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Solid-phase synthesis of *N*,*N*′-substituted acylguanidines

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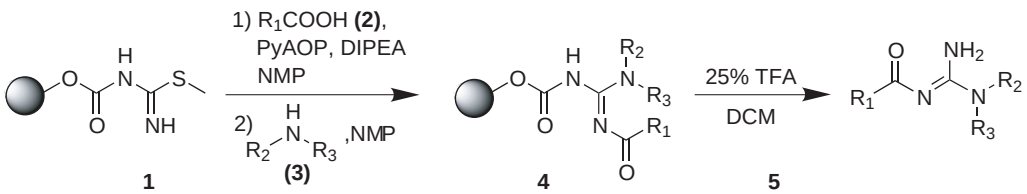
Abstract—An efficient method for the solid-phase synthesis of *N*,*N*′-substituted acylguanidines is presented. The key-step involves the *N*-acylation of resin immobilized *S*-methylisothiourea with a variety of carboxylic acids using PyAOP as the coupling agent. The resulting resin bound *N*-acyl-derivatives are reacted with a host of amines and the *N*-acyl,*N*′-alkyl(aryl)guanidines liberated from the resin upon exposure to TFA. © 2001 Published by Elsevier Science Ltd.

Compounds containing the guanidine moiety are known to elicit a variety of pharmacological responses and are present in several marketed drugs or drug candidates.[1,2] Acylguanidines are an important class of these compounds that are currently being evaluated for the treatment of cardiovascular[2a–f] and neurological disorders,[2g] among others.

Solid-supported organic synthesis has proven to be a powerful tool in the rapid assembly of small molecules.[3] Several methods for the solid-phase synthesis of guanidines have been reported,[4,5] including the preparation of *N*-acylguanidines[5a] and *N*-acyl-*N*′-carbamoylguanidines.[5b] Although, these methods[5] are useful for the generation of smaller focused sets of *N*-acylguanidines, they are limiting in that they necessitate the use of acid chlorides to introduce the *N*-acyl diversity element. This imposes restrictions on the library size as well as the chemical diversity by limiting this input to a small number of commercially available acid chlorides.[6] We herein describe a protocol for the synthesis of substituted *N*-acylguanidines using the much larger pool of commercially available carboxylic acids[6] as the *N*-acyl donors. Our strategy utilizes the previously described resin bound *S*-methylisothiourea as the masked guanidine in the synthesis of *N*-acyl-*N*′-carbamoylguanidines[5b] for the preparation of *N*-acyl,*N*′-alkyl(aryl)guanidines (Scheme 1).

N-Acylation of the resin bound *S*-methylisothiourea[7,8] **1** is best carried out with carboxylic acids (**2**) using 7-azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium–hexafluorophosphate (PyAOP) as the coupling agent. The resin (**1**), carboxylic acid and PyAOP are mixed in a reaction vessel, and suspended in 1-methyl-2-pyrrolidinone (NMP), and the reaction is initiated by the addition of diisopropylethylamine (DIPEA). The progress of the acylation is monitored by reacting a small sample of the resin from the reaction[9a] with benzylamine in NMP[8] followed by treatment with trifluoroacetic acid (TFA) in dichloromethane to liberate the *N*-acyl,*N*′-benzylguanidines. In general, the reactions are allowed to proceed for 60 h at room temperature.[8] For most simple acids, carbodiimide or 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (IIDQ) mediated acylations were also successful; however, the reactions were sluggish and in some cases required double treatments of reagents for complete



Scheme 1.

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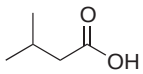
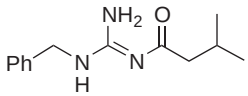
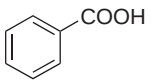
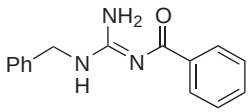
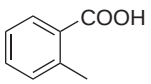
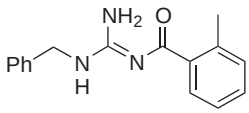
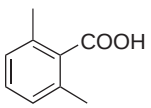
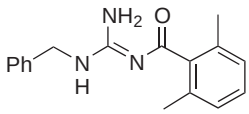
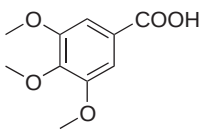
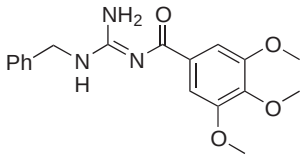
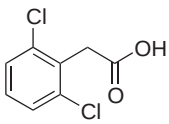
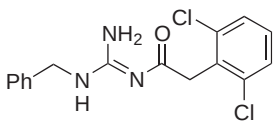
Table 1.

