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Solid-phase synthesis of *N*-acyl-*N'*-carbamoylguanidines

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Abstract: Amino acids immobilized on polystyrene-Wang or Rink amide resin were reacted with *p*-nitrophenyl chloroformate to give an activated urethane that was displaced by *S*-methylisothiourea. Following *N*-acylation with an acid chloride, the thiomethyl group was displaced by primary or secondary amines with the aid of mercury (II) chloride to yield the unsymmetrically substituted title compounds after resin cleavage.

Keywords: combinatorial chemistry, solid-phase synthesis, thioformamidines, guanidines.

The application of solid-phase techniques to the preparation of non-oligomeric organic compounds was first pioneered by Leznoff[1] over twenty years ago. Until recently, this remained a relatively unexplored area of organic synthesis. However, the advent of high-throughput screening within the pharmaceutical industry and the resulting capacity to assay large libraries of compounds has rejuvenated the field. Solid-phase variants now exist[2] for a wide range of organic reactions.

The guanidine functional group is an important component in many biologically active natural products[3] as well as medicinal agents.[4] Several solid-phase syntheses[5] of small-molecule alkylguanidines have recently appeared. Here, we report[6] a combinatorial route to unsymmetrical *N*-acyl-*N'*-carbamoylguanidines, a substitution pattern that has hitherto been unexplored on solid-phase.

Our approach was to use *S*-methylisothiourea (2-methyl-2-thiopseudourea) as a latent guanidine. We anticipated that unsymmetrical substitution of the two nitrogens could be efficiently achieved on solid-phase by stepwise reaction. First, the isothiourea is carbamoylated by a resin-bound species, followed by reaction with an acylating agent in solution. On the basis of solution-phase precedent,[7] subsequent aminolysis of the thiomethyl group in the presence of mercury (II) salts would lead to guanidines.

The above route was first investigated on polystyrene(PS)-Wang resin (Scheme 1). Commercially available α-amino acids loaded on the resin were reacted with *p*-nitrophenyl chloroformate to afford activated urethane **1**, which was displaced by the free base of *S*-methylisothiourea to give urea **2**. This intermediate is subjected to acylation to provide *N,N'*-disubstituted *S*-methylisothiourea **3**. Independent model studies in solution-phase (data not shown) helped establish suitable conditions for the subsequent mercury (II) promoted aminolysis. Finally, the *N*-acyl-*N'*-carbamoylguanidines **4** were released by TFA cleavage from the resin to yield the desired compounds **5**. Three examples[8] of unsymmetrical guanidines prepared in this manner are shown in Scheme 1.

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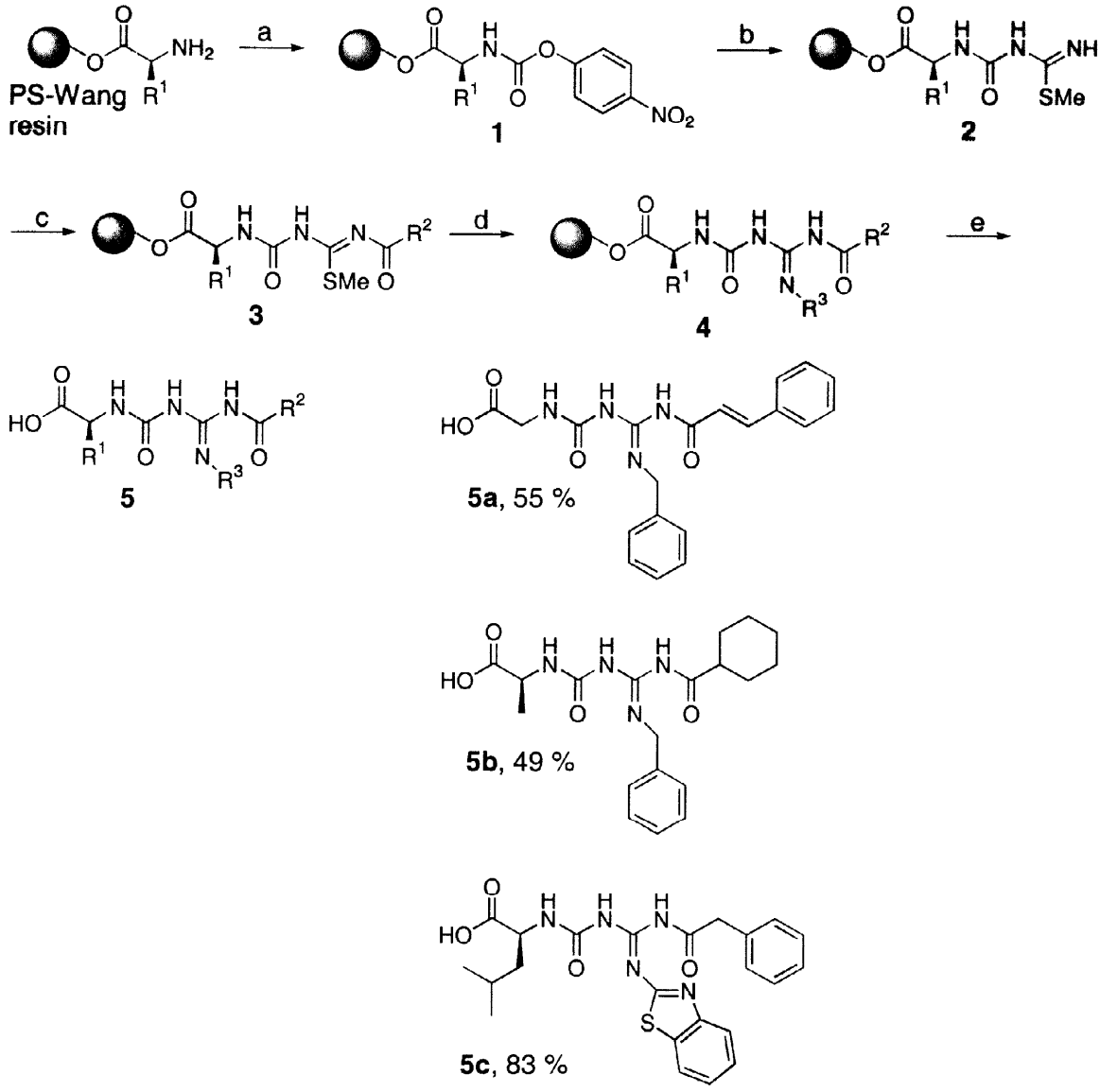

