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Mild and convenient one-pot synthesis of 2-amino-1,3,4-oxadiazoles promoted by trimethylsilyl isothiocyanate (TMSNCS)†

Cite this: *RSC Advances*, 2013, **3**, 7684

Received 2nd March 2013,
Accepted 14th March 2013

DOI: 10.1039/c3ra41044g

www.rsc.org/advances

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Published on 20 March 2013 on http://pubs.rsc.org | doi:10.1039/C3RA41044G
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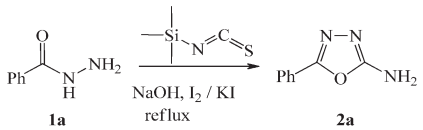
A mild, convenient, and efficient one-pot synthesis of amino-1,3,4-oxadiazoles is described. *In situ* preparation of various thiosemicarbazides by the reaction of different carboxylic acid hydrazides with trimethylsilyl isothiocyanate (TMSNCS), followed by cyclodesulfurization of thiosemicarbazides under basic conditions in the presence of I_2/KI resulted in 2-amino-1,3,4-oxadiazoles in high yields (79–94%).

Organosilicon compounds play an important role in organic synthesis due to the ambient nature of silicon. Recently, the use of organosilicon compounds as reagents and as intermediates in organic synthesis has increased rapidly. It leads to an increasing number of new methodologies that allow useful synthetic transformations. Silicon compounds having functional groups, such as silyl cyanides and silyl azides show considerable synthetic applications in organic synthesis.[1–4] Among various silicon reagents, we particularly focused on trimethylsilyl isothiocyanate (TMSNCS) due to its broad synthetic application. TMSNCS is a useful reagent for thiocyanation or isothiocyanation of alkyl halides,[5] acetals,[6] aldehydes,[6] unsaturated compounds,[7,8] aziridines,[9] oxiranes[9] and aromatic hydrocarbons.[10]

Very recently we reported one-pot, convenient synthesis of mercapto-1,2,4-triazoles using TMSNCS.[11] As part of our continuing studies on TMSNCS, we extended the synthetic utility of trimethylsilyl isothiocyanate for the synthesis of other important heterocycles. In this report we describe a new, simple, and efficient one-pot synthesis of 2-amino-1,3,4-oxadiazoles from carboxylic acid hydrazides using TMSNCS.

1,3,4-Oxadiazoles are a class of heterocycles which display a wide range of biological activities.[12] In particular, 2-amino-1,3,4-oxadiazoles exhibit a wide variety of biological activities such as anti-microbial,[13] anti-inflammatory,[14] anti-cancer,[15] anti-convulsant[16] and anti-mitotic[17] activities. In addition to these, some of the aminooxadiazole analogues are currently undergoing clinical evaluation for the treatment of diabetes.[18] Due to these broad applications, the chemistry of 2-amino-1,3,4-oxadiazoles has

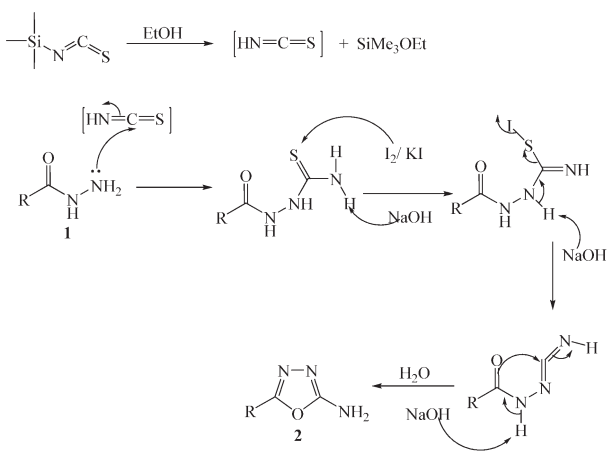
Table 1 Optimization of reaction conditions for the synthesis of 2-amino-5-phenyl-1,3,4-oxadiazole(**2a**)



1a **2a**

Entry	Solvents	Time (h)[a]	Yield (%)[b]
1	Toluene	14	15
2	THF	12	39
3	H_2O	8	68
4	MeOH	7	73
5	EtOH	4	94

[a] Monitored by TLC until **1a** was fully consumed. [b] Isolated yield.



