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Trimethylsilyl-1,3,4-oxadiazoles—new useful synthons for the synthesis of various 2,5-disubstituted-1,3,4-oxadiazoles

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ABSTRACT

The reactivity of 2-aryl-5-trimethylsilyl-1,3,4-oxadiazoles toward different types of electrophiles was investigated. These silanes readily react with chlorine, bromine, aliphatic acyl chlorides, 2-nitrobenzenesulfenyl chloride, and some reactive isocyanates affording the corresponding substituted 1,3,4-oxadiazoles. The reactions with carbonyl compounds proceed only in the presence of F^- anions.

1. Introduction

1,3,4-Oxadiazoles[1] have attracted an interest in medicinal chemistry as ester and amide bioisoesters for a number of biological targets.[2] Moreover, these compounds have also demonstrated a broad spectrum of biological properties in both pharmaceutical and agrochemical fields such as antibacterial, anti-inflammatory, antimitotic, antiarrhythmic, and insecticidal activities.[3] Also, 1,3,4-oxadiazole derivatives are among the most widely employed electron-transporting and hole-blocking materials in the development of organic light-emitting diodes (OLEDs) used in energy efficient, full-color, flat-panel displays.[4]

The classical synthetic routes to substituted 1,3,4-oxadiazoles involve ring-forming reactions. Widely used methods are cyclodehydratation of 1,2-diacylhydrazines with various reagents such as thionyl chloride, phosphorus oxychloride, PPA or sulfuric acid;[5] oxidation of *N*-acylhydrazones with different oxidizing agents;[6] and direct reaction of acyl chlorides or carboxylic acids with hydrazine or acid hydrazides.[7] Another convenient method of 1,3,4-oxadiazole synthesis is the thermal recyclization of *N*-acyltetrazoles, which are commonly generated in situ from appropriate *N*-unsubstituted tetrazoles and acyl chlorides.[8] Preparative methods via ring-metalated 1,3,4-oxadiazoles are much less common because of the opening of the heterocycle. Thus, the synthesis of the substituted 1,3,4-oxadiazoles via lithium derivatives was described for the first time only several years ago.[9] Only a few examples of direct electrophilic substitution reactions in 1,3,4-oxadiazole ring is known—acylation,[10] phosphorylation,[11] and silylation.[12] Therefore, the elaboration of new methods for 1,3,4-oxadiazoles functionalization is of interest.

Over the last years, *C*-silyl azoles have gained an increasing importance in heterocyclic chemistry. They provide a convenient alternative to organometallic compounds as they easily enter into electrophilic substitution with a wide range of electrophiles.[13] Thus, commercially available 2-(trimethylsilyl)thiazole is widely used in asymmetric syntheses with chiral aldehydes affording amino hydroxy aldehydes and *C*-glycosyl amino acids—precursors to modified peptides.[14]

Recently, we have developed a new synthetic approach to 2-aryl-5-trimethylsilyl-1,3,4-oxadiazoles via direct silylation of 2-aryl-1,3,4-oxadiazoles with bromotrimethylsilane in the presence of triethylamine.[12] With a ready source of these compounds at hand, their reactivity toward electrophiles was explored and the results are presented in this paper.

2. Results and discussion

2-Phenyl-5-trimethylsilyl-1,3,4-oxadiazole (**1a**) reacted with Cl_2 or Br_2 in hexane at 0 °C for 0.25–1.5 h affording the corresponding 2-halogen-5-phenyl-1,3,4-oxadiazoles **2** and **3**, which precipitated

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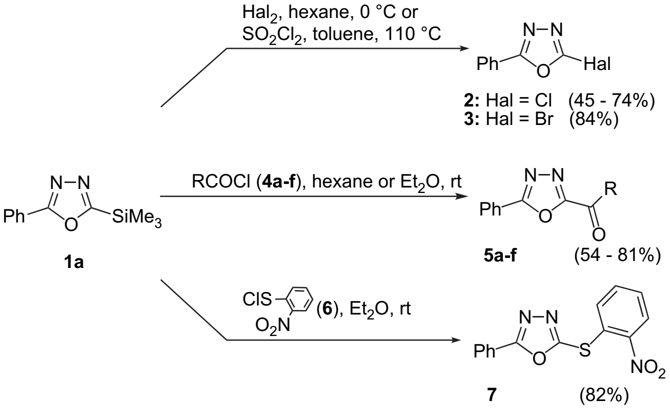
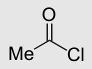
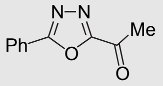
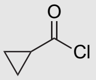
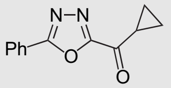
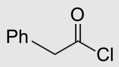
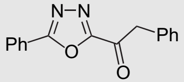
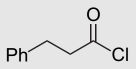
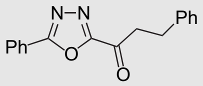
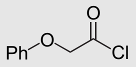
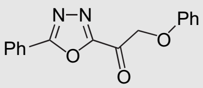
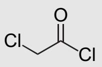
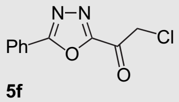
from the reaction mixture and were isolated in good yields (74% and 84%, respectively) (Scheme 1). A simple synthetic procedure makes this method complementary to known synthetic pathways to chloro- and bromosubstituted 1,3,4-oxadiazoles.[15] Sulfuryl chloride could also be employed in the reaction with **1a** but in this case the yield of **2** was lower (45%). Unfortunately, our attempts to use I_2 or ICl in this reaction failed.



