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PII: S0040-4039(19)31065-2
DOI: https://doi.org/10.1016/j.tetlet.2019.151285
Reference: TETL 151285

To appear in: *Tetrahedron Letters*

Received Date: 8 August 2019
Revised Date: 11 October 2019
Accepted Date: 14 October 2019

Please cite this article as: Han, J., Zhou, R., Huang, C., Zeng, Q., Long, Q., Zhang, Q., Cong, H., Zhou, Q., Wei, G., Liu, M., Efficient synthesis of sulfonylguanidines via reaction of tetra-substituted urine with $ArSO_2NCO$, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.151285

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Efficient synthesis of sulfonylguanidines via reaction of tetra-substituted urine with $ArSO_2NCO$

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
sulfonylguanidine
urine
sulfonyl isocyanate
guanidine

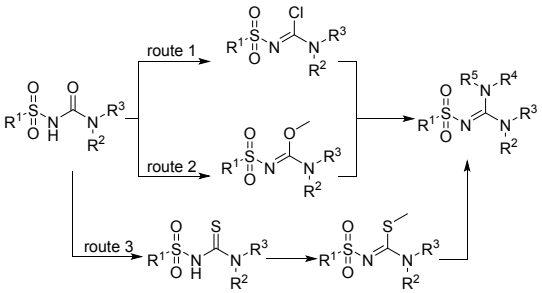
ABSTRACT

An efficient synthesis of sulfonylguanidines via reaction of tetra-substituted urines with $ArSO_2NCO$ has been developed with good yields, which provides a convenient way for synthesis of sulfonyl group protected guanidine from urine in one step.

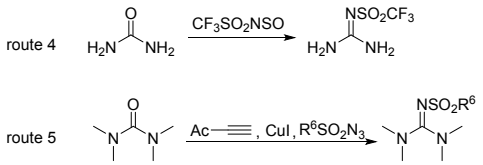
1. Introduction

Sulfonylguanidine as a versatile unit for constructing some inhibitors has shown activities against tumor,[1] liver fibrosis,[2] cancer and HIV,[3,4] and so on.[5,6] They are always straightly synthesized by sulfonylation of the corresponding guanidine.[7-9] As guanidine group exhibits strong nucleophilicity and basicity, it is sometimes not suitable for guanidine group directly presenting in the molecule and further exposing to sulfonylation for synthesis of sulfonylguanidine. Urines, as a large class of organic compound, are easy to construct and can be employed as the precursors for sulfonylguanidines.

Urines are converted to sulfonylguanidines mostly by firstly constructing sulfonylureas, next reacting with $POCl_3$,[10-12] PCl_5,[13-18] or triphosgene[19] to form the corresponding halide, and then exposing to amines (Scheme 1, route 1). They can also be alkylated by CH_3I to form methyl ethers, which subsequently react with amines to get the desired products (Scheme 1, route 2).[20,21] Achieving this conversion, sometimes the carbonyl group of the urines even need to be converted into thiocarbonyl group for thiocarbamoyl is relatively easier to proceed for constructing sulfonylguanidine (Scheme 1, route 3).[22-25] If a complicated molecule contains other nuclear group or the corresponding intermediate is unstable, these multi-step synthesis maybe not appropriate as the generated intermediate may be caught by the nuclear group or decompose, which could prevent the subsequent reaction with the amine. For direct synthesis of sulfonylguanidines with urines in one step, *N*-sulfinyltrifluoromethanesulfonamide has been used to react with urea for preparing *N*-triflyl guanidines with SO_2 released (Scheme 2, route 4).[26-28] Tetramethylurine has been converted to the corresponding sulfonylguanidine by CuAAC/ring-opening method with sulfonyl azides and 3-butyn-2-one (Scheme 2, route 5).[29]



Scheme 1. The multi-step synthesis of sulfonylguanidine from urines.



Scheme 2. The one-step synthesis of sulfonylguanidine from urines.

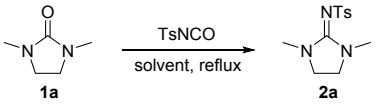
In our research on synthesis of guanidine derivatives, we need not only synthesis of guanidine fragment, but also a sulfonyl group protected guanidine as the guanidine fragment is unstable in the target molecule, which needs to be protected with an electron withdrawing group (sulfonyl group). Achieving this goal, we need to modify a tetra-substituted urine to sulfonylguanidine in one step. Fortunately, we happened to realize the formation of sulfonylguanidine by reacting tetra-substituted urine with TsNCO in one step. For converting

ca but [2+2]-type cycloaddition with carbonyl group and subsequent CO_2 elimination.[30] They has been used to react with arylaldehyde in a solvent or in neat to form *N*-sulfonylimine,[31] and mix with *N,N*-dialkylamides to give *N,N*-dialkyl-*N'*-*p*-toluenesulfonylamides.[32,33] Herein, we wish to introduce our present work in synthesis of tetra-substituted sulfonylguanidines from tetra-substituted urines with $ArSO_2NCO$.

