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A Novel Solid-Phase Synthesis of Highly Diverse Guanidines: Reactions of Primary Amines Attached to the T2* Linker

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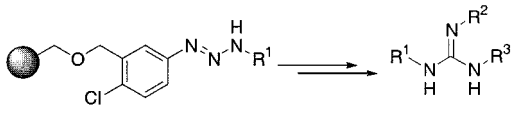
ABSTRACT



The reaction of primary amines with the T2* diazonium resin generates polymer-bound triazenes, which can in turn be acylated by the addition of isothiocyanate. The formed thioureas are readily transformed into the corresponding guanidines by the reaction with amines in the presence of mercury(II) oxide, tosyl chloride, or silver nitrate. This reaction sequence furnishes trisubstituted guanidines that are potentially useful pharmacophores.

Guanidines are basic molecules with the capacity of forming H-bonding interactions. They are therefore a promising class of potentially useful pharmacologically active compounds,[1] and the synthesis of guanidines in liquid phase has found widespread application in organic chemistry.[2]

The solid-phase synthesis of guanidines, however, mainly focuses on three different approaches, namely, the formation of resin-bound carbodiimides[3] and their reaction with amines, the solid-phase synthesis involving electrophiles in solution,[4] and the reaction of supported thioureas with amines.[5] All of these methods have a common drawback. At least one of the three possible substituents of the guanidine moiety is directly connected to the polymeric backbone, which limits the diversity of the products significantly. Often even larger building blocks containing the guanidine function are applied, which have to be presynthesized in liquid phase. So far, only a very recent publication offers the possibility of creating

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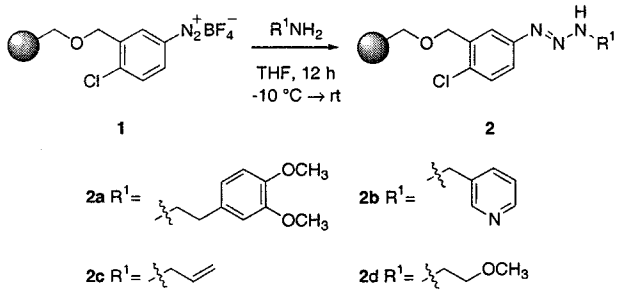
trisubstituted guanidines on solid phase via a supported guanylating agent.[6] However, purities were largely in the range of 50−75%.

The T2 linker[7] and the improved T2* linker[8] developed in our group offer a unique possibility to immobilize and modify amine derivatives on solid support. The formation of amides, ureas, alkylated ureas, thioureas, and isothioureas has already been demonstrated.[8b,c] We here present a unique approach to the formation of guanidines in which all three substituents can be varied to a wide extent.

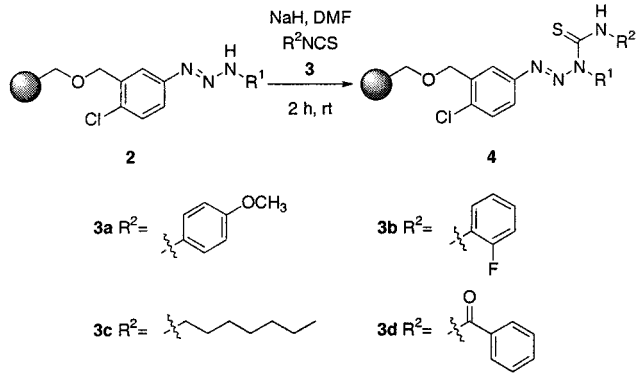
The attachment of primary amines to the T2* diazonium resin **1** was conducted under standard conditions (Scheme 1).[8b,9] The resin-bound triazenes **2** could be deprotonated

Scheme 1. Attachment of Primary Amines to the T2* linker



using NaH/DMF and subsequently acylated by the addition of isothiocyanates **3** (Scheme 2). Although acylations with

Scheme 2. Formation of Resin-Bound Thioureas **4**



acid chlorides or isocyanates can be achieved in the presence of tertiary amine bases,[8c] the reaction with isothiocyanates required deprotonation.

IR spectroscopic analyses of the resins **4** and cleavage experiments showed that all but one isothiocyanate could be cleanly coupled under the given conditions.[10] The more reactive benzoyl isothiocyanate **3d**, however, lead to the formation of byproducts presumably because of double acylation of the intermediately formed thioureas on either the nitrogen or sulfur atom. These resins were therefore not submitted to further reactions conditions.

Usually, the formation of guanidines from thioureas is achieved by the application of coupling reagents such as DCC, EDC,[11] or Mukaiyama reagent[12] leading to the intermediate formation of activated thioureas or carbodiimides.

