11)

To a suspension of phthalic anhydride (182mg, 1.2mmol) in 2ml dioxane, N^{ω}-nitro -L-arginine (6) (219mg, 1mmol) was added. The reaction mixture was refluxed at 100-110 °C for 9 hours. After cooling, the precipitate was filtered off and the filtrate was concentrated to dryness under reduced pressure. The crude product (11) was recrystallized from hot water to give a white crystalline solid, 175mg (50.3%); m.p., 207-209 °C (lit.[10] 204-206 °C).

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