2. Results and discussion

1, 3-Dimethyl-2-imidazolidinone **1a** was used as the substrate for screening the reaction conditions (Table 1). The reactions were conducted with various solvents under reflux. The solvents with relative low boiling point gave low conversions. With the rise of the boiling point, the conversions increased. It showed that the conversion increased to 76.3% when the solvent was xylene (2.5 mL) and the reaction was stirred for 24 h (Table 1, entry 10). When the volume of solvent dropped from 2.5 mL to 1.25 mL, the conversion raised up to 88.5% (Table 1, entry 11). When the reaction time was prolonged to 48 h, the best conversion of 95.2% was obtained (Table 1, entry 12). We have introduced the lewis acid ($FeCl_3$ $AlCl_3$, and $CuCl_2$) to check whether the reaction temperature could be lowered or the reaction time could be reduced, but no catalytic effect was found (Table 1, entries 13-15).

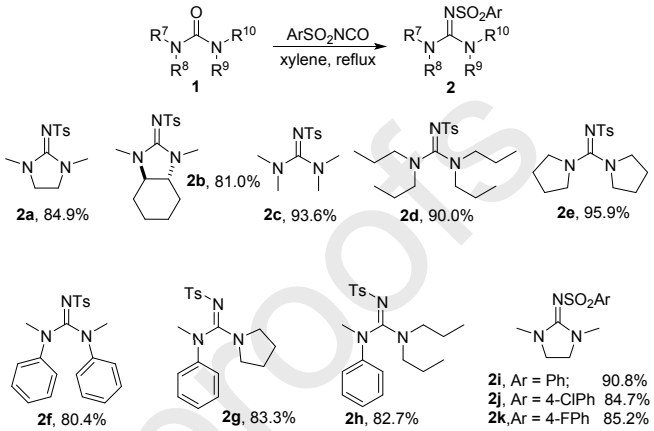
Table 1. Studies on Reaction Conditions[a]



entry	solvent	addictive	Volume of solvent (mL)	Time (h)	Conv.[b] (%)
1	CH_2Cl_2	no	2.5	24	trace
2	$CHCl_3$	no	2.5	24	trace
3	CCl_4	no	2.5	24	5.8
4	$CHCl_2CHCl_2$	no	2.5	24	59.5
5	Et_2O	no	2.5	24	3.7
6	THF	no	2.5	24	trace
7	dioxone	no	2.5	24	19.1
8	CH_3CN	no	2.5	24	trace
9	Toluene	no	2.5	24	22.8
10	xylene	no	2.5	24	76.3
11	xylene	no	1.25	24	88.5
12	xylene	no	1.25	48	95.2
13	xylene	$FeCl_3$ (0.1 eq)	1.25	48	59.2
14	xylene	$AlCl_3$ (0.1 eq)	1.25	48	86.2
15	xylene	$CuCl_2$ (0.1 eq)	1.25	48	74.6

[a]The reactions were carried out with **1a** (2.00 mmol) and TsNCO (4.00 mmol) in solvent.
[b]conversions were determined by ^1H NMR based on **1a**.

To generalize our method, the scopes of the substrates and products were tested. As shown in scheme 1, the $ArSO_2NCO$ can be efficiently applied to react with various tetra-substituted urines with good yields, the cyclic urines **1a** and **1b** can be used as the substrates with 84.9% yield and 81.0% yield respectively. The non-cyclic urines **1c**, **1d**, **1e** can also be efficiently converted to corresponding sulfonylguanidines. Based on the X-ray structure of **2g** (Figure 1), pyrrolidino group is basicly coplanar with guanidine group, so the pyrrolidino group could be largely coplanar with urine group in the substrate **1e**. The substrate **1e** could be easier attacked with TsNCO for the smaller steric hindrance with 95.9% yield for 3 h. The partial aromatic substituted urines could be employed as the substrate to form the sulfonylguanidine **2f** with 80.4% yield. The asymmetric sulfonylguanidines **2g** and **2h** can also be gotten with 83.3% yield and 82.7% yield respectively. As for **2g** and **2h**, there could but only one isomer was detected. Based on the X-ray structure of **2g** and **2h,** the Ts group of **2g** and **2h** is trans to the pyrrolidino group and dipropylamino group respectively (Figure 1). The benzenesulfonyl isocyanate, 4-chlorobenzenesulfonyl isocyanate and 4-fluorobenzenesulfonyl isocyanate can also react with urine **1a** to form corresponding sulfonylguanidines with 90.8% yield for **2i**, 84.7% yield for **2j** and 85.2% yield for **2k** respectively (Scheme 3).



