Solid-Phase Organic Synthesis

Edited by Kevin Burgess
SOLID-PHASE ORGANIC SYNTHESIS
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Method development in combinatorial chemistry has, to all intents and purposes, happened. The insights of people like Geysen, Furka, Houghton, Lam, Lebl, Hruby, Gallop, Pirrung, and Schultz led the rest of us to realize that we could, and should, be doing what we were doing much faster and more efficiently. The pharmaceutical industry has changed dramatically because of this, and others, like the oil and polymer industries, are beginning to appreciate the value of these approaches.

Conversely, development of methods for solid-phase synthesis is happening. Supported methods pioneered by Leznoff and others attracted little interest until the right person, at the right place, at the right time, Jon Ellman, reinstated them to a prominent position. Many other groups were working on solid-phase methods to support combinatorial efforts, but Jon’s papers were certainly the first to attract widespread attention in the 1990s. Most of the combinatorial and high-throughput methods that are finding practical application today use solid-phase chemistry in some form, and these methods would be used even more extensively if supported organic chemistry were refined further. It seems inevitable that the literature on solid-phase organic synthesis will continue to expand rapidly over the next decade as researchers explore the scope of this technique.

This book is a compilation of reviews from some leaders in various aspects of solid-phase syntheses. I undertook to compile them because of a conviction that a collection of specialized reports in this area would be useful. In fact, I believe that, if the demand exists, it might be useful to
publish similar compilations annually or biannually. Certainly, not all the important aspects of solid-phase syntheses are covered in this book; there is room for a sequel.

To encourage top people to contribute to this book, I tried to keep the style close to something familiar and chose that of *The Journal of Organic Chemistry*. In some cases the format is not quite the same, however. Most of those deviations are my mistakes or a compromise with Wiley’s standard format, but inclusion of titles in the reference section was a deliberate transgression designed to make the work more reader-friendly. The abbreviations used throughout this book are the same as those listed in *The Journal of Organic Chemistry*. The preferred format of each chapter was a reasonably comprehensive review of a narrowly defined area. Jiong Chen and I wrote Chapter 1 to illustrate the type of format that might be useful to a large number of readers. Some authors preferred to concentrate on work from their own laboratories, though, and I encouraged this when authors had a coherent and well-rounded story to tell from their own research. A single chapter in this book includes some illustrative experimental procedures because, in that particular case, the methods have not been widely used in the pharmaceutical industry, and a few protocols seemed especially valuable. In general, constructive criticism and suggestions regarding the format of this book would be welcome (burgess@mail.chem.tamu.edu).

I want to thank Barbara Goldman and her associates at Wiley for their guidance, all the contributors for coming through in the end, Armin Burghart and Jiong Chen (two postdoctoral associates at A&M) for proofreading some chapters that I changed a lot, and my research group for tolerating this distraction.

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SOLID-PHASE ORGANIC SYNTHESIS
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1.1. INTRODUCTION

Guanidines are basic molecules (p$K_a$ of guanidine = 12.5) with a capacity to form intermolecular contacts mediated by H-bonding interactions. Consequently, they are potentially useful pharmacophores in medicinal chemistry, have proven applications as artificial sweeteners, and are useful as probes in academic studies of intermolecular associations, including “supramolecular complexes.” Expedited access to these molecules via solid-phase synthesis is therefore a worthy goal. This chapter outlines various
solution-phase syntheses of guanidines, then gives a more detailed description of work that has been done to adapt these methods to supported syntheses.

1.2. OUTLINE OF SOME SOLUTION-PHASE APPROACHES TO GUANIDINES

It is difficult to formulate retrosynthetic analyses of guanidines because their substitution patterns determine the most efficient routes to these materials. Some generalities are outlined in Scheme 1. These syntheses are discussed more fully in the following subsections, although the coverage is intended to be an outline of the approaches most relevant to solid-phase syntheses, not a comprehensive summary.

1.2.1. From Electrophiles Containing One Nitrogen Atom

Imidocarbonyl dichlorides that are functionalized with an electron-withdrawing group (e.g., 1) react with amines at room temperature or below, affording symmetrical guanidines. It was originally suggested that guanidines with less symmetrical substitution patterns could not be formed.
1.2. OUTLINE OF SOME SOLUTION-PHASE APPROACHES TO GUANIDINES

by stepwise displacement of leaving groups from imidocarbonyl dichlorides, but that suggestion has been shown to be incorrect, as illustrated in Scheme 2.

