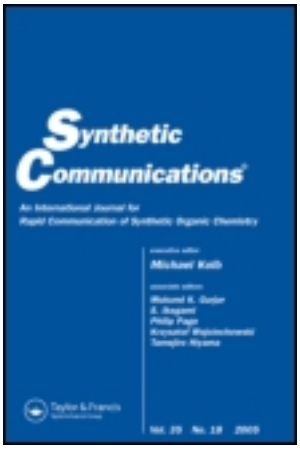

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A Facile Route to Cyclic and Acyclic Alkyl-Arginines

Kevin J. Kennedy [a] , Tiberiu L. Simandan [a] & Thomas A. Dix [a]
[a] Department of Pharmaceutical Sciences , Medical University of South Carolina , Charleston, South Carolina, 29425
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A FACILE ROUTE TO CYCLIC AND ACYCLIC ALKYL-ARGININES

Kevin J. Kennedy, Tiberiu L. Simandan and Thomas A. Dix*

Department of Pharmaceutical Sciences, Medical University of South Carolina, Charleston, South Carolina 29425

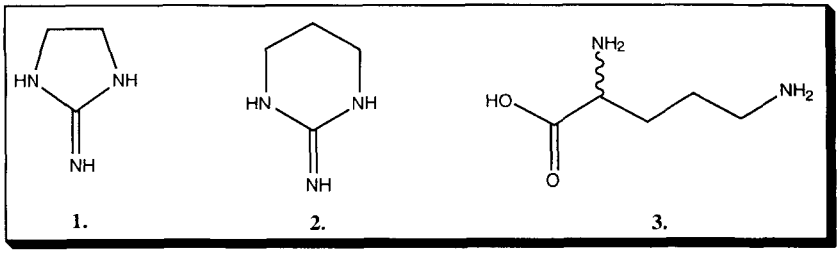
Abstract: Treatment of commercially available alkyl and cycloalkyl thioureas with methyl iodide provides the corresponding S-alkylisothiouronium iodide which reacts directly with ornithine to yield the title compounds.

Key stabilizing interactions in protein structure and protein-protein recognition events are ion pairs between anionic amino acid carboxylates and cationic arginine or lysine residues. In an aqueous environment, alkylation of cationic amino acids can enhance the stabilizing interaction of ion pairs through "steric inhibition of solvation" of the free ion.[1] Further, therapeutic peptides in which Nω,Nω´-dialkylated arginines were substituted have exhibited improved pharmacokinetic parameters resulting from increases in overall hydrophobicity.[2,3] New arginine analogues of interest along these lines result from incorporation of the two ω-nitrogen atoms of the guanidine group in five- or six-membered rings. The

* To whom correspondence should be addressed.

synthesis of these compounds can be conceptualized as attachment of the ring system (either 2-amino-2-imidazoline (**1**) or 2-amino-3,4,5,6-tetrahydropyrimidine (**2**)) to L- or D-ornithine (**3**) (Scheme 1).

Scheme 1



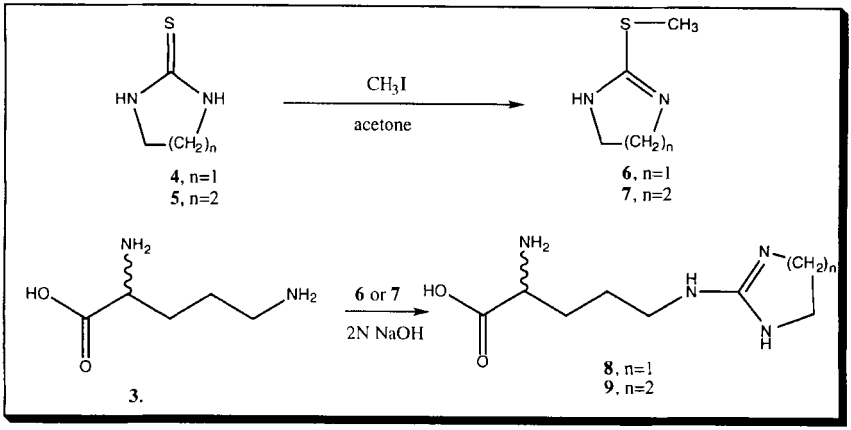
1. 2. 3.

Cyclic guanidines were synthesized by Rodricks and Rapoport[4] reacting both aliphatic and aromatic diamines with S,S-dimethyl-N-tosyliminodithiocarbonimidate. The reaction is interesting if there is a need for tosyl protected guanidines, otherwise deprotection requires treatment with anhydrous HF. This is an alternative to the classical reaction of cyanogen bromide with diamines[5] to prepare the five-membered 2-amino-2-imidazoline and the six-membered 3,4,5,6-tetrahydropyrimidine rings. The hydrogenation of 2-aminopyrimidine[6] and the reaction of guanidine with 4,5-diamino-6-hydroxypyrimidine to afford 8-amino-6-hydroxypurine[7] are two other routes, but with limited applicability.

An attractive method was first presented by Aspinall and Bianco in 1951[8] and extended by McKay *et. al*[9,10]. The method involves the reaction of 2-methylthio-1,3-diazines with amines and was later used to prepare derivatives of guanidine[11] and Nω-methylated arginine.[12,13] The commercial availability of starting materials, the simplicity, mild conditions and high yielding reactions prompted us to use this

method as a general route to novel "ring" arginines and to other mono and dialkylated arginines, as well. Of particular utility is the ability to access a variety of unsymmetric thioureas by reaction of primary or secondary amines with alkylisothiocyanates.[14] Generally, the method consists of two steps (Scheme 2).

