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Efficient synthesis of tetramethylsulfonylguanidines between a free sulfonamide group and HBTU

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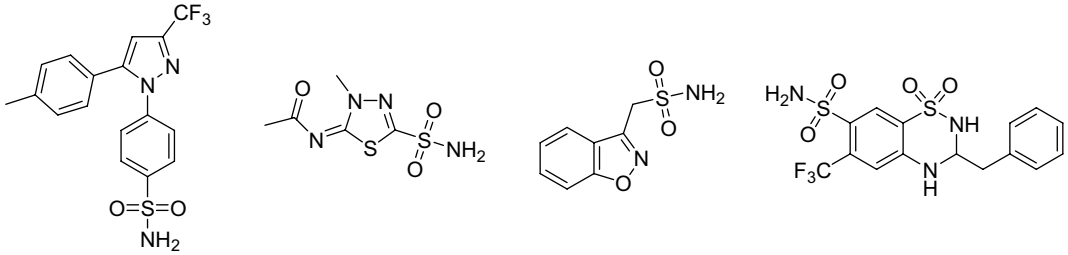
Abstract—The reaction of a sulfonamide moiety with HBTU (*O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) during amide coupling, leading to the formation of tetramethylsulfonylguanidines, is described. Optimised conditions showed that HBTU was as a convenient agent for the synthesis of tetramethylsulfonylguanidines, in basic conditions. A panel of diverse sulfonamides was used to demonstrate the scope of this procedure.

The PI3K/Akt pathway plays a pivotal role in several fundamental cellular functions, such as growth, survival metabolism and motility.[1,2] Mutations and constitutive activation of this pathway observed in many cancer cell lines made it particularly attractive for therapeutic strategies. In the course of our continuing search for new therapeutic agents potentially useful in prostate cancer treatment,[3–5] and in order to switch-off the constitutive activation of this pathway, we focused our efforts towards the design of new inhibitors of PDK-1.[6] We also attempted to design a new series of amide compounds containing a heterocyclic scaffold and a sulfonamide moiety. A large range of pharmaceutical compounds are known to contain the sulfonamide group: many drugs, such as celecoxib (cyclooxygenase-2 inhibitor),[7] methazolamide (carbonic anhydrase inhibitor),[8] bendroflumethiazide (thiazide diuretic),[9] zonisamide (new antiepileptic drug)[10] illustrate the importance of such a functional group in medicinal chemistry (Fig. 1).

In this letter, we report an unexpected reaction between the well known peptidic coupling agent HBTU and an unprotected sulfonamide moiety during the amidification reaction, leading to the formation of stable tetramethylsulfonylguanidines. Optimised reaction conditions were studied, and provided a new simple method for the synthesis of tetramethylsulfonylguanidines.

During the synthesis of pharmaceutical compounds, the sulfonamide moiety often needs to be protected because



Celecoxib **Methazolamide** **Zonisamide** **Bendroflumethiazide**

Figure 1. Structure of pharmaceutical compounds containing the sulfonamide moiety.

Keywords: HBTU; Sulfonamide; Tetramethylsulfonylguanidines.
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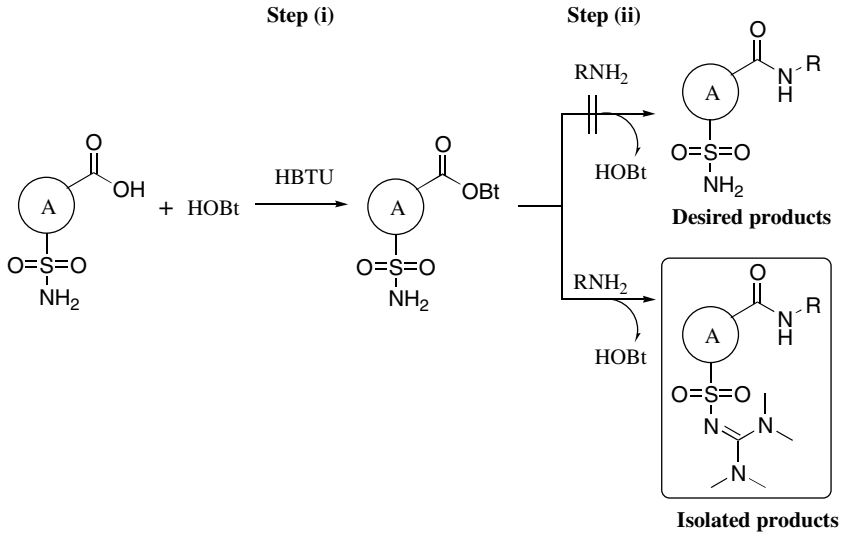


Scheme 1. Formation of tetramethylsulfonylguanidine (Central heterocycle (not detailed) is designed by the ring named A).

