Tetrahedron Letters 50 (2009) 5145–5148

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

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ARTICLE INFO

Article history:
Received 3 June 2009
Revised 24 June 2009
Accepted 26 June 2009
Available online 1 July 2009

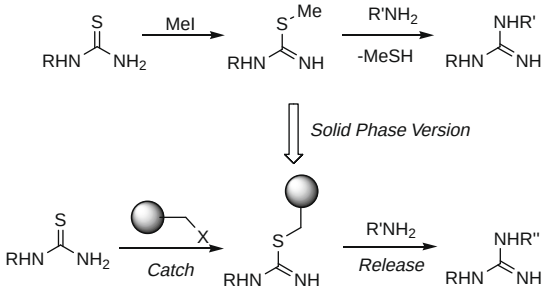
ABSTRACT

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.

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]

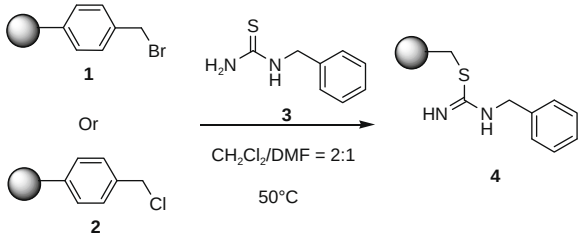
In connection with ongoing research efforts, we needed a direct and practical synthetic method that would allow us to access the guanidine moiety from diverse sets of amines and thiourea scaffolds using readily available reagents. The method should also be amenable for library automation. Here we report 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*-alkylisothiourea, in particular, *S*-methyl isothiourea. 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*-methylisothiourea 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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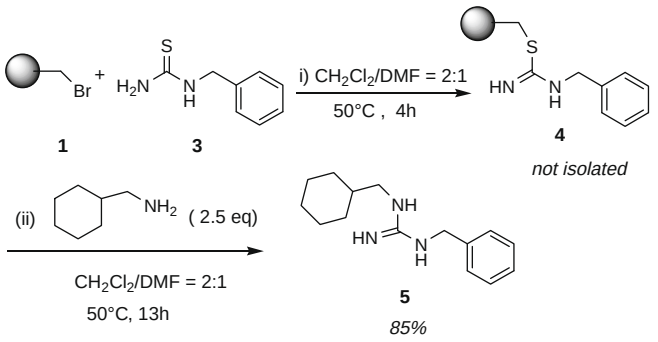
doi:10.1016/j.tetlet.2009.06.113

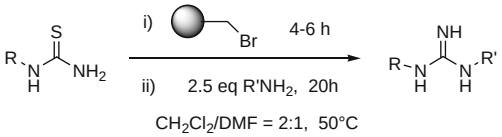


Scheme 2. One-pot synthesis of guanidine **5**.

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



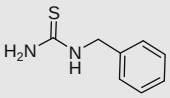
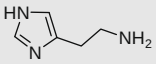
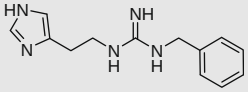
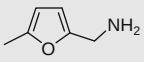
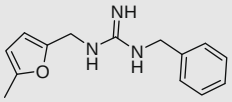
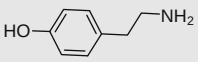
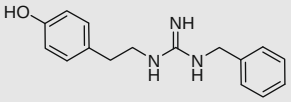
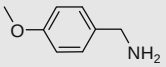
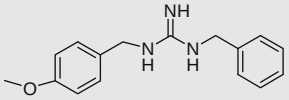
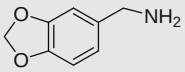
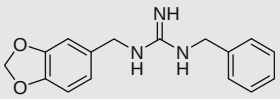
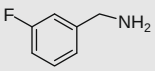
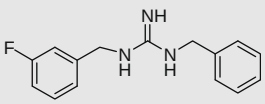
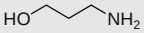
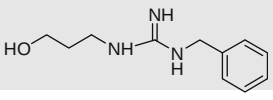
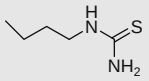
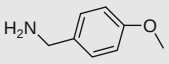
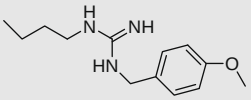
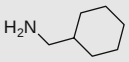
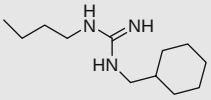
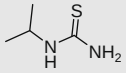
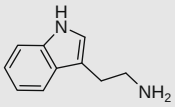
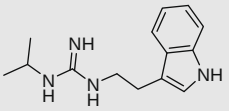
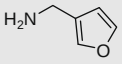
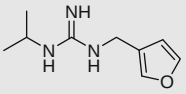
Entry	Thiourea	Amine	Product[a]	Yield (%)
1				80
2				99
3				84
4				82
5				97
6				82
7				43

Table 2 (*continued*)

Entry	Thiourea	Amine	Product[a]	Yield (%)
8				75
9				42
10				80
11				69

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

the reaction. As shown in Table 1, the brominated resin afforded higher loadings in all cases examined with much shorter reaction time (4 h vs 30 h).[5] Thus, resin **1** was used throughout our study. Especially noteworthy is that with 1.5 equiv of the brominated resin, the thiourea substrate was completely loaded onto the resin in 4 h.