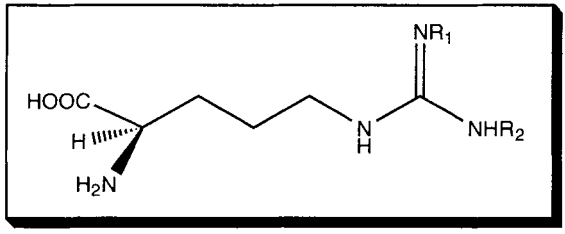
Scheme 2



Initial dropwise addition of methyl iodide to a slurry of **4** or **5** in acetone forms the corresponding salts of **6** or **7**. The intermediates then were reacted with L- or D-**3** in 2 N NaOH at room temperature for 9 days or 5 hours at 100° C to provide both enantiomers of the five- or six-membered "ring" arginine **8** and **9** with yields above 80%.

The same method was used to prepare mono- and di-alkylated arginines (Table 1). Alkyl L-arginines **10**, **11**, and **13** have been prepared previously while Nω-ethyl-L-arginine (**12**) is a new compound. The D-arginines also have been prepared. A series of non-natural homolysine analogues that are conceptually related to the alkyl arginines have been reported recently.[15] Non-natural **10** is also an inhibitor of the pharmacologically significant enzyme, nitric oxide synthase.[16]

Table 1. Arginine Analogues



Molecule	R_1	R_2
10	H	CH_3
11	CH_3	CH_3
12	H	CH_2CH_3
13	CH_2CH_3	CH_2CH_3

A typical experimental procedure for the synthesis of "ring" and N-ω-alkyl arginine is as follows. Methyl iodide (1.0 g, 9.8 mmoles) was added dropwise to a slurry of the alkylthiourea in 10 mL of acetone. After the initial reaction subsided, the mixture was refluxed for 10 min and ethanol added to dissolve the precipitate. The solution was saturated with hexane while hot and the white crystals that formed after cooling were recovered by filtration. The procedure yields greater than 70 % of the alkylthiouronium salt. The salt (10 mmol) and the HCl salt of **3** (10 mmol, 1.69 g) were dissolved in 10 ml 2 N NaOH and stirred at room temperature for 9 days. At that time the solution was brought to neutral pH with conc. HCl and chromatographed on 500 grams strongly-acidic 50x8 Dowex ion exchange resin. After loading, the column was first washed with water until the eluent is neutral, followed by a wash with 500 ml 0.2 N NH_4OH. The product was eluted with 1 N NH_4OH. Collected fractions were spotted on silica gel TLC plates, developed with phenol:water (3:1) and visualized with ninhydrin. Arginine derivatives can be

distinguished from the slower moving, lighter purple-colored ornithine. Product and starting material were not completely separated but mixed fractions can be recombined and subjected to another round of ion-exchange chromatography. Total yield after two purifications is typically 80% of the enantiomerically pure alkylamino acid isolated as the ammonium salt. Analytical data for the synthesized compounds are as follows:

2-(5-Carboxypentyl-2,5-diamino)-4,5-dihydroimidazole: ^{1}H NMR (300 MHz, D_2O) 3.44 (1H,t), 3.21(2H,t), 1.9-1.3(8H,m); ^{13}C NMR (75.5 Mhz, D_2O) 178.3, 160.1, 56.2, 55.1, 42.5, 41.8, 28,4, 24.5; HRMS calculated, 201.1353; observed, 201.1337.

2-(5-Carboxypentyl-2,5-diamino)-3,4,5,6-tetrahydropyrimidine: ^{1}H NMR (300 MHz, D_2O) 3.33 (1H, t), 3.05 (2H, m), 1.9-1.3 (10H, m); ^{13}C NMR (75.5 MHz, D_2O) 180.7, 180.5, 55.2, 54.9, 40.8, 39.6, 30.8, 24.2, 23.9. This product was unstable to HRMS analysis.

Nω-Methyl L-Arginine: ^{1}H NMR (300 MHz, D_2O) 3.45 (1H, t) 3.25 (2H, t) 2.82 (3H, s) 1.9-1.6 (4H, m); ^{13}C NMR (75.5 MHz, D_2O) 178.6, 156.6, 55.1, 40.9, 29.7, 27.5, 24.2; HRMS calculated, 189.1352; observed, 189.1323.

Nω-Ethyl L-Arginine: ^{1}H NMR (300 MHz, D_2O) 3.45 (1H, t) 3.20 (4H, m) 1.8-1.5 (4H, m) 1.15 (3H, t); ^{13}C NMR (75.5 MHz, D_2O) 180.1, 155.8, 55.3, 40.9, 36.4, 30.4, 24.6, 13.4; HRMS calculated, 203.1508; observed, 203.1509.

Nω,Nω´-Methyl L-Arginine: ^{1}H NMR (300 MHz, D_2O) 3.45 (1H, t) 3.18 (2H, t) 2.79 (6H, s) 1.8-1.5 (4H, m); ^{13}C NMR (75.5 MHz, D_2O) 179.4, 155.9, 54.9, 40.5, 30.2, 27.3, 24.2; HRMS calculated, 203.1508; observed, 302.1505.

Nω,Nω´-Ethyl L-Arginine: ^{1}H NMR (300 MHz, D_2O) 3.55 (1H, t) 3.20 (6H, m) 1.9-1.5 (4H, m) 1.15 (6H, t); ^{13}C NMR (75.5 MHz, D_2O) 179.0, 154.3, 55.1, 40.8, 36.4, 29.3, 24.6, 13.7; HRMS calculated, 231.1871; observed, 231.1846.

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