Scheme 3. Synthesis of sulfonylguanidine **2a-2k**[a, b]
[a]The reactions were carried out with **1** (2.00 mmol) and $ArSO_2NCO$ (4.00 mmol) in xylene (1.25 mL) under reflux for 48 h, except for **2e** which was refluxed for only 3 h.
[b]The yield was isolated yield.

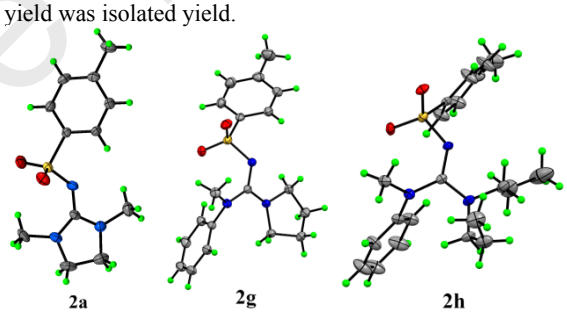
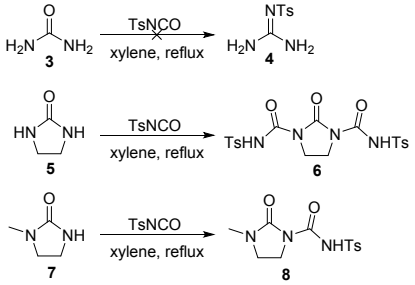


Figure 1. The X-ray structure of ketimine **2a** (CCDC 1945207), **2g** (CCDC 1957967), **2h** (CCDC 1955505)

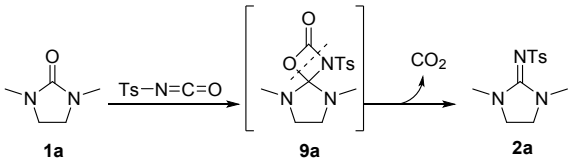
The reactions of the unsubstituted, di- and tri-substituted urines with TsNCO in xylene under reflux have also been conducted (Scheme 4). The ratios of urea/TsNCO (1:2, 1:3 and 1:4) has been tested, but all the reactions went mess. When reactions were conducted with the ratios of ethyleneurea/TsNCO (1:2, 1:3 and 1:4), **6** was obtained as the product. When 1-methyl-imidazolidin-2-one was reacted with TsNCO with the ratios (1:2 and 1:3), **8** was obtained as the product. The substrates **5** and **7** were acylated on the unsubituted nitrogen atom. Although we raised the amout of TsNCO, no sulfonylguanidine was found.



Sch

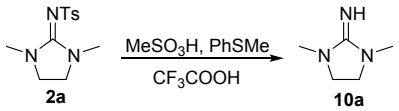
methyl-imidazolidin-2-one

The proposed mechanism for formation of sulfonylguanidine from urine is elucidated in Scheme 5. TsNCO is firstly introduced to urine **1a** to form a four-membered lactone **9a**, and then CO_2 is released from the lactone to give the corresponding sulfonylguanidine **2a**. The X-ray structure of ketimine **2a** is shown in Figure 1.



Scheme 5. The proposed mechanism for the reaction.

Solvolysis of sulfonylguanidine **2a,** which was conducted in CF_3COOH with methanesulfonic acid and thioanisole,[34] formed guandine **10a** with 70% yield (Scheme 6).



Scheme 6. Solvolysis of sulfonylguanidine **2a** to corresponding guanidine **10a**.

Conclusions

In summary, we have developed a simple way to synthesize sulfonylguanidines from tetra-substituted urines with good yields, which provides a convenient method for synthesis of sulfonyl group protected guanidine in one step.

Acknowledgments

The authors gratefully acknowledge the Science and Technology Project of Guizhou Province (QKHJC [2017]1027), the Science and Technology Project of Guizhou Province (QKHPTRC[2017]5788), “Chun Hui” Project of the Chinese Ministry of Education (Z2017007), the talent introduction Program of Guizhou University (GDRJHZ2014-21), and the National Natural Science Foundation of China (No. 21901053).

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1. Aone-step synthesis of sulfonylguanidinesfrom urineswith $ArSO_2NCO$.
2. Thisreactioniscompatiblewith various substrates.
3. This method has been developed with good yields.
4. Theoperation is very simpleandconvenient.
5. This methodwill be of broad interest to synthetic and mechanistic chemists.