Report

Modular Three-Component Solid-Phase Synthesis of Unsymmetrical Guanidines via Resin Capture of Carbodiimides

Paul A. Boguszewski, Shahzad S. Rahman, and A. Ganesan

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Modular Three-Component Solid-Phase Synthesis of Unsymmetrical Guanidines via Resin Capture of Carbodiimides†

Paul A. Boguszewski,‡ Shahzad S. Rahman,§ and A. Ganesan*,‡

Department of Chemistry, University of Southampton, Southampton SO17 1BJ, United Kingdom, and High Throughput Chemistry, GlaxoSmithKline, NewFrontiers Science Park, Harlow CM19 5AW, United Kingdom

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Because of their basicity and hydrogen-bonding properties, guanidines are an important functional group in many biologically active compounds of natural or synthetic origin (Figure 1). Consequently, methodologies for the parallel synthesis of guanidines have attracted much attention from both academia and industry. Numerous solid-phase routes have been reported,[1] and the vast majority of these involve either urea or thiourea precursors[2] or guanidine synthesis from pseudoureas or similarly activated amidines.[3]

Mechanistically, guanidine synthesis involving ureas, thioureas, or amidine derivatives often proceeds through carbodiimide intermediates. For the formation of unsymmetrically substituted guanidines, this method necessarily requires the prior synthesis of an unsymmetrical urea or thiourea. Meanwhile, the Staudinger (aza-Wittig) reaction[4,5] is a convenient and direct route to unsymmetrical carbodiimides. Nevertheless, it has seldom been employed for solid-phase guanidine synthesis,[6] and previous examples have featured a specific immobilized carbodiimide reacting with an external amine. Here, we describe a flexible approach whereby crude carbodiimides in solution are converted to guanidines by solid-phase resin "catch and release".[7] This procedure facilitates the preparation of diverse unsymmetrical guanidines from three building blocks, namely, iminophosphoranes, isocyanates, and amines. A large variety of isocyanates and amines are commercially available, and iminophosphoranes are conveniently prepared from organic azides, in turn, arising from halides. In addition, iminophosphoranes can be accessed from amines by the Kirsanov reaction.[8] In principle, this allows for the synthesis of unsymmetrical guanidines in which all three of the substitutents are derived from amines.

Our initial studies (Scheme 1, R_3 = H) involved the synthesis of unsymmetrical carbodiimides via the Staudinger reaction between an iminophosphorane and an isocyanate. This reaction was easily monitored by IR spectroscopy (N═C═N stretch, ∼2200 cm^{-1}). Extraction of the reaction mixture with hexane effected significant purification, as

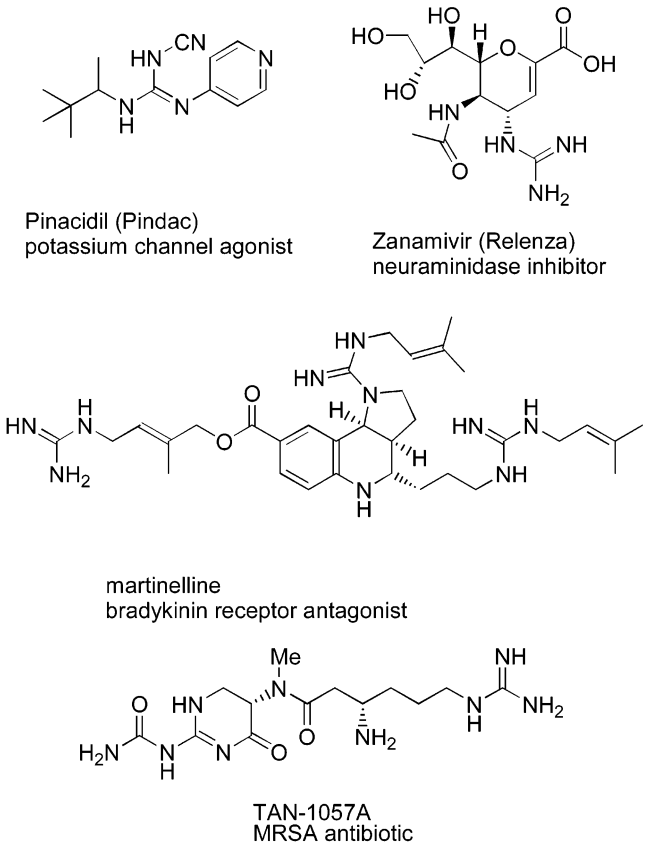

Figure 1. Examples of biologically active guanidines.