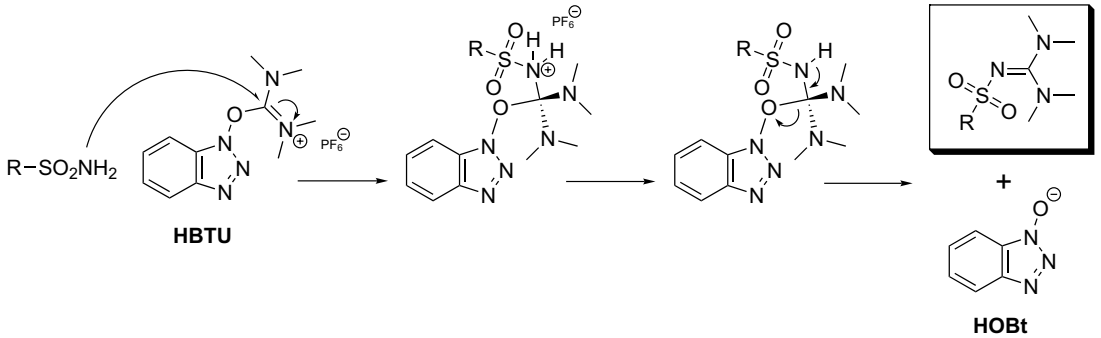
of the acidic character of protons. Nevertheless, there are generally few examples of protecting groups for this functionality. It is often protected with *tert*-butyl group[11] or *N*-benzyl moiety.[12]

To obtain the chemical diversity, an amide coupling procedure was set up, using HOBt (*N*-hydroxybenzotriazole) as the coupling reagent.[13] This method is a two step procedure: (i) first the formation of activated ester of carboxylic acid, using secondary coupling agent HBTU; (ii) then the release of the target amide in solution, which is performed by treatment of an activated ester with various amines. In our case, ^{1}H NMR spectra of the crude products isolated after reaction, indicated the presence of an unexpected singlet (12 protons) at about 3 ppm. The mass spectra also showed a difference of 98 with the expected mass. As uronium salts are suspected to be guanidinylation agents,[13] we supposed that the corresponding product could be a tetramethylsulfonylguanidine (Scheme 1).

In view of these results, we tried to understand the mechanism of the reaction. Series of experiments have also been carried out to explain the formation of such tetramethylsulfonylguanidines. First we found that the presence of a base (diisopropylethylamine, DIEA) was necessary to afford the reaction, but HOBt is not essential. The DIEA is ordinarily used to convert carboxylic acids into carboxylates and enhances nucleophilicity of amines during the peptidic coupling. The suggested mechanism probably involves a nucleophilic attack (enhanced by DIEA) of the tetramethyluronium by sulfonamide moiety; an intramolecular reaction gives the guanidine and the by-product HOBt (Scheme 2).

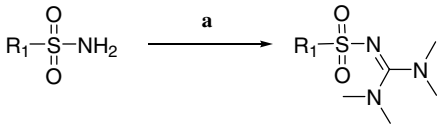
We were interested in applying this practical method to a set of diverse sulfonamides in order to test the generality of the reaction conditions.

