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Synthesis of 3-trialkylsilyl pyrazoles from β-oxo acylsilanes

Stéphane Gérard,[a] Richard Plantier-Royon,[a,*] Jean-Marc Nuzillard[b] and Charles Portella[a,*]

[a]*Laboratoire ≪Réactions Sélectives et Applications≫, Associé au CNRS (UMR 6519), Université de Reims, Faculté des Sciences, B.P. 1039, 51687 Reims Cedex 2, France*

[b]*Laboratoire de Pharmacognosie, Associé au CNRS (UMR 6013), Université de Reims, Faculté des Sciences, B.P. 1039, 51687 Reims Cedex 2, France*

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Abstract

The synthesis of β-oxo acylsilanes via cyclic sulfates is described and applied to carbohydrates. These compounds are used for the synthesis of new silylated pyrazoles linked to a carbohydrate moiety by the addition of hydrazines. The regiochemistry of the reaction was determined by NMR analyses ($^{1}H/^{13}C$ and $^{1}H/^{15}N$ correlations). © 2000 Elsevier Science Ltd. All rights reserved.

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Acylsilanes have considerable interest in organic chemistry[1] and numerous syntheses of these compounds are available in the literature. Recently, we reported a general strategy for the synthesis of functionalized and carbohydrate-derived acylsilanes (β-hydroxy, β-oxo, α,β-unsaturated) by ring opening of an epoxide[2] or substitution of a leaving group[3] with a silylcarbonyl anion equivalent: 2-lithio-2-trimethylsilyl-1,3-dithiane (LTD). On the other hand, several routes are available for the synthesis of trimethylsilyl heteroarenes.[4] Introduction of a trimethylsilyl group onto a pyrazole heterocycle takes place selectively at the 4-position by a Friedel–Crafts reaction and at the 5-position by activation with a base. However, the synthesis of alkyl-3-(trimethylsilyl)pyrazoles is not well described. To our knowledge, the methods which are available to obtain these compounds are: 1,3-dipolar cycloaddition reaction of a diazo compound with an alkynylsilane,[5] or reaction of lithium trimethylsilyldiazomethane with ketenimines[6] or α,β-unsaturated nitriles.[7] The presence of a trimethylsilyl group is interesting owing to the possibility of its substitution by different electrophilic groups.[8]

In this paper, we report a new approach for the formation of functionalized acylsilanes from α-diols via a cyclic sulfate.[9] This methodology was successfully applied to β-oxo acylsilanes derived from diacetone D-glucose: 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose,[10] 3-*O*-

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* Corresponding author. Fax: 33 3 26 91 31 66; e-mail: charles.portella@univ-reims.fr