Scheme 1 Plausible mechanism for the formation of 2-amino-1,3,4-oxadiazoles (**2**).

Department of Chemistry & Medical Chemistry, College of Science and Technology, Research & Education Center for Advanced Silicon Materials, Yonsei University, Wonju, Gangwon-do 220-710, South Korea. E-mail: melgg@yonsei.ac.kr; Fax: + 82-33-760-2182; Tel: + 82-33-760-2237

† Electronic supplementary information (ESI) available: IR, ^{1}H NMR, ^{13}C NMR and GC-MS spectra. See DOI: 10.1039/c3ra41044g

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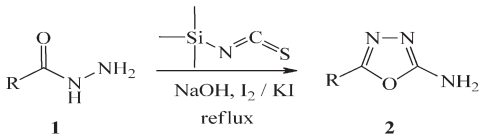
Table 2 One-pot synthesis of 2-amino-1,3,4-thiadiazoles (**2**)



1 **2**

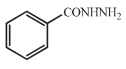
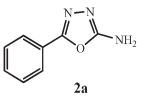
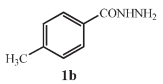
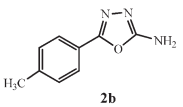
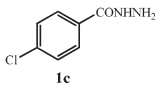
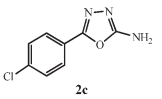
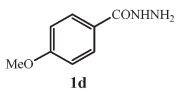
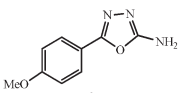
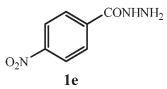
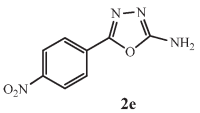
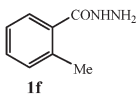
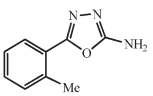
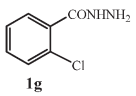
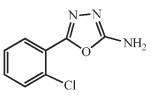
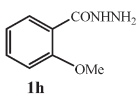
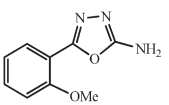
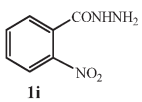
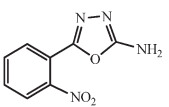
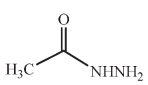
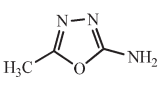
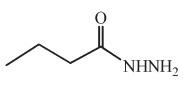
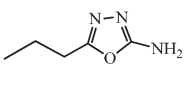
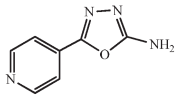
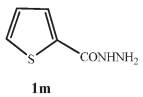
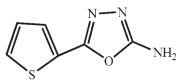
Entry	Hydrazides	Products	Yield (%)
1	 **1a**	 **2a**	94
2	 **1b**	 **2b**	91
3	 **1c**	 **2c**	92
4	 **1d**	 **2d**	91
5	 **1e**	 **2e**	88
6	 **1f**	 **2f**	86
7	 **1g**	 **2g**	87
8	 **1h**	 **2h**	84
9	 **1i**	 **2i**	83
10	 **1j**	 **2j**	79
11	 **1k**	 **2k**	81

Table 2 (*Continued*)

Entry	Hydrazides	Products	Yield (%)
12	 **1l**	 **2l**	86
13	 **1m**	 **2m**	88

evoked significant interest in the field of synthetic organic chemistry. Hence there is a need to develop newer synthetic routes for 2-amino-1,3,4-oxadiazoles.

There are various methods available in the literature for the synthesis of 2-amino-1,3,4-oxadiazoles, which include cyclodehydration of semicarbazide derivatives,[19] cyclodesulfurization of thiosemicarbazide derivatives[20] and amination of oxadiazol-2-one at the C2 carbon.[21] However, there are limitations to these methods, such as byproduct formation, handling of harsh and toxic reagents, use of anhydrous solvents, chromatographic purification, *etc*.

In contrast, we report herein a highly efficient one-step protocol to prepare 2-amino-1,3,4-oxadiazoles from the reaction of commercially available hydrazides and TMSNCS in EtOH under basic conditions in the presence of I_2/KI at 70 °C. Importantly, the procedure does not require an anhydrous solvent, inert gas atmosphere, and any chromatographic purification.

