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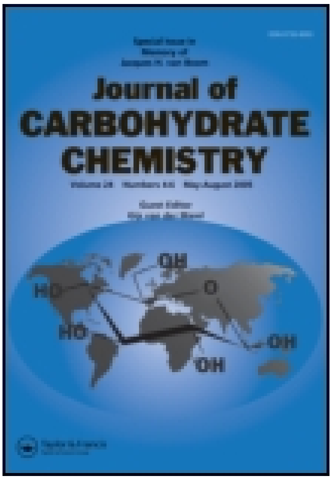

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1,6-C-H and 1,5-O-Si Insertion Reactions of Alkylidenecarbene Derivatives of Monosaccharides

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This work is dedicated to the memory of Professor Jacques H. van Boom.
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A new protocol has been developed for the generation of alkylidenecarbene derivatives of monosaccharides based on the reaction of trimethylsilylazide and Bu_2SnO with α-cyanomesylates derived from uloses. When this method is applied to conveniently functionalized carbohydrate derivatives it provides novel heterocyclic ring systems by the rare 1,6-C-H or 1,5-O-Si insertion reactions.

Keywords Alkylidenecarbenes, α-Cyanomesylates, Trimethylsilylazide, Dibutyltin oxide, Sugar templates, 1,6-C-H Insertion, 1,5-O-Si Insertion

The synthesis and subsequent transformations of alkylidenecarbenes continue to attract much interest.[1] Therefore, a number of methods have now been documented for the generation of such highly reactive species.[2] In sugar chemistry, Czernecki was the first to use α-cyanomesylates derived from uloses to produce acetylenic derivatives[3] by treatment with sodium azide/DMF. Such conversions are presumed to involve an alkylidenecarbene intermediate, which undergoes a 1,2-H shift. A few years later it was reported that the reaction of sodium azide in methylene chloride with various α-cyanomesylates, in the presence of tetrabutylammonium hydrogen sulfate, rendered the corresponding branched-chain sugars and nucleosides via a mechanism involving an alkylidenecarbene being trapped in *intermolecular* association with an azide anion, solvent, and an appropriate alkene.[4] The advantage of such direct route has been offset by the potential explosive combination of sodium azide and halogenated solvents. In fact, with this result relatively few papers[3,4] referring to its use have been published. In spite of this drawback, Czernecki's discovery[3] paved the way for further improvements.[4,5]

In this paper we report a safer and improved protocol for the synthesis of alkylidenecarbene derivatives of monosaccharides and some intramolecular transformations of these species, including the rare 1,6-C-H insertion reaction.[6]

Taking into account the accepted mechanism for the generation of alkylidenecarbenes from α-cyanomesylates,[4] involving reaction of an azide anion with a nitrile to afford a tetrazolyl anion, which undergoes rearrangement, α-elimination of the mesyl group, and subsequent loss of nitrogen, we reasoned that Wittenberger's method for the synthesis of 5-substituted tetrazoles (trimethylsilyl azide, dibutyltin oxide, in toluene)[7] would most likely provide α-mesyltetrazolyl intermediates easily as precursors of the expected alkylidenecarbenes and under mild reaction conditions.

For our preliminary experiments we made a comparative study with the reported[4] intermolecular reaction of the alkylidenecarbene derived from the benzoate **1a** with cyclohexene to generate the *exo* methylenecyclopropyl derivative **2**. Using our conditions, the reaction of **1a** with cyclohexene (40, equiv.) in the presence of $TMSN_3$ (1.2 equiv.) and Bu_2SnO (1 equiv.) at 98°C for 6 hr afforded **2** in a higher yield, 42% (vs. 35%)[4] in the isomeric ratio 1 : 1.2 (Sch. 1), than the previously reported reaction.[4] Interestingly, using the same experimental conditions [$TMSN_3$ (1.2–1.5 equiv.), Bu_2SnO (1–1.5 equiv.), 98°C, 16–20 hr] precursor **1b** afforded an isomeric mixture of **3α** and **3β** in 45% yield, in a 4 : 1 ratio (Sch. 2).[a] It is important to note that the use of TBAF[8] (0.5–1 equiv.) in this reaction gave a similar result. The isomers **3α** and **3β** were separated and their structures readily assigned by ^{1}H NMR, ^{13}C NMR, IR, MS(ES), and elemental analysis data.[b] The absolute configuration at the newly formed stereocenter was determined by the selective positive n.O.e effects observed between the protons H-5**β** and H-7 in compound **3α**, showing that the major isomer (**3α**) has a *trans* arrangement between these protons H-4 and H-7. These compounds are the result of a very unusual 1,6-C-H insertion reaction[6] on the intermediate alkylidenecarbene **A**. To the best of our knowledge, this is the first example of such a