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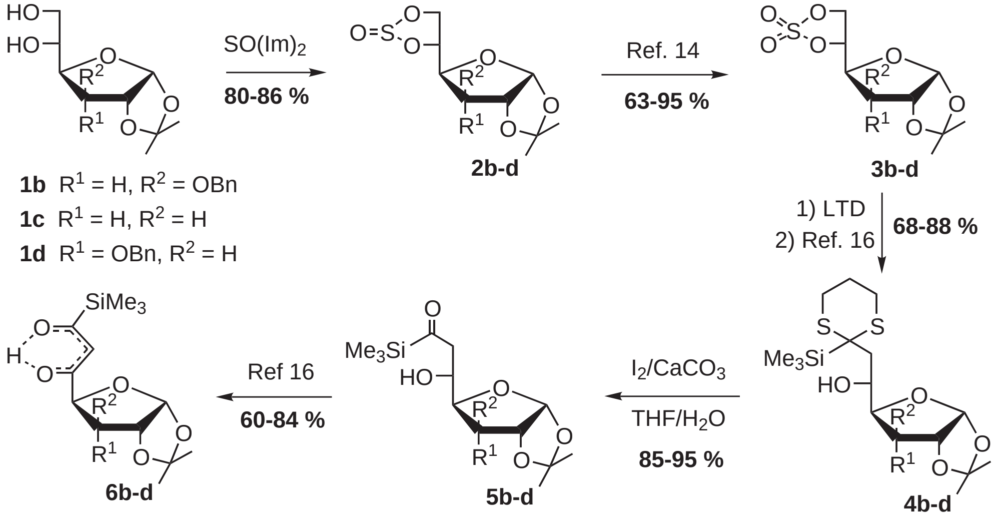
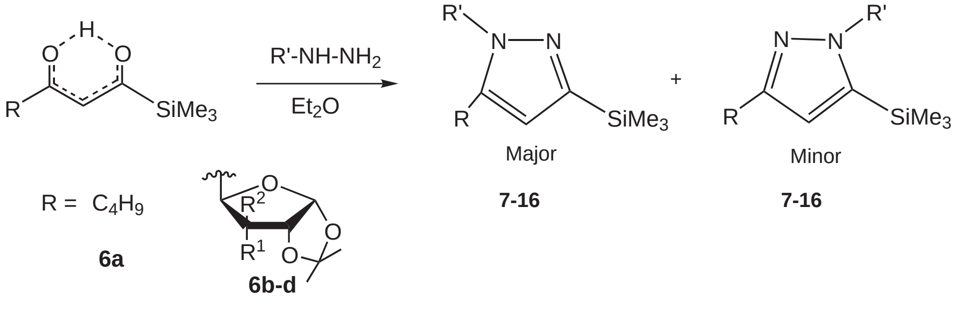
benzyl-1,2-*O*-isopropylidene-α-D-allofuranose[11] and 3-deoxy-1,2-*O*-isopropylidene-α-D-ribohexofuranose.[12] Condensation of these β-oxo acylsilanes with hydrazines led to silylated pyrazoles bearing a carbohydrate moiety.

Cyclic sulfites **2a**–**d** were prepared by reaction of hexane-1,2-diol **1a** or sugars **1b**–**d** with $SOCl_2$ in the presence of Et_3N. The best results were obtained using a freshly prepared thionyl diimidazole $SO(Im)_2$ solution.[13] Scheme 1 exemplifies the synthetic pathway in carbohydrates series. The diastereomeric mixtures of cyclic sulfites were directly used in the oxidation reaction with the $NaIO_4/RuCl_3$ system[14] to give efficiently cyclic sulfates **3a**–**d**. The key step of this synthesis is the regiospecific opening of these cyclic sulfates with LTD to give dithioketals **4a**–**d** after a mild acid-catalyzed hydrolysis.[15] Dethioketalization using iodine in a buffered medium converted compounds **4** to the β-hydroxy acylsilanes **5a**–**d** with excellent yields. Swern oxidation of the resulting β-hydroxy acylsilanes using trifluoroacetic anhydride[16] led to compounds **6a**–**d**. As previously observed,[2] compounds **6a**–**d** are totally enolized [singlet at 14.45 (*δ* ppm/TMS) in ^1H NMR and two carbonyl groups at 193 and 199 (*δ* ppm/TMS) in ^{13}C NMR].



Scheme 1.

These β-oxo acylsilanes were converted into the corresponding silylated pyrazoles by reaction with hydrazines in ether at room temperature (Scheme 2 and Table 1).[17,18] The β-oxo acylsilane



Scheme 2.

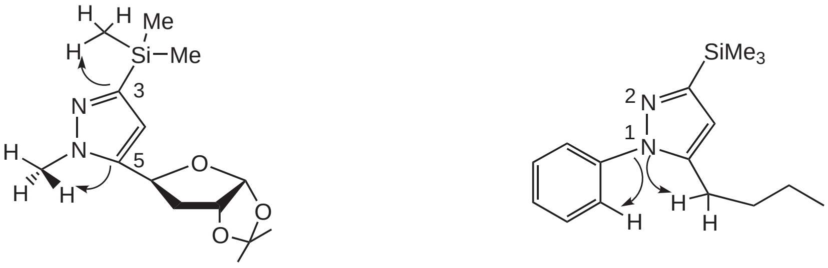
with the alkyl chain **6a**, upon addition of different hydrazines, gave the corresponding pyrazoles with good yields (entries 1–3).