Scheme 1. Solid-phase synthesis of unsymmetrical *N*-acyl-*N'*-carbamoylguanidines, with crude mass recovery of three examples (purity 72-95 % by HPLC UV detection). a. *p*-nitrophenyl chloroformate, pyridine, CH_2Cl_2; b. *S*-methylisothiourea, Et_3N, DMF; c. R^2-COCl, Et_3N, CH_2Cl_2; d. R^3-NH_2, $HgCl_2$, Et_3N, DMF / CH_2Cl_2; e. 95 % TFA.

The use of PS-Wang resin results in guanidines with a free carboxylic acid at the point of resin attachment. We have also adapted[9] the route in Scheme 1 to α-amino acids loaded on PS-Rink amide resin, yielding a carboxamide terminus instead. All steps in this reaction sequence occur under mild conditions at room temperature and a wide variety of amino acid, acid chloride and amine building blocks are tolerated (for examples, see Figure 1). An advantage of mercury (II) accelerated aminolysis is that both primary and secondary amines can be employed. Dodd and Wallace have recently reported[5e] displacement of an

alkylthiourea linker by primary amines at 80 °C without activation by metal salts. In their case, complex mixtures were formed with secondary amines.

In summary, our synthesis provides convenient access to unsymmetrical *N*-acyl-*N'*-carbamoylguanidines from simple building blocks available with a high degree of diversity. We are presently applying this methodology to the preparation of a 1,000-member library of discrete guanidines.