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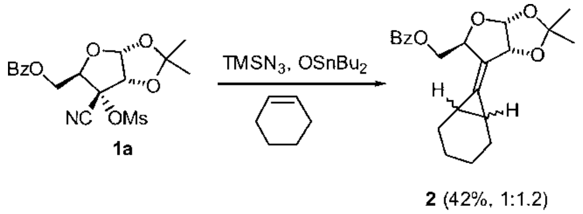
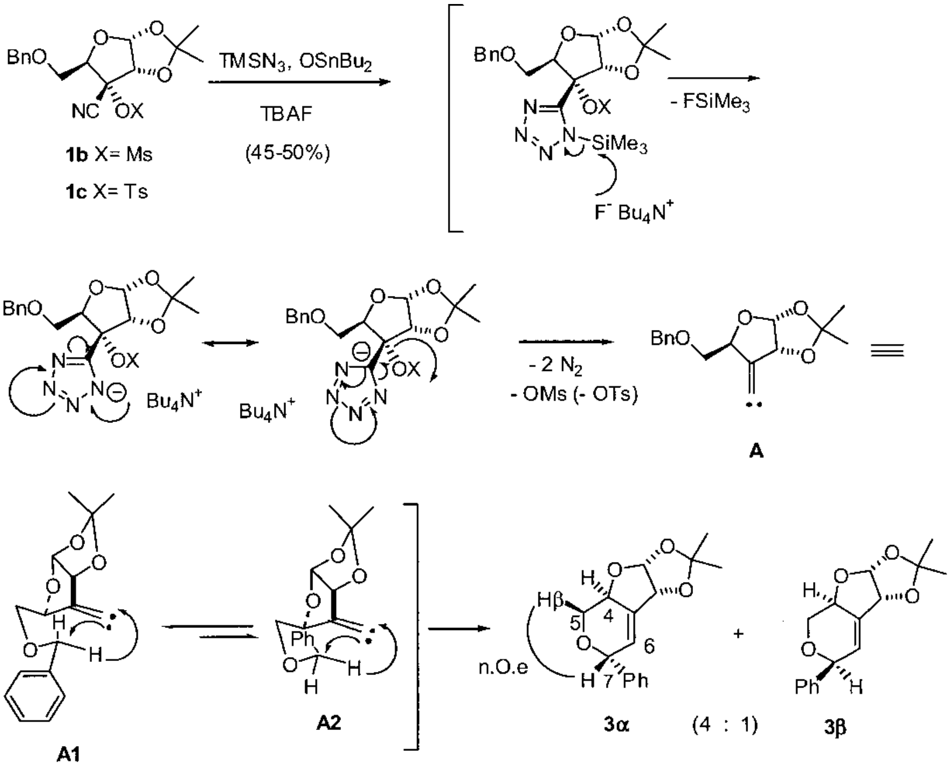
[a] In a typical experiment, to a solution of compound **1b** (400 mg, 1.04 mmol) in dry toluene (16 mL) under argon, dibutyltin oxide (260 mg, 1.04 mmol) and $TMSN_3$ (0.21 mL, 1.56 mmol) were added. The reaction was heated to 98°C and stirred for 16 hr and then the solvent was removed under vacuo. The crude product was submitted to flash chromatography (EtOAc: petroleum ether, 18 : 82) to give successively compound **3**β (26 mg) and **3**α (105 mg). Total **3**β + **3**α (131 mg, 45%, 1 : 4 ratio).

