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TFA-Sensitive Arylsulfonylthiourea-Assisted Synthesis of N,N′-Substituted Guanidines

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Abstract: An efficient synthesis of N,N′-substituted guanidine derivatives was developed via an aromatic sulfonyl-activated thiourea intermediate. The use of certain aromatic sulfonamides, such as $PbfNH_2$, as the key reagent to incorporate a TFA-labile guanidine protection group greatly facilitates solid-phase synthesis of N,N′-substituted guanidine compounds.

The guanidine group plays important roles in biological systems and is therefore a component of many therapeutic agents that aim to mimic or block the function of a guanidine-containing biomolecule.[1] The synthesis of guanidine derivatives has also attracted continued research interests in recent years, resulting in many new efficient synthetic methods and guanidinylation reagents for different classes of guanidine compounds.[2−43]

We are interested in the preparation of N,N′-substituted guanidines using common solid-phase supports that can be conveniently cleaved with TFA treatment. Currently, preparation of this class of guanidine compounds is possible through two major synthetic routes. One route is based on di-Boc (or equivalent TFA-labile group)-activated pyrazole- or triazolecarboxamidines[8,19,20,23,44] or triflyl guanidines,[11,27,45] either in solution or on solid support. In these cases, it usually requires reaction with a primary alcohol under Mitsunobu conditions before the guanidinylation step to produce the desired substitution. However, this may limit the diversity of compounds generated because Mitsunobu conditions work best with primary alcohols. The other widely used route is based on modification of a thiourea, of which the solid-phase methods have been reviewed recently.[2] Common ways of improving reaction efficiency through this type of reaction are the activation of thiourea with electron-withdrawing groups such as alkoxycarbonyl, acyl, triazene, or *N*-aryl.[4,14,15,21,22,26,41] Subsequent guanidinylation is usually done with the assistance of a carbodiimide,[41] heavy metal salts,[7,40] or Mukaiyama reagent.[46] The characteristic of

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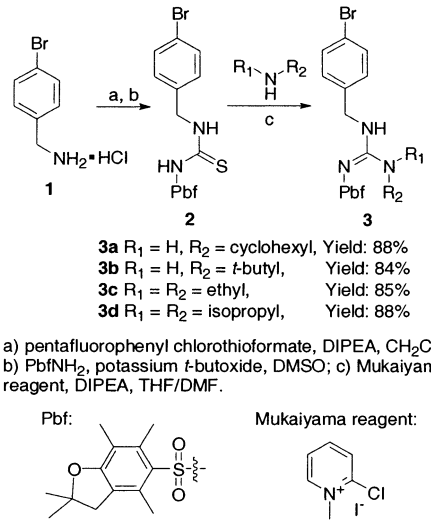
this route is that N,N′-substitution can be introduced with two amine starting materials, although di-Boc-activated isothiourea still requires Mitsunobu conditions to introduce desired substitution patterns.[30] Despite the extensive knowledge about solid-phase synthesis of guanidines, current solid-phase methods for the preparation of N,N′-substituted guanidines starting from two amines only demonstrate limited success.[19,24,25,28,29] Here, we report an extension of current methodologies by exploration of thiourea activation using a single TFA-sensitive aromatic sulfonyl group, along with a comparison to existing methods.

The major goal of our investigation is to achieve in solid-phase synthesis concomitant cleavage of product and removal of the activating arylsulfonyl group, without any loss in overall synthetic efficiency. The question then comes down to (i) if an arylsulfonyl group can sufficiently activate thiourea for guanidine synthesis and (ii) if a TFA-labile protection group can be generated after the guanidinylating step. In addition, we would like to learn if guanidinylation with arylsulfonylthiourea can be carried out under mild experimental conditions for amines with steric hindrance without the need of using toxic heavy metal salts or excessive heating. We should point out that the recently reported use of bismuth nitrate for promoting guanidinylation[7] should be much more environmentally friendly as compared to the use of $HgCl_2$ or analogous salts; however, such a reaction protocol still requires heating (>18 h) or prolonged time at room temperature (up to 117 h) to achieve satisfactory yields.