Table 1. Disubstituted Guanidines Prepared from the Rink Amide AM Resin

R_1	R_2	yield (%)
p-NC−C_6H_4−	Ph−	88
c-C_6H_{11}−	Ph−	72
n-C_3H_7−	Ph−	81
p-MeO−C_6H_4−	Ph−CH_2CH_2−	64
c-C_6H_{11}−	Ph−CH_2CH_2−	55
n-C_3H_7−	Ph−CH_2CH_2−	65

excess iminophosphorane and triphenylphosphine oxide remain behind as a precipitate. The crude carbodiimide was then captured by polystyrene−Rink amide AM resin to give an immobilized guanidine and released by TFA resin cleavage as a trifluoroacetate salt. Ion exchange through a sulfonic acid resin cartridge and elution with methanolic ammonia yielded the guanidine freebase. A series of disubstituted guanidines was prepared in this manner (Table 1), attesting to the general viability of the method.

A limitation in the above synthesis is that the Rink amide AM resin behaves as an ammonia equivalent. Further extension to trisubstituted guanidines would require the use of alkylated versions of the Rink amide AM resin. Although there are procedures[9] for this transformation, they were not completely satisfactory for our purposes. An additional disadvantage was the relatively low loading and high cost of the Rink amide AM resin. For these reasons, we turned to the 4-formyl-3-methoxyphenyloxymethyl polystyrene resin

* To whom correspondence should be addressed. E-mail: ganesan@soton.ac.uk

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‡ University of Southampton.

§ GlaxoSmithKline.

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Scheme 1. Synthesis of Unsymmetrical Guanidines by Resin Capture of Carbodiimides

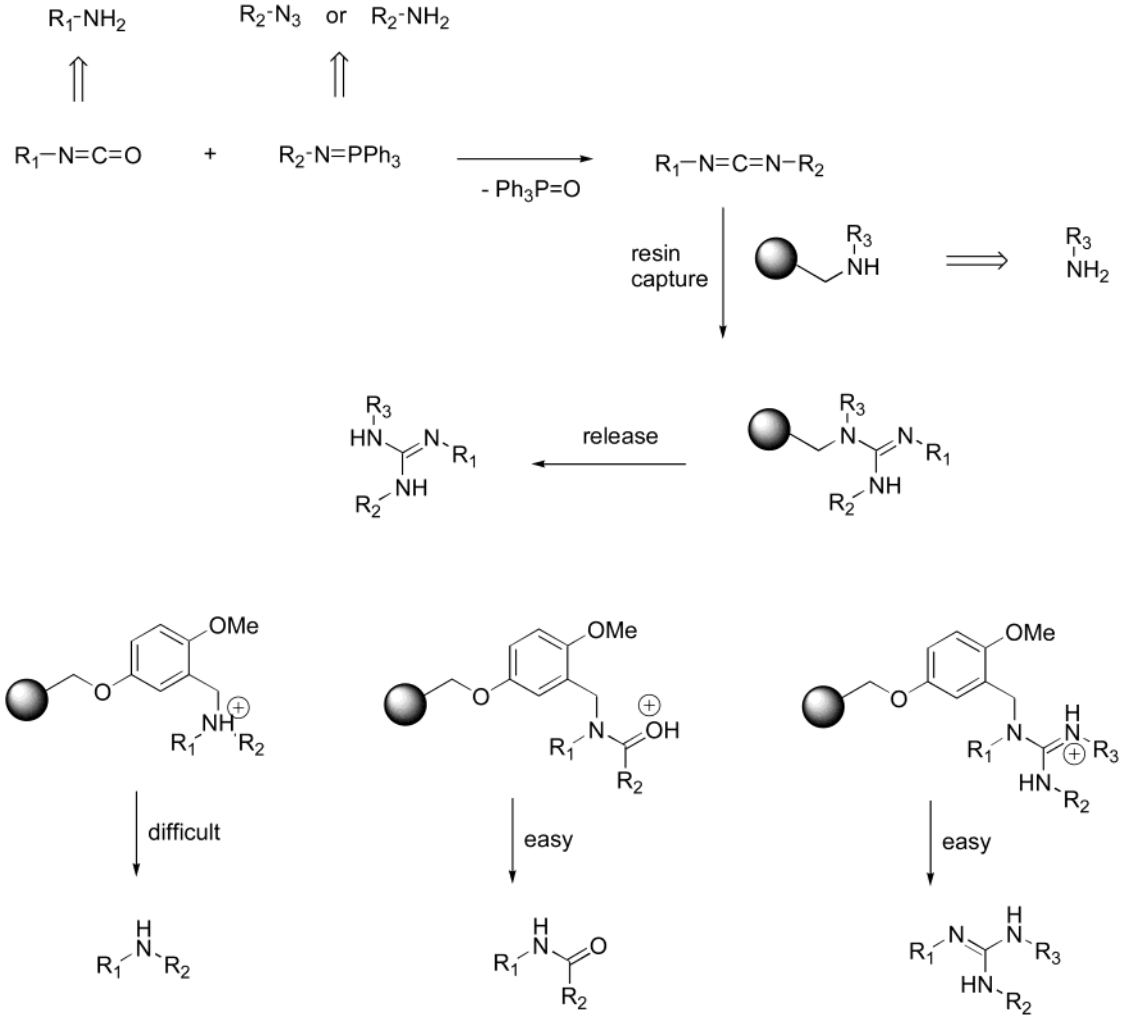
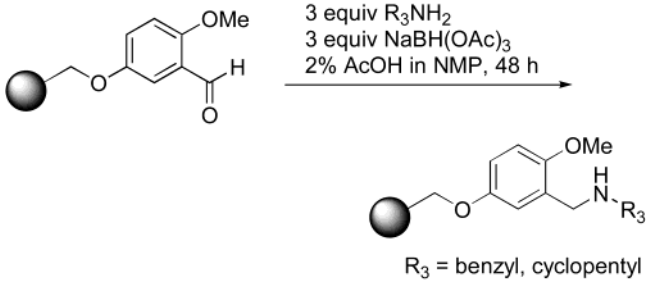


