



A facile and practical one-pot ‘catch and release’ synthesis of substituted guanidines

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ABSTRACT

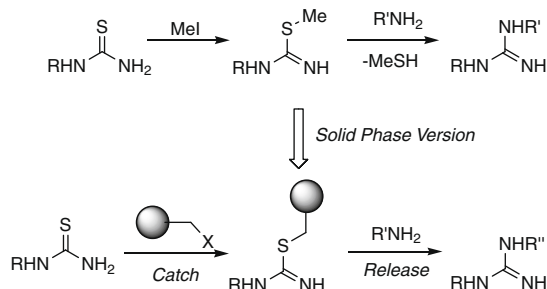
A ‘catch and release’ two-step one-pot protocol has been developed for the facile and practical synthesis of substituted guanidines from thioureas and various amines utilizing readily available brominated polystyrene resin.

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The functionality of guanidines has been found in many natural products and medicinally interesting molecules mainly due to their basicity and hydrogen-bonding properties. They are important pharmacophores in various therapeutic areas with biological activities ranging from antimicrobial, antiviral, antifungal to neurotoxic.¹ As a result, methods have been developed for the synthesis of guanidines both in solution and on solid support.² Solid phase synthesis offers the unique advantage that excess reagents or resins can be used to drive the reaction to completion thus simplifying purification. However, most of the known solid phase methods for guanidine synthesis either involve lengthy preparation of the specially designed linkers, or leave the generated guanidine with a ‘handle’ after cleavage, which in many cases may not be desirable.^{2a,3}

In connection with ongoing research efforts, we needed a direct and practical synthetic method that would allow us to access the guanidine moiety from diverse sets of amines and thiourea scaffolds using readily available reagents. The method should also be amenable to library automation. Here we report a facile and practical method we have developed for the synthesis of substituted guanidines.

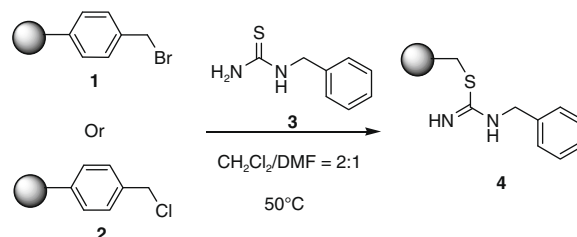
Typically, the synthesis of guanidines involves treating of an amine or amine equivalent with an electrophilic amidine species. The most commonly used such species is *S*-alkylisothiurea, in particular, *S*-methyl isothiurea. With this method, guanidines can be easily synthesized from amines and thioureas in a two-step process (Scheme 1). The advantages of this method are that no extra coupling reagent is needed, mild reaction conditions are utilized, and in many cases, high yields of the final products can be obtained with diverse amines. However, the major drawback of this method is the generation of noxious and toxic methyl mercaptan, which is unpleasant to work with and not suitable for high throughput



Scheme 1. Guanidine formation through *S*-methylisothiurea in solution and on solid support.

Table 1

Determination of the loading of benzylthiourea 3



Entry	Equiv of the resin relative to 3	Resin 1 ^a (4 h)	Resin 2 ^a (30 h)
1	0.8	100% ^b	69% ^b
2	1	91%	56%
3	1.5	100% ^c	83% ^c

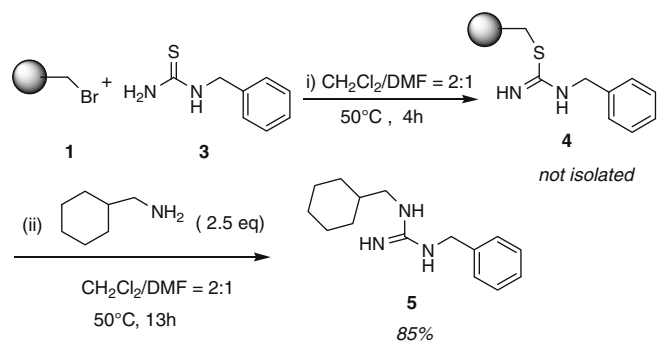
^a All percentages are determined based on the limiting reagents.

^b Percentages are determined based on the consumption of the resin.

^c Percentages are determined based on the consumption of **3**.

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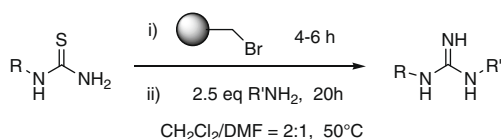
Scheme 2. One-pot synthesis of guanidine **5**.

automated library production. To circumvent this problem and take advantage of this synthetic route, a corresponding 'catch and release' solid phase version was designed (Scheme 1).⁴ In this approach, there's no additional 'handle' required for the thiourea scaffold, as the resin is attached through the sulfur atom. Subsequently, the 'SH' group is retained by the polymeric solid support upon displacement by amines.

For our initial studies, we chose to examine the guanidination of benzylthiourea with aminomethylcyclohexane. Both brominated and chlorinated polystyrene resins **1** and **2** were tested in the first loading step (Table 1). Initial experiments showed that the reaction proceeded faster in a CH_2Cl_2 –DMF (2:1) solvent system than in DMF, which was used to facilitate the dissolution of the thioureas. Addition of base, such as diisopropylethylamine, did not facilitate

Table 2

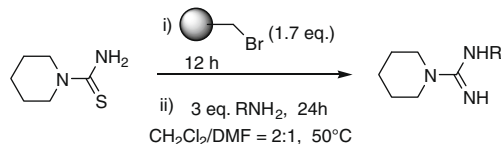
One-pot synthesis of N,N'-disubstituted guanidines



Entry	Thiourea	Amine	Product ^a	Yield (%)
1				80
2				99
3				84
4				82
5				97
6				82
7				43

Table 4

Synthesis of trisubstituted guanidines from N,N-disubstituted thiourea and primary amines



Entry	Amine	Product ^a	Yield (%)
1			82
2			77

^a Products were isolated as their TFA salt and the purities of the compounds thus obtained were greater than 95% as determined by ¹H NMR and LC–MS.

Acknowledgements

We thank Jan Waters for the NMR spectroscopic analysis and Dr. Michael Ochse and Dr. Adrian Hobson for helpful discussions.

Supplementary data

Synthetic procedures, ¹H NMR, ¹³C NMR and Masspec data of all the compounds are provided. Spectra of ¹H NMR and ¹³C NMR of all

the compounds are also included. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.113.

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- The resin was purchased from Novabiochem (Cat. No. 01-64-0400). The loading of the resin used in this study is 1.06 mmol/g. The loading of the thiourea was determined by calibration of the HPLC traces of the solution using internal standard and was further confirmed by ¹³C–GELMAS experiments. See [Supplementary data](#) for details.