Although sulfonylguanidines are known, especially in the patented preparation of herbicides, most of the syntheses were done by preformation of the guanidine moiety followed by sulfonylation with sulfonyl chlorides. A survey of literature reporting use of arylsulfonyl activated thiourea for guanidine synthesis showed, to the best of our knowledge, only three reports in solution synthesis.[47−49] Two of these reports used mercury salts to promote the reaction,[47,48] while the third report showed only one example of arylsulfonylthiourea-based guanidinylation using a carbodiimide.[49] In all cases, the formed arylsulfonyl guanidines were not adaptable to solid-phase synthesis using TFA for cleavage/deprotection. We envisioned that if TFA-sensitive arylsulfonyl groups could be introduced into the thiourea-based synthetic method, then adaptation to resin-supported synthesis should be straightforward. The use of the TFA-sensitive sulfonyl group in guanidine synthesis through other types of guanidinylating reagents has also been reported.[36,39] Since many arylsulfonyl protection groups for the arginine side chain are known in Fmoc chemistry, we demonstrate our synthetic method based on one of the best TFA-sensitive arginine protecting groups: 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf).[50]

Since the original report of carbodiimide-promoted arylsulfonylthiourea-assisted guanidine synthesis did not provide enough information about the reactivity for different amines and only sulfamoyl-based systems were

SCHEME 1



studied in more detail,[49] we first tested the Pbf-thiourea-assisted guanidine formation reaction in solution in the hope of obtaining basic knowledge about the guanidinylating step with a variety of amine nucleophiles. As shown in Scheme 1, a primary amine **1** was first turned into the corresponding pentafluorophenyl thiocarbamate. This allowed for the smooth synthesis of the arylsulfonyl-activated thiourea **2**, using PbfNHK (formed by treating $PbfNH_2$ with potassium *tert*-butoxide) as nucleophile.[48] This preparation of arylsulfonyl modified thiourea has some advantages over an alternative procedure through the use of arylsulfonyl isothiocyanate[48] in that both the starting materials (thiocarbamate and $PbfNH_2$) are fairly stable and easy to handle, while the alternative synthesis of arylsulfonyl-activated thioureas involves the preparation and handling of highly labile arylsulfonyl isothiocyanate, which can react with alcohol without activation under neutral conditions.[51] The resulting compound **2** is an excellent guanidinylating reagent. Treatment of **2** with an amine in the presence of Mukaiyama reagent produced the subsequent guanidine derivatives **3a**−**d** in very good yields at room temperature in 12−18 h, while most of the product was formed within 1−2 h as judged by TLC. The reaction works for either primary or secondary amine nucleophiles, including the sterically hindered *tert*-butylamine, as well as diethylamine and diisopropylamine, both of which are known to cause problems in other guanidine syntheses performed in solution.[11] In addition, the high efficiency of Mukaiyama reagent in promoting the guanidinylating reaction is also in contrast to its role in sulfamoylthiourea based systems.[49] The transformation was similarly good with the use of EDC in place of Mukaiyama reagent. The use of toxic heavy metal salts or excessive heating proved to be unnecessary.

The success in solution transformation led us to investigate a facile solid-phase route for guanidine synthesis via Pbf-activated thiourea, so that free N,N′-substituted guanidines could be obtained directly after TFA cleavage. The adaptation of solution synthesis to

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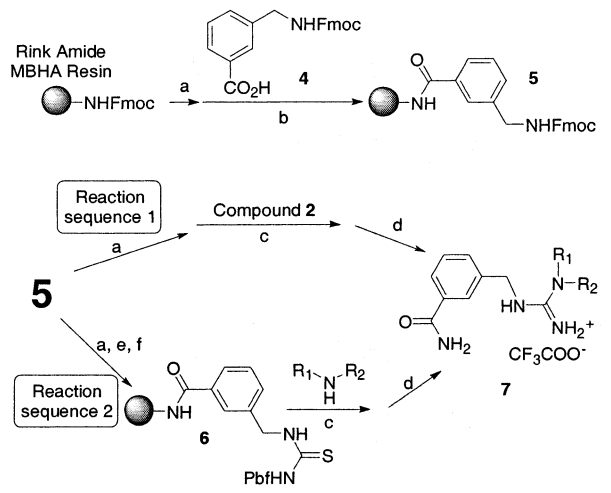
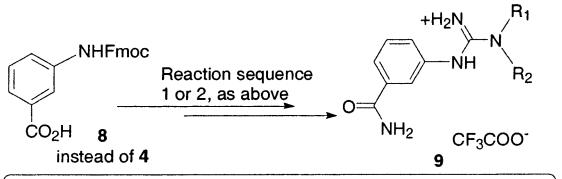
SCHEME 2