Figure 2. Cleavage of various functional groups from the reductively alkylated resin.

Scheme 2. Synthesis of Secondary Amine Resins by Reductive Alkylation



(AMEBA resin),[10] readily obtained by the alkylation of high-loading Merrifield resin with 4-hydroxy-2-methoxybenzaldehyde. Reductive alkylation[11] of the aldehyde resin (loading of ~2 mmol/g) by two test primary amines, benzylamine and cyclopentylamine, proceeded smoothly to afford the corresponding alkylamine resin (Scheme 2). These reactions were quantitative as judged by the disappearance of the C═O IR stretch and MAS (magic angle spinning) NMR spectroscopy.

Subjecting these alkylamine resins to the above catch-and-release procedure with carbodiimides furnished the trisubstituted guanidine. Interestingly, these reductively alkylated amine resins are normally inefficient for the synthesis of amines by acidic cleavage of the protonated amine. Conventionally, they are used for the cleavage of functional groups such as amides or sulfonamides, where the protonation site is not the atom of attachment to the support. Presumably, the same is true for our guanidines (Figure 2), thus enabling the facile cleavage of a basic functional group, which we believe to be unprecedented with these resins.

To illustrate the scope of this three-component process, a small array was prepared. The building blocks were the two reductively alkylated amine resins; four commercially available isocyanates; and two iminophosphoranes, phenyl and phenethyl[12] (Table 2). Parallel synthesis was carried out with the aid of a Bohdan MiniBlock instrument, and the desired trisubstituted guanidines were produced in good yield and purity after the ion-exchange purification.

In conclusion, we have developed a novel and facile way of making diverse guanidines from three readily available monomers, one of which is in the solid phase. As the synthesis proceeds by resin capture, there is no need for full purification of the carbodiimide precursor. We have demonstrated the effective use of sulfonic acid ion-exchange cartridges as a means for liberating the guanidine freebase after resin cleavage with TFA. This procedure is ideally suited for the construction of large combinatorial libraries.

Table 2. Trisubstituted Guanidines Prepared from the Reductively Alkylated Resins

R_1	R_2	R_3	yield (%)
c-C_6H_{11}−	Ph−	Ph−CH_2−	80
c-C_6H_{11}−	Ph−	*c*-C_5H_9−	92
p-MeO−C_6H_4−	Ph−	Ph−CH_2−	62
p-MeO−C_6H_4−	Ph−	*c*-C_5H_9−	70
n-C_3H_7−	Ph−	Ph−CH_2−	77
n-C_3H_7−	Ph−	*c*-C_5H_9−	81
p-NC−C_6H_4−	Ph−	*c*-C_5H_9−	89
p-NC−C_6H_4−	Ph−CH_2CH_2−	*c*-C_5H_9−	83
c-C_6H_{11}−	Ph−CH_2CH_2−	Ph−CH_2−	58
c-C_6H_{11}−	Ph−CH_2CH_2−	*c*-C_5H_9−	66
p-MeO−C_6H_4−	Ph−CH_2CH_2−	Ph−CH_2−	63
p-MeO−C_6H_4−	Ph−CH_2CH_2−	*c*-C_5H_9−	42
n-C_3H_7−	Ph−CH_2CH_2−	Ph−CH_2−	78
n-C_3H_7−	Ph−CH_2CH_2−	*c*-C_5H_9−	64

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Supporting Information Available. Detailed experimental procedures and characterization data for all new guanidines. This material is available free of charge via the Internet at http://pubs.acs.org.

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