Scheme 1.

Treatment of **1a** with acyl chlorides (**4a**–**f**) at ambient temperature gave the corresponding ketones **5a**–**f** in moderate to good yields (Scheme 1, Table 1). Hexane and diethyl ether were found to be the best solvents for running the reaction as ketones **5a**–**f** precipitated from the reaction mixture and byproducts remained in solution. While aliphatic acyl chlorides reacted with **1a** at room temperature, their aromatic counterparts remained intact under these conditions. The reaction of **1a** with cyclopropanecarbonyl chloride (**4b**) was carried out in toluene under reflux to give compound **5b** in moderate yield. When we tried to conduct the reactions of **1a** with aromatic acyl chlorides under such drastic conditions inseparable mixture of products were formed.

Table 1
Yields of products of the reaction of silane **1a** with acyl chlorides

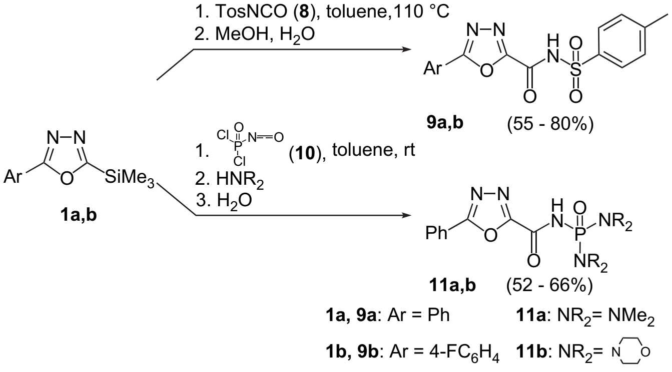
Entry	Acyl chloride	Product	Solvent	Reaction time (h)	Yield[a] (%)
1	 **4a**	 **5a**	Hexane	96	61
2	 **4b**	 **5b**	Toluene[b]	2	57
3	 **4c**	 **5c**	Et_2O	24	54
4	 **4d**	 **5d**	Et_2O	96	56
5	 **4e**	 **5e**	Hexane	18	81
6	 **4f**	 **5f**	Et_2O	18	67

[a] Isolated yield of analytically pure product.

[b] The reaction was run under reflux.

The reaction of **1a** with 2-nitrobenzenesulfenyl chloride (**6**) in diethyl ether at room temperature for 9 days afforded **7** in 82% yield (Scheme 1). Less reactive tosyl chloride even under drastic conditions (6 h in toluene under reflux) does not enter into the reaction with **1a**.

Then, we tried to introduce heterocumulenes to the reaction with 2-aryl-5-trimethylsilyl-1,3,4-oxadiazoles. Unfortunately, none of the desired products was obtained when acyl and aryl isocyanates or isothiocyanates were employed, even under F^- catalysis. Only such activated isocyanates as tosyl isocyanate (**8**) and isocyanatophosphoryl dichloride (**10**) were found to react with 2-aryl-5-trimethylsilyl-1,3,4-oxadiazoles **1a**,**b**. Thus, tosyl isocyanate (**8**) was cleanly converted into the corresponding sulfonamides **9a**,**b**. These reactions were carried out in toluene under reflux. More reactive isocyanatophosphoryl dichloride (**10**) readily reacted with **1a** at room temperature followed by treatment with dimethylamine or morpholine affording phosphoric triamides **11a**,**b** (Scheme 2).



Scheme 2.

In contrast to such silylazoles as 2-trimethylsilylthiazole,[16] 1-alkyl-2-trimethylsilylimidazoles[17] and 2-trimethylsilyl substituted oxazoles,[18] 2-phenyl-5-trimethylsilyl-1,3,4-oxadiazole (**1a**) did not react with carbonyl compounds in the absence of a catalyst, even with an active ones (such as trifluoromethylketones). However, alkyl and aryl aldehydes (**12a**–**i**), isatins (**12j**–**n**), carbocyclic (**12o**,**p**) and diaryl (or aryl-hetaryl) ketones (**12q**–**u**), chalcones (**12v**,**w**), and trifluoromethylkethones (**12x**,**y**) react smoothly with **1a** in the presence of F^- anion to give trimethylsilyl ethers of 1,3,4-oxadiazolylcarbinoles **13a**–**y**, which in most cases were directly converted into the corresponding alcohols **14a**–**y** (Scheme 3, Table 2). KF/dibenzo-18-crown-6 system was used as the F^- anion source. The reaction was carried out in toluene or xylene under reflux. In almost all cases, excess amounts of silane **1a** were required to obtain **14a**–**y** in high yields. It is noteworthy that the treatment of **1a** with chalcones gave only the 1,2-addition products **14v** and **14w**. It was found that trimethylsilyl ethers **13a**–**y** are considerably stable in protic solvents and need F^- catalysis for solvolysis. In one case, the initial trimethylsilyl ether **13a** was isolated and characterized by ^1H and ^{13}C NMR spectroscopy.

3. Conclusion

The reactions of 2-aryl-5-trimethylsilyl-1,3,4-oxadiazoles with different electrophiles, such as chlorine, bromine, aliphatic acyl chlorides, 2-nitrobenzenesulfenyl chloride, isocyanates, and various carbonyl compounds were investigated. It has been found that