Stepwise displacement of phenoxide from diphenyl carbonimidates (e.g., 2) is also possible, as in Scheme 3.

Imidoyl dichlorides are formed by chlorination of the corresponding S,S-dialkylimidodithiocarbonimidates, but the latter compounds can also be used as starting materials for syntheses of guanidines. In this type of synthesis, an amine is generally heated with the S,S-dialkylimidodithiocar-
bonimidate (e.g., 3) to cause the first displacement; then the product is treated with the second amine and a metal salt with high affinity for sulfur to give the guanidine (Scheme 4).\(^7\)\(^8\)

1.2.2. From Electrophiles Containing Two or More Nitrogen Atoms

Cyanamides like 4 (from amines and cyanogen bromide) provide access to guanidines. This approach allows for introduction of different substituents, and alkylating intermediates can further increase the diversity of products produced. However, high temperatures are required, especially with aromatic amines, for the final addition to give the guanidine products (Scheme 5).\(^9\)

A comparatively large selection of thioureas can be formed from the reaction of amines with isothiocyanates, hence they are attractive starting materials for formation of guanidines. A common solution-phase approach to this reaction involves abstraction of the sulfur via a thiophillic metal salt, like mercuric chloride.\(^10\) For solid-phase syntheses, however, formation of insoluble heavy-metal sulfides can have undesirable effects on resin properties and on biological assays that may be performed on the product. A more relevant strategy, with respect to this chapter, is S-alkylation of thioureas and then reaction of the methyl carbamimidothioates formed (e.g., 5, Scheme 6) with amines. This type of process has been used extensively in solution-phase syntheses.\(^11\)\(^–\)\(^14\) Two examples are shown in Scheme 6;\(^11\) the second is an intramolecular variant, which involves concomitant detritylation.\(^15\)
Methanethiol is a by-product of reactions of the type illustrated in Scheme 6. This is unlikely to be produced in amounts that would cause problems in solid-phase syntheses, but alternatives are available that avoid this noxious by-product. For instance, an $S_{N}Ar$ displacement of fluoride
from 2,4-dinitrofluorobenzene gives the activated system 6.\textsuperscript{16} The latter can be reacted with amines to give guanidines (Scheme 7), though complications occur for deactivated aromatic amines.

Other electrophiles have been used to activate thioureas in one-pot processes to give guanidines directly. These include water-soluble carbodiimides\textsuperscript{17,18} and the Mukaiyama reagent 7, as illustrated in Scheme 8.\textsuperscript{19} The thioureas shown in Schemes 7 and 8 have two electron-withdrawing substituents. Issues relating to the generality of these reactions are not well documented for thioureas having less electron-withdrawing \textit{N}-substituents.

Shown below are some other electrophiles that have been used to form guanidines from amines. The pyrazole derivatives 8\textsuperscript{20} have been used extensively in peptide syntheses.\textsuperscript{21} The aminominomethanesulfonic acid derivative 9\textsuperscript{22} might be the intermediate formed when thioureas are oxidized and then reacted with amines to form guanidines; certainly 9 is a useful
guanylating agent. Triflylguanidines 10 as guanidinylation agents are a relatively new innovation.\textsuperscript{23} This is a potentially useful discovery because the triflylguanidines can be formed in two steps from guanidine hydrochloride.

Guanidines may also be formed by reaction of amines with carbodiimides. This reaction is limited by the availability of carbodiimides, which are usually formed by several methods,\textsuperscript{24} including dehydration of ureas with the Edward Burgess reagent 11 (Scheme 9).\textsuperscript{25-27}

![Scheme 9.](image)

![Scheme 10.](image)
Finally, alkylation reactions can be used to add substituents to guanidines. These may be performed under quite basic conditions (e.g., NaH/alkyl halide)\(^{28,29}\) or via the Mitsunobu process, as illustrated in Scheme 10.\(^{30}\)

### 1.3. SOLID-PHASE SYNTHESES INVOLVING RESIN-BOUND ELECTROPHILES

#### 1.3.1. Supported Carbodiimides

Supported carbodiimides can be produced via aza-Wittig reactions. The example in Scheme 11 shows the reaction of a benzylic azide with triphenylphosphine to give an aminophosphorane.\(^{31}\) This was then coupled with phenylisothiocyanate to give the corresponding carbodiimide.