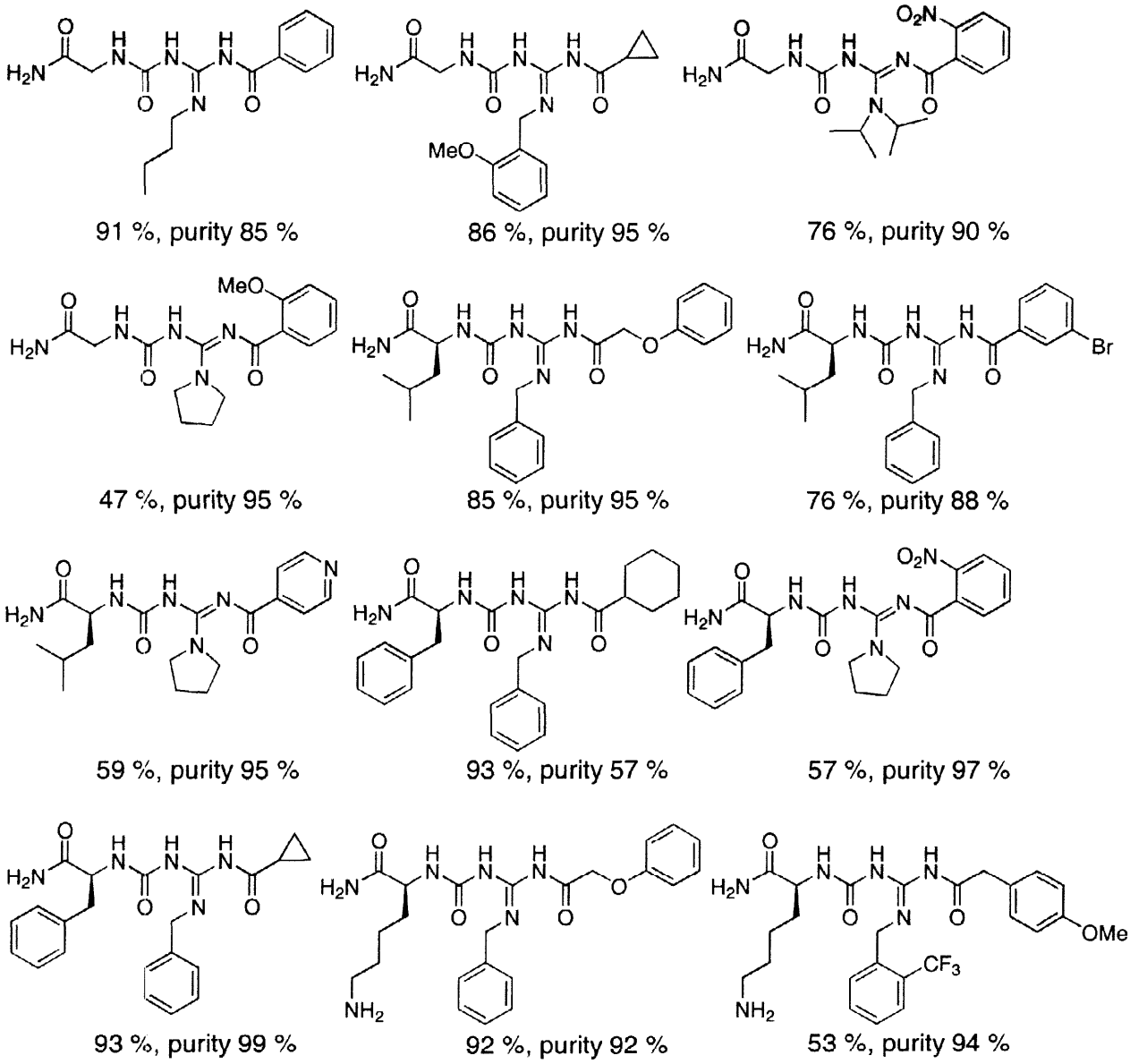

Figure 1. Examples of *N*-acyl-*N'*-carbamoylguanidines prepared on Rink amide resin. Crude mass recovery is indicated (%, based on the initial loading of Rink-NH_2). Purity was assessed by reverse phase HPLC with UV diode array detection at 210 nm. For simplicity, a single structure is shown in each case, although guanidine tautomers and amide rotamers exist.

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8. The identity of all new compounds was determined spectroscopically (NMR, MS).
9. Typical experimental procedure: Rink amide-Fmoc resin (Novabiochem, loading of 0.67 mmol/g) was deprotected under standard conditions. The resin (100 mg) was swelled in DMF (2 mL) and coupled with Fmoc-protected amino acids (10 equiv) for 24 h in the presence of diisopropylcarbodiimide and hydroxybenzotriazole hydrate (10 equiv each).
   After resin washing and drying, the Fmoc protecting group was removed and the resin swelled in CH_2Cl_2 (1.5 mL). *p*-Nitrophenyl chloroformate (10 equiv) and pyridine (11 equiv) were added, and the resin agitated for 4-8 h. The resin was washed and swelled in DMF (1.2 mL), followed by addition of *S*-methylisothiourea (10 equiv, free base generated from the sulfate salt by treatment with 1 N NaOH) and triethylamine (10 equiv). The resin was shaken (24 h), washed (DMF, CH_2Cl_2, iPrOH, MeOH), and dried.
   The resin was swelled in CH_2Cl_2 (1.2 mL) and shaken with an acid chloride (5 equiv) and triethylamine (5 equiv) for 3-4 h. After washing and drying, the resin was swelled in DMF/ CH_2Cl_2 (5:1, 1.2 mL) and reacted with an amine (10 equiv), $HgCl_2$ (2 equiv), and triethylamine (15 equiv) for 1-3 days. After resin washing, the products were cleaved with 95 % TFA/ CH_2Cl_2 (1.5 mL) for 1 h. The cleavage was repeated for 30 min, and the combined filtrates concentrated under vacuum. The residue was redissolved in MeOH/ CH_2Cl_2 /EtOAc (7.5:42.5:50), passed through a short silica gel column to remove the inorganic salts, and concentrated to yield the guanidines.