Reaction Sequence 1:
7a R_1 = H, R_2 = *p*-bromobenzyl, overall yield from **5**: 82%
Reaction Sequence 2:
7b R_1 = H, R_2 = *t*-butyl, overall yield from **5**: 77%
7c R_1 = R_2 = ethyl, overall yield from **5**: 84%
7d R_1 = R_2 = isopropyl, overall yield from **5**: 76%
7e R_1 = H, R_2 = Ph, overall yield from **5**: 95%

a) 20% piperidine/DMA; b) PyBOP, DIPEA, DMA; c) EDC or Mukaiyama reagent, DMF; d) 94:3:3 TFA:H_2O:TIS (triisopropylsilane); e) pentafluorophenyl chlorothioformate, DIPEA, CH_2Cl_2; f) $PbfNH_2$, potassium *t*-butoxide, DMSO.



Reaction Sequence 1:
9a R_1 = H, R_2 = *p*-bromobenzyl, overall yield: 78%
Reaction Sequence 2:
9b R_1 = H, R_2 = *t*-butyl, overall yield: 88%
9c R_1 = H, R_2 = Ph, overall yield: 70%

solid phase is shown in Scheme 2. A protected amino acid molecule **4** was first attached to Rink Amide MBHA resin through standard peptide chemistry. After removal of the amine protection, the free amine was turned into the desired guanidine function through two routes. The first method is the direct guanidinylation with a Pbf-thiourea such as **2** (reaction sequence 1 in Scheme 2). This route produced the desired final N,N′-substituted guanidine in high overall yield (82% for **7a** from resin-supported amine **5**). However, this method is sometimes less attractive due to the requirement for pre-synthesis of Pbf-thioureas in solution. Alternatively, we demonstrated that one can form the Pbf-thiourea on solid support and subsequently produce the desired guanidine compounds. As shown by reaction sequence 2 in Scheme 2, the resin-supported amine **5** was first turned into pentafluorophenyl thiocarbamate. Reaction with PbfNHK, as in the solution synthesis, produced the desired Pbf-thiourea **6** on solid-support. Subsequent guanidinylation on solid support was smoothly carried out with a variety of amine nucleophiles in the presence of either EDC or the Mukaiyama reagent. Again, sterically hindered aliphatic amines or electron-deficient arylamines all gave very high overall isolated yields of the final guanidine compounds after TFA cleavage and HPLC purification.

Our solid-phase synthesis was also demonstrated with an alternative amino acid starting material in place of **4**. Starting with an aromatic Fmoc-protected amino acid **8**, compounds **9a**−**c** were efficiently synthesized following either route in Scheme 2. We should note here that using α-amino acids as starting materials for the preparation of the corresponding guanidine derivatives will not lead to isolation of desired products under our reaction conditions since this class of compounds is known to go through intramolecular cyclizations.[2,41]

The fate of the side product due to the removal of Pbf protection by TFA treatment is also worth noting. TFA-based removal of Pbf from a guanidine group is expected to generate the corresponding aromatic ring moiety without trapping. Since we use TIS ($(i\text{-Pr})_3SiH$) as a scavenger, Pbf may also be trapped by TIS. In either case, however, none of these byproducts has significant solubility in aqueous solution while in contrast our desired guanidine products as their TFA salts do. A simple aqueous extraction and filtration removed most of these contaminants before the final HPLC purification (see the Supporting Information). Alternatively, washing the crude cleavage product with ethyl ether also served to remove most of the contaminants before HPLC purification.

With the success of either solution- or solid-phase guanidinylation using Pbf activated thiourea, it is worth comparing in more detail our method to other known procedures for preparing N,N′-substituted guanidines, with regard to our goals stated earlier. The foremost concern is the reaction efficiency of our approach. To this end, our methodology proved to be comparable to many other approaches. For example, in solution synthesis, the yields of guanidinylation (Scheme 1) are similar to solution phase guanidinylation using alkoxycarbonyl thioureas.[21] On solid-phase synthesis, our method produced slightly better isolated yields (Scheme 2) than syntheses performed with *N*-ethoxycarbonyl thiourea (63−83%).[9] Certainly, our method does not leave a guanidine protecting group after TFA cleavage, which is advantageous when water soluble guanidinium compounds are desired.