The sequence shown in Scheme 11 was more effective if the isothiocyanate was premixed with the azide, rather than added after the phosphine. Aza-Wittig reagents can undergo exchange reactions with carbodiimides;

![Scheme 11](image-url)
in the absence of isothiocyanate, this occurs between supported aza-Wittig and supported carbodiimide, giving undesirable symmetric guanidines. This illustrates an important feature in solid-phase syntheses; that is, 

*reactive centers on a support are close enough to perform intermolecular reactions unless the resin loading is kept low.* Our group has found that intermolecular reactions are effectively suppressed in one particular reaction when resin loadings of 0.3 mmol/g or less were used. The support used in Scheme 11 was a Rink functionalized pin (Chiron) with an unspecified loading level.

The presence of the aryl spacer groups, derived from the benzylic azide, in Scheme 11 was critical; the reaction failed when short-chain aliphatic linkers were used. We suspect this may be due to unwanted cyclization.

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**Scheme 12.**
reactions. Moreover, sterically encumbered isothiocyanates and acyl isothiocyanates did not react well in the sequence. Overall, the scope of this process is relatively limited.

Scheme 12 features a similar approach to that shown in Scheme 11, except that the guanidines were designed to undergo Michael addition to give a bicyclic system. Mitsunobu reaction of the corresponding nitro cinnamic acid with Wang resin followed by reduction of the NO$_2$ functionality (SnCl$_2$) formed the required amino cinnamic acid ester starting material. Formation of the carbodiimide and conversion to the guanidines were monitored by IR (N=C—N, 2135 cm$^{-1}$). Formation of the guanidines was slower than the Michael addition step, hence the temperature had to be raised in the penultimate step of the sequence.

A carbodiimide-grafted polystyrene resin was reacted with tetramethylguanidine to give an interesting biguanide structure (Scheme 13). This was assayed as a catalyst for a transesterification reaction. Incidentally, resin-bound guanidines are useful bases for processes involving resin capture.

1.3.2. Supported Thioureas

Scheme 14 shows a typical example in a series of reactions in which a supported amino acid reacted with fluorenylmethoxycarbonyl isothiocyanate to give a supported (on Rink’s amide) thiourea. Removal of the $N$-protection followed by S-alkylation gave supported isothioureas. Reaction of these with amines, then cleavage from the resin, afforded substituted guanidines. For 10 examples the purities were between 40 and 92%. An aryl group separates the resin from the guanidine, just as in the sequences shown in Schemes 11 and 12.
Another strategy in which thioureas were \( N \)-linked to a carboxyimidazole resin and then converted to guanidine products is shown in Scheme 15.\(^{37}\) Thus the supported BOC-protected thiourea 12 reacted with aliphatic amines without any activating agent. Aromatic amines, however, required activation, and the Mukaiyama pyridinium 7 was used for this. Conversely, acyl-, aryl-, allyl-, and alkyl-substituted thioureas 13 were linked to the resin as a precursor to other guanidines, many lacking the activating effect of electron-withdrawing groups. The intermediate thioureas were treated with EDC, then with amine, to give the products. The authors of this work state that the method was used extensively to form many different products (>45), but lists of the specific compounds produced were not given.

A very similar method has been used by Lin and Ganesan to produce \( N \)-acyl-\( N' \)-carbamoylguanidines.\(^{38}\) The activating agent used by them was mercuric chloride, and the waste heavy metal was removed by filtration at the end of the synthesis. Scheme 16 shows two compounds prepared by this method.
Work by Dodd and Wallace on solid-phase guanidine syntheses is unique insofar as an S-linked thiourea 14 was used. Their approach exploits the previous findings of one of these researchers regarding the efficacy of bis-BOC-protected guanidines in Mitsunobu reactions (Scheme 10). They treated Merrifield resin with excess thiourea to give a supported thioonium salt, as illustrated in Scheme 17. Both nitrogen atoms of this material were masked on the solid phase by reactions with (BOC)$_2$O and Hünig’s base. Mitsunobu reactions of the supported bis-BOC-protected isothiourea gave a monoalkylated product. This was then reacted with...
ammonia or primary alkylamines to give guanidines with concomitant cleavage from the resin. This paper featured 13 examples and a typical experimental procedure was given; it describes what appears to be an excellent solid-phase synthesis of many guanidines.