The loaded resin **4** could be washed, dried and stored for the second displacement step if desired. More conveniently, a one-pot procedure was developed without the need to isolate the loaded resin **4** (Scheme 2). Thus, adding 1.5 equiv of resin **1** to a solution of benzylthiourea at 50 °C afforded the loaded resin **4** after 4 h as indicated by the complete disappearance of the benzylthiourea in the solution. Subsequently 2.5 equiv of amine was added and the resulting mixture was heated at 50 °C. After 13 h, the resin was filtered off and washed with additional CH_2Cl_2–DMF. Guanidine **5** was isolated with a 85% yield as its TFA salt after HPLC purification.

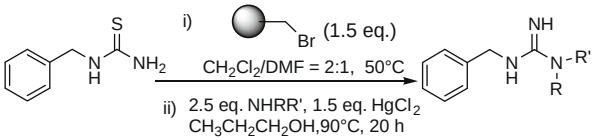
The advantages of this approach are threefold. First, the method ensures the complete loading of the thiourea substrate, which makes the maximum use of the substrate. Second, the reaction can be conveniently monitored by traditional methods such as TLC and LC–MS, as the completion of the loading step is indicated by the disappearance of the thiourea substrate. Third, by eliminating the washing and drying step, this one-pot process dramatically cuts down compound or library production time. Also the capture of the 'SH' group by the resin makes the synthesis less odorous.

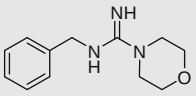
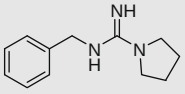
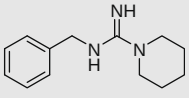
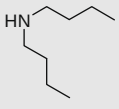
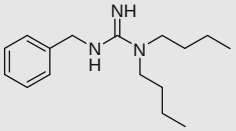
This procedure worked well with a broad spectrum of primary amines to generate N,N′-disubstituted guanidines as illustrated in Table 2. All the thiourea substrates used in Table 2 were completely loaded onto the resin in 6 h. Amines were then added to the resulting solutions and the reaction was continued for another 20 h before work-up. The yields range from fair to excellent (42–99%).

Secondary amines also reacted with thiourea under these two-step one-pot conditions, although the yield was low and the reaction time needed for the second displacement step was significantly longer. However, when resin **4** was washed and dried, and then reacted with amines in the presence of 1.5 equiv $HgCl_2$ in methoxyethanol for the displacement step, the corresponding trisubstituted guanidines were obtained in fair to good yields (Table 3). A simple filtration after the reaction removed the resin and the mercury salts altogether. With anilines, only low yields of the guanidines were obtained. Trisubstituted guanidines could also be obtained from N,N-disubstituted thioureas in our two-step one-pot procedure, albeit with longer loading time and higher equivalents of amines (Table 4).

In summary, a facile and practical two-step one-pot 'catch and release' method has been developed for the synthesis of substituted guanidines with good to excellent yields. The protocol uses readily available resin under mild reaction conditions with maximal use of the thiourea substrate. Furthermore, the process can be easily adapted to library production in a simple and straightforward manner.

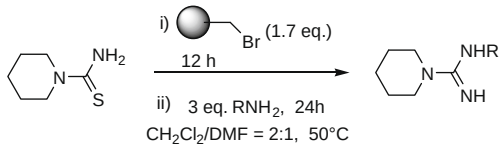
Table 3
Synthesis of trisubstituted guanidines from thiourea and secondary amines

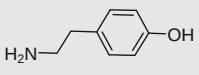
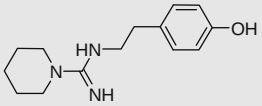
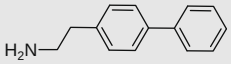
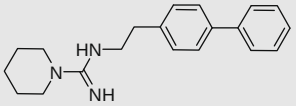


Entry	Amine	Product[a]	Yield (%)
1			76
2			70
3			82
4			51

[a] Products were isolated as their TFA salt and the purities of the compounds thus obtained were greater than 95% as determined by ^{1}HNMR and LC–MS.

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 ^{1}H 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, ^{1}H NMR, ^{13}C NMR and Masspec data of all the compounds are provided. Spectra of ^{1}H NMR and ^{13}C 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.

References and notes

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