Entry	R_1COOH (2)		Product (5 R_2=Bn, R_3=H)		Purity[a,b]
1		**(2a)**		**(5a)**	>95%
2		**(2b)**		**(5b)**	>95%
3		**(2c)**		**(5c)**	>95%
4		**(2d)**		**(5d)**	–[c]
5		**(2e)**		**(5e)**	>95%
6		**(2f)**		**(5f)**	>95%

[a]HPLC purity is of the crude material after cleavage determined by evaporative light scattering (ELS); peak identity based on LC/MS analysis. [b]Crude yield ranged from 75-85%, as the TFA salt, based on 100% loading of the *p*-nitrophenylcarbonate resin. [c]Trace amount of compound present.

acylation. Furthermore, the purity and yields of the final products were significantly lower than those with PyAOP. The acylations are also sensitive to steric hindrance. For example, benzoic acid (**2b**) and 2-methylbenzoic acid (**2c**) both coupled cleanly within 60 h using PyAOP as the coupling agent, whereas, 2,6-dimethylbenzoic acid (**2d**) gave only a trace amount of the expected product (see Table 1).

The displacement of the thiomethyl group with a variety of amines appears to be general as shown in Table 2. Ammonia, primary or secondary amines, and aniline all reacted cleanly at room temperature to give products **5**.[8,9b] This is in contrast to previous observations[4d,5b] where the resin-immobilized *N*-acylisothioureas failed to react with secondary amines or anilines in the absence of mercury or silver metal salt assisted activation, even at elevated temperatures.[4d] The final compounds were liberated from the resin by exposure to 25% TFA in dichloromethane.[8]

In summary, an efficient route to the solid-phase synthesis of substituted *N*-acyl,*N*′-alkyl(aryl)guanidines using carboxylic acids is presented. This procedure is mild and general and takes advantage of the large pool of commercially available carboxylic acids[6] to introduce the *N*-acyl diversity element. It allows for a high level of flexibility and is amenable for parallel array or combinatorial synthesis. The resulting resin bound *N*-acyl,*S*-methylisothiourea intermediates react with ammonia, amines, or anilines to provide *N*-acyl,*N*′-alkyl(aryl)guanidines in high purity and yield.

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Table 2.

Entry	R_2-NH-R_3 (3)	Product (5 R_1=2,6-dichlorobenzyl)		Purity[a,b]
1	NH_3	**(3a)**	**(5g)**	85%
2	*n*-$PrNH_2$	**(3b)**	**(5h)**	>95%
3	*i*-$PrNH_2$	**(3c)**	**(5i)**	>95%
4	allylNH_2	**(3d)**	**(5j)**	>95%
5	$(CH_3)_2NH$	**(3e)**	**(5k)**	>95%
6	aniline	**(3f)**	**(5l)**	90%

[a]HPLC purity is of the crude material after cleavage and determined by evaporative light scattering (ELS); peak identity based on LC/MS analysis. [b]Crude yield ranged from 75-85%, as the TFA salt, based on 100% loading of the *p*-nitrophenylcarbonate resin.

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6. ACD(Available Chemical Directory); MDL Information Systems, San Leandro, CA, USA.
7. *p*-Nitrophenylcarbonate resin was prepared from Wang resin according to the procedure of Ho, C. Y.; Kukla, M. J. *Tetrahedron Lett.* **1997**, *38*, 2799.
8. Typical procedure: A mixture of *p*-nitrophenylcarbonate resin[6] (2.5 g, 1.1 mmol/g, 2.75 mmol), *S*-methylisothiouro-

nium sulfate (1.9 g, 6.88 mmol) and Cs_2CO_3 (9 g, 28 mmol) was suspended in dry DMF (70 mL). The contents were shaken vigorously for 48 h at rt. The resin was washed successively with 10% H_2O/DMF (3×50 mL), DMF (3×30 mL), THF (3×30 mL), and CH_2Cl_2 (3×30 mL). Resin **1** was dried under high vacuum for 10 h. A mixture of the resin **1** (0.1 mmol), carboxylic acid (**2**) (0.3 mmol) and PyAOP (160 μg, 0.3 mmol) was slurried in NMP (2 mL) and treated dropwise with $(i\text{-Pr})_2$EtN (175 μL, 1 mmol) and gently shaken for 60 h, although the reactions in most instances are complete within 24–48 h. The resin was washed using the sequence of solvents described above and dried under high vacuum. A sample of the acylated resin (0.05 mmol) in dry NMP (1 mL) was treated with the appropriate amine (**3**) (0.25 mmol) and shaken at rt for 48 h (for amine hydrochlorides, 1 mmol of $(i\text{-Pr})_2$EtN was added to the reaction). The resin (**4**) was washed thoroughly with DMF (3×2 mL), THF (4×2 mL), and CH_2Cl_2 (4×2 mL) and suspended in 25% TFA/CH_2Cl_2 (1 mL) and shaken for 1.5 h. The filtrate was collected and concentrated in vacuo. The purity of the isolated product **5** was established by HPLC using a UV(220 nm) and a ELS detector.

9. (a) *N*-acyl,*S*-methylisothiourea intermediates are sensitive to TFA cleavage conditions and thus require reaction with an amine for purity determination; (b) Sluggish reactions can be heated gently ($\sim$50–60°C) to speed up the aminolysis.