Compared to other synthetic methods using solid or soluble support for N,N′-substituted guanidines starting from two amines, our methodology also has its own merits. For example, Kearney et al.[29] and Chang et al.[25] each described a methodology through activation of thioureas by methylation to form isothioureas, while the Burgess group reported direct conversion of thioureas to carbodiimides through the use of Mukaiyama reagent.[19] These methods have the advantage that there is no need to handle protecting groups for the guanidine moiety during synthesis or cleavage. However, even though our method has to deal with the Pbf protecting group, its removal is achieved concomitantly with product cleavage and the side product was readily removed with simple aqueous extraction and filtration. On the other hand, the isothiourea method by Kearney et al. requires heating in sealed pressure-tube for 12 h at 80 °C for guanidinylation. In some instances, the final product purities were less than 50%, which may be attributed to a variety of

reasons including repeated treatment of the resin-bound materials with MeI for activation.[29] The isothiourea method described by Chang et al. also requires heating in DMSO, and the obtained yields vary widely (11−74%). The carbodiimide method described by the Burgess group is currently restricted to the starting amine being aniline derivatives bearing electron-withdrawing groups.[19] Compared to these three methods, our synthetic route can produce equivalent or better yields at room temperature for 12−18 h and is applicable to starting alkylamines.

There are two other syntheses of N,N′-substituted guanidines on solid-support, each using a carbonyl-based thiourea activation strategy.[24,28] The use of Wang resin to form TFA-labile alkoxycarbonyl activated thiourea allowed Josey at al to achieve efficient synthesis of guanidines with N,N′ and other types of substitution patterns.[28] However, the authors only specifically described product purity for phenyl and allyl based thioureas, and left out yield information for other starting alkyl thioureas. This makes it hard to compare with our current method. The method described by Wilson et al. used a novel carboxypolystyrene to produce acyl activated thiourea for guanidinylation. However, this method generally produced isolated yields in the 40% range,[24] while our method produced yields in the 70−95% range.

Compared to other guanidinylating methods based on TFA-sensitive arylsulfonyl groups (Mtr- and Pmc-based isothioureas,[36] and Mtr-based carbonimidodithioate,[39] Mtr: 4-methoxy-2,3,6-trimethylbenzenesulfonyl; Pmc: 2,2,5,7,8-pentamethylchroman-6-sulfonyl), our methodology can carry out guanidinylation at room temperature while the other methods invariantly require heating to displace the final MeS− group in the isothiourea moiety. Although we chose to use Pbf-based reagents, we expect that alternative use of either Mtr or Pmc should provide equal efficiency in reaction because the Pbf group contains a more electron-donating aromatic moiety than either Pmc or Mtr.[50] As for concomitant removal of these arylsulfonyl groups during final TFA cleavage, the Pbf or Pmc would probably perform equally in practical terms (half-life in TFA as guanidine protection: Pbf, 8 min;[50] Pmc, 13 min[50]), while the Mtr group should also be adequate since its complete removal can be achieved in one to 5 h,[52,53] which is compatible to general solid-phase cleavage protocols.

In summary, we have demonstrated the synthesis of N,N′-substituted guanidine compounds through TFA-sensitive arylsulfonyl activated thiourea that meets our aforementioned goals. The high reaction yield, mild reaction condition, and the flexibility of solution or solid-phase synthesis should make it a valuable extension to current synthetic methodologies. In addition, TFA-sensitive arylsulfonyl moieties are excellent guanidine protection groups. It is well-known that a single arylsulfonyl modification is sufficient to suppress side reactions on an arginine side chain in peptide chemistry, in contrast to carbonyl based protections.[54] This suggests that our novel guanidine synthesis method can be incorporated into other multiple-step synthetic procedures and provide a desirable protection for the guanidine moiety during the entire process. We are currently investigating such properties and will report our findings in due course.

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Supporting Information Available: Experimental procedures and characterization of compounds **2**, **3**, **7**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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