Table 1
Formation of silylated pyrazole heterocycles

Entry	β-Oxo acylsilane	R′	Pyrazole (%)	Maj./Min.
1	**6a**	Me	**7** (60)	85/15
2	**6a**	H	**8** (82)	–
3	**6a**	Ph	**9** (74)[19]	88/12
4	**6b**	Me	**10** (73)	100/0
5	**6b**	H	**11** (72)	–
6	**6b**	Ph	**12** (0)[19]	
7	**6c**	Me	**13** (90)	100/0
8	**6d**	Me	**14** (36)[19]	100/0
9	**6d**	H	**15** (97)	–
10	**6d**	Ph	**16** (0)[19]	

In the case of substituted hydrazines, two regioisomers were obtained with a good regioselectivity (5.7/1, ratio determined by ^{1}H NMR). Under the same conditions, carbohydrate-derived β-oxo acylsilanes **6b–d** led, with quite good yields, to the pyrazoles (entries 4, 5, 7, 8, 9), except with phenylhydrazine, which gave formation of side-products (entries 6, 10).[19] The limited reactivity of phenylhydrazine with these compounds could be explained by the steric hindrance of phenylhydrazine with the furanose moiety. Owing to the lowest nucleophilicity of phenylhydrazine, a longer reaction time is needed favouring the formation of the hydrodesilylation by-product. Reactions with methylhydrazine yielded only one regioisomer of the expected pyrazole. In order to determine the regiochemistry of the addition of hydrazines on β-oxo acylsilanes, NMR analyses were performed.

For pyrazole **13**, a ^{13}C–^{1}H HMBC spectrum showed a correlation between C3 (140 ppm) and the methyl groups of $SiMe_3$ and between C5 (152 ppm) and the methyl group of the hydrazine moiety. In the case of pyrazole **9**, a ^{15}N–^{1}H HMBC spectrum showed a correlation between N1 and the CH_2 group of the butyl chain and aromatic proton. These observations confirm that the major isomers are the 3-trimethylsilyl-5-alkylpyrazoles depicted in Fig. 1.



13 **9**

Figure 1. NMR correlations in compounds **9** and **13**

According to previously reported works, the formation of the pyrazole ring should proceed by initial nucleophilic attack of the less hindered and more nucleophilic primary nitrogen of the hydrazine at the most electrophilic carbonyl group.[20] The observed regioselectivity indicates that the carbonyl group of the acylsilane moiety should be the most reactive. This is in accordance with some physico-chemical data reported for the acylsilane function.[2b,21] The steric hindrance of the TMS group is balanced by a longer C–Si bond (1.926 Å).[2b] Spectroscopic (IR, NMR) and basicity studies[21a] about acylsilanes showed an enhanced polarity of the carbonyl group compared to classical ketones due to the inductive effect of the silicon atom that stabilizes the positive charge on the carbon of the C=O bond. The favoured reaction pathway leads to the formation of the observed 3-trimethylsilyl pyrazoles.

This preliminary study on the synthesis of silylated pyrazoles illustrates the usefulness of acylsilanes in carbohydrate and heterocyclic chemistry. This methodology could be applied to the formation of different heterocycles and could lead to L-*C*-nucleosides analogues.

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17. General procedure: Hydrazine (1.5 equiv.) and a small amount of Na_2SO_4 were added to a solution of β-oxo acylsilane in Et_2O. After stirring at room temperature until completion of the reaction (TLC:PE/EtOAc), the mixture was washed with brine and extracted with Et_2O. The corresponding heterocycles were obtained by purification on silica gel column.
18. All new heterocycles give satisfactory analysis (IR, MS, ^1H and ^{13}C).
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