Clearly in the case of the T2* linker, the formation of carbodiimides is not a suitable way of activation, because one of the thiourea nitrogen atoms bears two substituents and therefore elimination of the sulfur fragment is not possible. Hence, a reagent capable of activating the sulfur fragment for substitution without elimination had to be found. The use of mercury(II) oxide (*caution*: very toxic) proved to be superior over a whole variety of coupling reagents that were envisaged (Table 1). Traces of the formed insoluble

Table 1. Optimization of Guanidine Formation

entry	reaction conditions	product found
1	$AgNO_3$, DMF, 60 °C, 2 h	−[a]
2	$AgNO_3$, MeCN, 45 °C, 12 h	+[b]
3	$Hg(OAc)_2$, MeCN, 60 °C, 2 h	−[a]
4	HgO, MeCN, 45 °C, 24 h	−[a]
5	HgO, THF, 45 °C, 24 h	+[b]
6	Mukaiyama reagent, DMF, 40 °C, 24 h	−[a]
7	TsCl, DCE, Hünigs base, 40 °C, 24 h	+[c]
8	EDC or DCC, DCE, 40 °C, 24 h	−[a]

[a] Starting material was completely recovered as judged by cleavage experiments and IR spectroscopy. [b] Insoluble silver or mercury salts could be removed by filtration over a short silica pad. [c] Conversion was not complete.

black mercury(II) sulfide could be efficiently removed by simple filtration of the cleavage solution over a short pad of silica.

In the final diversification step before cleavage, the reaction of the thiourea resins **4** with ammonia and primary and secondary amines was conducted under the optimized

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(9) Merrifield resin (0.93 mmol/g) was obtained from Polymer Laboratories. The T2* diazonium resin is commercially available from Calbiochem-Novabiochem.
(10) A library of 16 resin bound thioureas was produced in this way.
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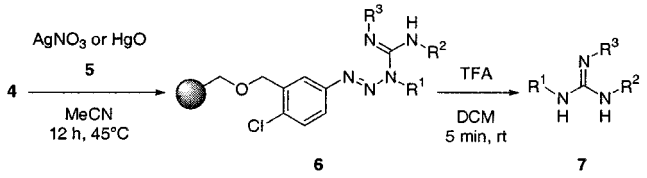
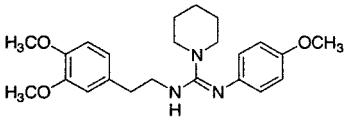
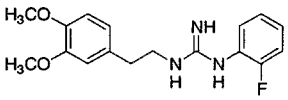
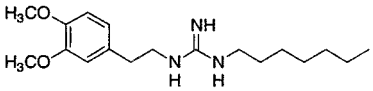
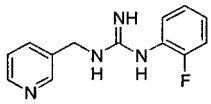
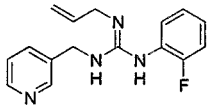
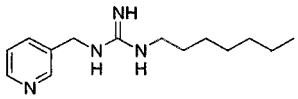
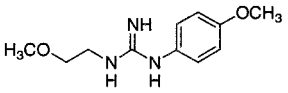
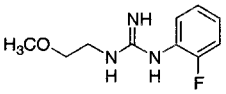
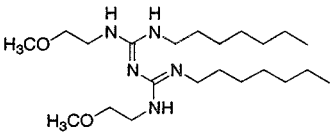
(13) The compound was characterized by MS spectroscopy. As the formation of the dimeric compound on solid support is unlikely because of the moderate loading of the Merrifield resin used (0.93 mmol/g for the starting material), the dimerization has presumably taken place under the acidic cleavage conditions.
(14) A strong anion-exchange resin (Lewatit MP 5080, Merck Darmstadt) was used in methanol.

Table 2. Synthesis of a Variety of Trisubstituted Guanidines **7**



5a $R^3NH = NH_3$
5b R^3NH = Allylamine
5c R^3NH = Piperidine

	product	yield (%)[a]
7a		84
7b		52
7c		quant.
7d		quant.
7e		88
7f		quant.
7g		52
7h		41
8		63

[a] Isolated yield of the trifluoroacetate salts. Yields refer to the loading of the amine resins **4**, which was established by CHN combustion analysis.

reaction conditions (Table 2). The cleavage yielding the guanidines **7** as their trifluoroacetate salts was carried out with 10% TFA in dichloromethane. All products were obtained in purities >90% as judged by integration of the ^{1}H NMR signals.

An attempt to increase the diversity of the products by incorporation of hydrazines in the final step failed because the hydrazines vigorously reduced the mercury(II) oxide. Also, the presence of allyl groups in the intermediate thiourea resins was not tolerated by the mercury(II) oxide protocol. The obtained products from the allylamine resins (the **2c** series in Scheme 1) all showed a selective removal of the allyl moiety. Nevertheless, allyl-substituted guanidines such as **7e** could be obtained by the silver nitrate (entry 2 in Table 1) or tosyl chloride protocol (entry 7 in Table 1).

The aqueous workup of the protonated guanidines proved to be difficult because of the high water solubility of the products. In one case, basic workup with concentrated sodium carbonate solution and extraction with dichloromethane led to the isolation of dimeric compound **8** as the only product.[13] However, elution of the TFA salts in methanol over a short column of basic anion-exchange resin[14] efficiently produced the nonprotonated guanidines **7a**−**h** in high yield.

In conclusion, a novel synthetic route to trisubstituted guanidines starting from readily available compounds is presented. The products were obtained in good overall yield and high purity. The presented work substantially extends the chemical transformations to be carried out on triazene-bound amine fragments using the T2* linker.

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Supporting Information Available: Experimental procedures and characterizations for compounds **7a**−**h** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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