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Guanidino-substituted arginines via *N*-silyl intermediates

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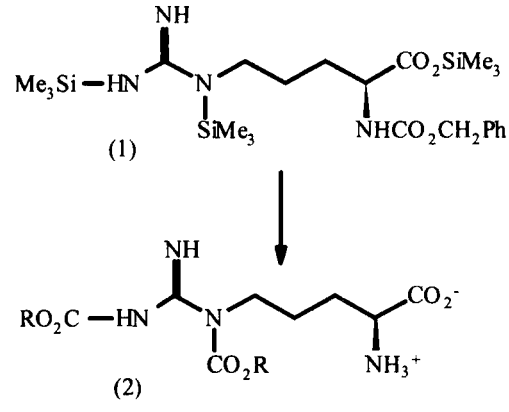
Guanidino-substituted arginines are the commonest class of nitric oxide synthase inhibitor. Examples include N^{ω}-methyl-, N^{ω}-amino- and N^{ω}-nitro-L-arginine Macdonald (1996). These compounds are generally obtained from L-ornithine by multiple-step syntheses which involve the use of guanidine forming methodology in conjunction with several protective and deprotective steps Moynihan et al (1994). We have investigated a method for the direct functionalisation of the arginine guanidine group via the intermediacy of N-silyl arginines.

N^{α}-carbobenzyloxy-N^{δ},N^{ω},O-tris(trimethylsilyl)-L-arginine (1) can be generated from N^{α}-carbobenzyloxy-L-arginine by treatment with chlorotrimethylsilane and diisopropylethylamine (DiPEA) in dichloroethane Jetten et al (1991). In situ reaction of (1) with alkylchloroformates and DiPEA yields N^{δ},N^{ω}-bis(alkoxycarbonyl)-N^{α}-carbobenzyloxy-L-arginines, which can be selectively deprotected by catalytic hydrogenation to yield N^{δ},N^{ω}-bis(alkoxycarbonyl)-L-arginines (2). Use of a range of alkylchloroformates, alkylthiochloroformates and trialkylchlorosilanes has been investigated.



Jetten, M., Peters, C. A. M., van Nispen, J. W. F. N., Ottenheijm, H. C. J. (1991) Tetrahedron Letters 6025-6028

Macdonald, J. E. (1996) Annual Reports in Medicinal Chemistry 31: 221-230

Moynihan, H. A., Roberts, S. M., Weldon, H., Allcock, G. H., Anggard, E. E., Warner, T. D. (1994) J. Chem. Soc. Perkin Transactions 1 769-771