[b] All new compounds showed excellent analytical data. *Selected spectroscopic data*. **3**β: pale yellow solid: mp 100–102°C; $[\alpha]_D^{20}$ +29 (*c* 0.18, $CHCl_3$); IR (ATR) ? 2921, 2351, 2110, 1452, 1370, 1244, 1162, 1040, 1011 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (m, 5 H, C_6H_5), 6.20 (t, $J_{6,4} = 2.0$ Hz, $J_{6,7} = 2.0$ Hz, 1 H, H-6), 5.90 (d, $J_{1,2} = 3.7$ Hz, 1 H, H-1), 5.30 (t, $J_{7,4} = 2.0$ Hz, 1 H, H-7), 5.03 (d, 1 H, H-2), 4.73 (m, 1 H, H-4), 4.08 (dd, $J_{4,5a} = 6.0$ Hz $J_{5a,5b} = 10.4$ Hz, 1 H, H-5a), 3.29 (dd, $J_{4,5b} = 8.6$ Hz, 1 H, H-5b), 1.61 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.5–127.8 (C-3, C_6H_5), 125.3 (C-6), 113.4 [$O\mathit{C}(CH_3)_2$], 105.8 (C-1), 80.0 (C-2), 73.9 (C-7), 70.2 (C-4), 62.5 (C-5), 27.4 (CH_3), 27.0 (CH_3); MS (ES): 297.1 $[M + Na]^+$. **3**α: pale yellow solid: mp 93–94°C; $[\alpha]D^{20}$ + 176 (*c* 0.16, $CHCl_3$); IR (ATR) ? 2981, 2932, 2104, 1441, 1370, 1216, 1161, 1047, 1017 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5 H, $C_6\mathit{H}_5$), 5.99 (t, $J_{6,4} = J_{6,7} = 2.0$ Hz, 1 H, H-6), 5.87 (d, $J_{1,2} = 3.7$ Hz, 1 H, H-1), 5.08 (t, $J_{7,4} = 2.0$ Hz, 1 H, H-7), 4.97 (d, 1 H, H-2), 4.81 (m, 1 H, H-4), 4.45 (dd, $J_{4,5a} = 5.9$ Hz, $J_{5a,5b} = 10.0$ Hz, 1 H, H-5a), 3.35 (dd, $J_{4,5b} = 9.1$ Hz, 1 H, H-5b), 1.61 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.6–127.8 (C-3, C_6H_5), 126.2 (C-6), 113.4 [$O\mathit{C}(CH_3)_2$], 105.3 (C-1), 80.3 (C-2), 77.4 (C-7), 70.3 (C-4), 69.0 (C-5), 27.5 (CH_3), 27.0 (CH_3); MS (ES): 297.1 $[M + Na]^+$. **16**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68 (d, $J_{4,5} = 1.8$ Hz, 1 H, H-4), 6.63 (d, 1 H, H-5), 4.64 (dd, $J_{1a,OH} = 4.6$ Hz, $J_{1a,1b} = 19.8$ Hz, 1 H, H-1a), 4.57 (dd, $J_{1b,OH} = 4.6$ Hz, 1 H, H-1b), 3.45 (t, 1 H, OH), 0.97 [s, 9 H, $SiC(CH_3)_3$], 0.36 (s, 6 H, 2 × $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.6 (C = O), 167.3 (C-6), 147.4 (C-5), 132.3 (C-3), 108.6 (C-4), 67.0 (C-1), 27.0 [$Si(CH_3)_2C(\mathit{C}H_3)_3$], 18.4 [$Si(CH_3)_2\mathit{C}(CH_3)_3$], –5.8 [$Si(\mathit{C}H_3)_2C(CH_3)_3$].



Scheme 1

reaction involving a sugar derivative. The major isomer **3α** was possibly obtained by intramolecular cyclization and a subsequent 1,2-H shift on a chairlike conformer of type **A1** (Sch. 2) with most of the substituents being in a favored pseudoequatorial orientation (compared to less stable conformer **A2**, Sch. 2). The tosyl derivative **1c** (Sch. 2) also gave **3*α*** and **3*β*** in 46 to 51% in a 4 : 1 ratio.