In our previous report we optimized the reaction conditions for the *in situ* preparation of thiosemicarbazides.[11] Based on our previous report we synthesized 2-amino-1,3,4-oxadiazoles by the one-pot method without any isolation of thiosemicarbazides. Initially benzohydrazide **1a** (1.0 mmol), TMSNCS (1.0 mmol) and 5% KI/I_2 were selected for a model reaction and the effects of different solvents and reaction temperatures were investigated. The results are summarized in Table 1. EtOH was the best solvent among various solvents such as toluene, THF, H_2O, and MeOH. Benzohydrazide **1a** (1.0 mmol) and TMSNCS (1.0 mmol) in EtOH (10 mL) were refluxed for about 4 h, and then we added 5N NaOH and 5% I_2/KI solution to the reaction mixture and the solution was refluxed for 2 h. It was then cooled and poured into crushed ice to obtain the precipitated product, 2-amino-5-phenyl-1,3,4-oxadizole (**2a**) with a yield of 94%.

The plausible mechanism for the formation of 2-amino-5-aryl-1,3,4-oxadizole (**2**) is shown in Scheme 1. The nucleophilic cleavage of the Si–N bond in TMSNCS takes place in the presence of EtOH and forms a highly reactive isothiocyanic acid intermediate. Carboxylic acid hydrazides (**1**) immediately undergo nucleophilic addition to isothiocyanic acid, leading to the corresponding stable thiosemicarbazides. Iodine then catalyzes their cyclodesulfurization[20,22] to form 2-amino-5-aryl-1,3,4-oxadiazole (**2**).

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Having these preliminary observations in hand, we wished to extend our methodology to a variety of carboxylic acid hydrazides. The reactions of **1a–m** with TMSNCS in the presence of I_2/KI gave the 2-amino-1,3,4-oxadiazole (**2a–m**)[23] with high yields (Table 2). As shown in Table 2, compound **2a** (entry 1) was obtained in the highest yield compared to that of the electron-rich and the electron-poor aryl substituted derivatives **2b–i** (entries 2–9). As we observed, hydrazides carrying an electron-withdrawing group or an electron-donating group reacted successfully. In particular, 4-substituted derivatives **1b–c** (entries 2–5) reacted more efficiently than the corresponding 2-substituted regioisomers **1f–i** (entries 6–9), possibly because of the steric hindrance of the *ortho* substituent. To demonstrate the generality of our methodology, we extended our investigation to substrates bearing alkyl and hetero-aromatic groups. With heteroaryl acid hydrazides (entries 12 and 13), yields were similar to those with aromatic derivatives, but with alkyl acid hydrazides (entries 10 and 11), yields were slightly lower than those of the aromatic and heteroaromatic acid hydrazides.

Conclusions

In summary, the current protocol is a simple and straightforward route for the synthesis of 2-amino-1,3,4-oxadiazoles. Various aliphatic, aromatic, and heteroaromatic 2-amino-1,3,4-oxadiazoles were efficiently synthesized using TMSNCS and carboxylic acid hydrazides. The main advantage of this method is that the experimental procedure is operationally simple, and an anhydrous solvent, an inert gas atmosphere and chromatographic purification are not required. The use of harsh reagents was also avoided.

Acknowledgements

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2010-0024877).

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23 *Typical experimental procedure for synthesis of 2-amino-5-substituted-1,3,4-oxadiazole* (**2a–m**): A mixture of acid hydrazide (1.0 mmol) and trimethylsilyl isothiocyanate (1.0 mmol) and ethanol (10 ml) was refluxed for 2–4 h and then 1.0 ml of 5N NaOH was added, resulting in the formation of a clear solution. To this 5% iodine in potassium iodide solution was added dropwise with stirring until the colour of iodine persisted at room temperature. The reaction mixture was refluxed for an additional 1–2 h, cooled and poured into ice-cold water. The resultant solid was filtered on a Buchner funnel and dried. Recrystallization ofthe solid from ethanol afforded pure products.

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Published on 20 March 2013 on http://pubs.rsc.org | doi:10.1039/C3RA41044G