A few examples are described and a typical procedure of the reaction is presented (Table 1). The common procedure is the following: coupling reactions were performed by addition of HBTU (1.0 equiv) to a solution of sulfonamide (1.0 equiv) and DIEA (3.0 equiv) in anhydrous dichloromethane. The resulting solution is stirred at room temperature for 1 h. The reaction taken up in dichloromethane is washed with hydrochloric acid (0.1 M), sodium bicarbonate (5%), and brine. The combined organic layers are dried over sodium sulfate and concentrated under vacuum. The residue is purified by column chromatography or recrystallisation. Experimental conditions and yields following purification are summarised in Table 1. A set of derivatives differing in their electronical nature, steric hindrance, aromatic or

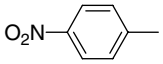
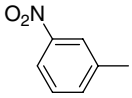
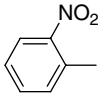
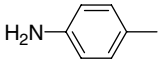
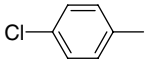
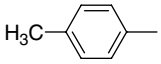
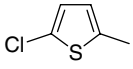


Scheme 2. Suggested mechanism for the formation of tetramethylsulfonylguanidines.

Table 1. Synthesis of tetramethylsulfonylguanidines with HBTU[a]



1 - 8

Entry	R_1	Purification	Yield[b] (%)
1		Recrystallisation (EtOH/H_2O; 5/5)	78
2		Chromatography (CH_2Cl_2/MeOH; 5/5)	90
3		Recrystallisation EtOH	95
4		Chromatography (CH_2Cl_2/MeOH; 95/5)	74
5		Chromatography (CH_2Cl_2/MeOH; 9/1)	88
6		Chromatography (CH_2Cl_2/MeOH; 95/5)	92
7		Chromatography (CH_2Cl_2/MeOH; 95/5)	69
8		Chromatography (CH_2Cl_2/MeOH; 98/2)	81

[a] The reaction is performed with 1 equiv of sulfonamide, 1 equiv of HBTU, 3 equiv of DIEA, in CH_2Cl_2 at room temperature for 1 h.
[b] Yields after purification.

non aromatic nature, were used. Yields are generally high and not affected by the nature of the substituents.[14]

Substituted sulfonamides are of great interest in medicinal chemistry,[15,16] or as fluorescent chemosensors,[17] for example. Tetramethylsulfonylguanidines have been synthesised from different ways: by condensation of acyl chloride with 1,1,3,3-tetramethyl-guanidine,[18] by reaction of fluoroalkanesulfonyl azides with tetrakis(dimethylamino)ethylene accompanied by the release of N_2.[19] These tetramethylsulfonylguanidine derivatives are actually poorly evaluated in pharmacology, but recent preliminary published results showed their ability to bind to biological targets of interest.[18,20] They can be considered as equivalent of guanidines with a variable extra site.[21]

In conclusion, a reaction between the unprotected sulfonamide group and the HBTU in basic conditions is described. We showed here the absolute necessity to protect the sulfonamide moiety during amide bound coupling with HBTU in basic conditions. We provided an efficient synthesis method of tetramethylsulfonylguanidines. The method is suitable for both aromatic and aliphatic sulfonamides. The main advantages are the flexibility of the reaction (room temperature, short reaction time, high yield). The use of derivatives of HBTU with different kinds of guanidines such as benzotriazolyloxy-bis(pyrrolidino)-carbonium-hexa-fluorophosphate (BCC another uronium reagent)[13] provides a new opportunity to design new substituted sulfonamides by using our method.

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14. Compound **2**: Brown solid, mp 122–124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.95 (s, 12H), 7.65 (t, $J = 8.9$ Hz, 1H), 8.26–8.34 (m, 2H), 8.79 (t, $J = 1.8$ Hz, 1H). LC–MS ($APCI^+$): (m/z) 301 $(M+H)^+$.
Compound **3**: White solid, mp 137–139 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.97 (s, 12H), 7.54–7.96 (m, 3H), 8.21–8.23 (m, 1H). LC–MS ($APCI^+$): (m/z) 301 $(M+H)^+$.
Compound **4**: White solid, mp 169–171 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.89 (s, 12H), 4.1 (br s, 2H), 6.62 (d, $J = 11.1$ Hz, 2H), 7.65 (d, $J = 11.1$ Hz, 2H). LC–MS ($APCI^+$): (m/z) 271 $(M+H)^+$.
Compound **8**: White solid, mp 95–97 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.98 (s, 12H), 6.82 (d, $J = 4.1$ Hz, 1H), 7.33 (d, $J = 4.1$ Hz, 1H). LC–MS ($APCI^+$): (m/z) 296 $(M+H)^+$.
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