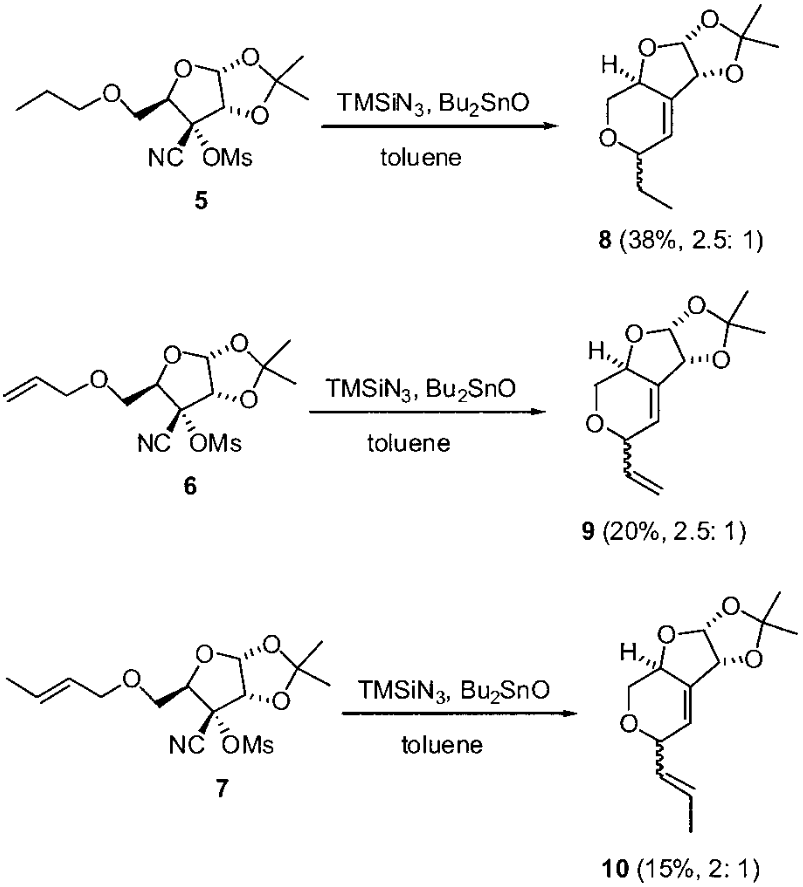


Scheme 2

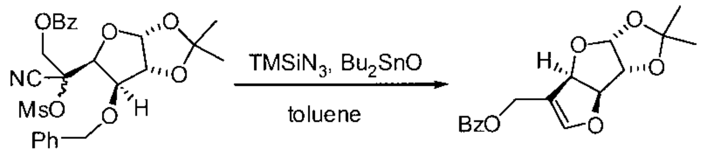
Scheme 3

In contrast, and surprisingly, the reaction of **1b** with NaN_3, DMF[3] provided the *CSIC*[9] product **4** (Sch. 3) in 46% yield.

The 1,6-C-H insertion reaction has been previously observed by Feldman in naphthol and anthrol derived alkylidenes rendering modest yields of the



Scheme 4



11 (1/1) **12** (55%)

Scheme 5

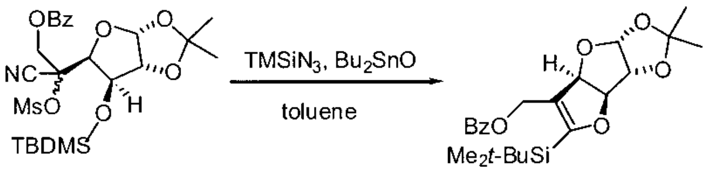
products.[6] This unusual conversion has been scarcely explored in other systems. Hence, we were prompted to investigate the use of similar reaction conditions to the suitably functionalized monosaccharides **5**–**7**. Interestingly, these compounds produced inseparable mixtures of isomers of the 1,6-C-H insertion products **8**–**10**, respectively, in albeit low to moderate yield (yields have not been optimized), with one stereoisomer predominating in each case, as illustrated in Scheme 4.[10]

We extended the scope of this reaction to include the monosaccharide derivative **11**. Surprisingly, the reaction took a different course and gave the unexpected product **12** in 55% yield (Sch. 5). Tronchet[11] reported a similar result in a related study a few years ago.

Interestingly, when the *O*-benzyl was substituted with an *O*-TBDMS group in compound **13**, compound **14** was obtained (Sch. 6) in 33% yield. This product is the expected 1,5-O-Si insertion product, which is in keeping with the known chemistry of alkylidenecarbenes[12,13] but is the first example of such a conversion in carbohydrate chemistry.

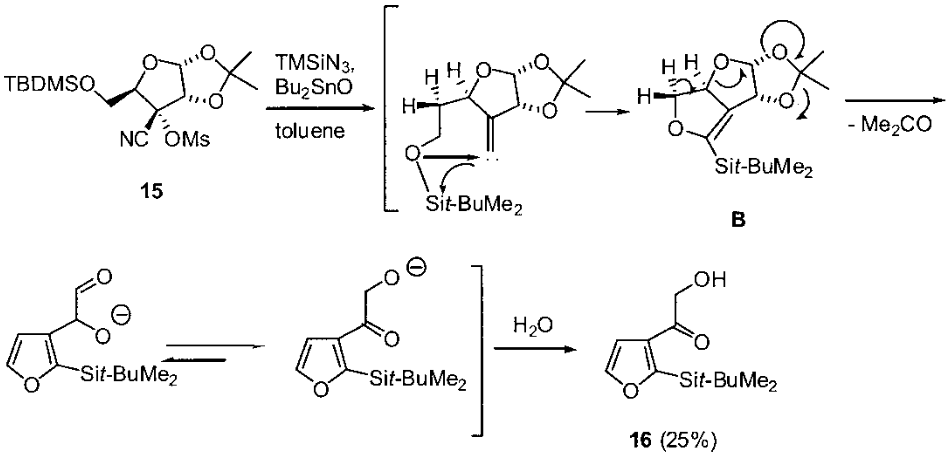
In contrast, compound **15** produced the unexpected 2,3-disubstituted furan **16** in 25% yield (Sch. 7). The formation of this product can be rationalized by a sequential process involving a 1,5-O-Si insertion to generate intermediate (**B**), not isolated, followed by a concerted fragmentation reaction initiated by H-5 abstraction, probably caused by an excess of TMSN$_3$.

In summary, we have reported a series of interesting and unexpected 1,6-C-H and 1,5-O-Si insertion reactions on alkylidenecarbene derivatives of



13 (1/1) **14** (33%)

Scheme 6



Scheme 7

carbohydrates using a new and direct protocol based on the reactions of conveniently functionalized α-cyanomesyl groups with $TMSN_3$ and Bu_2SnO. Work is in progress to extend these results to other precursors and will be reported in due course.

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