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Intramolecular alkylation of ε-iodo, α-alkoxy aldehydes

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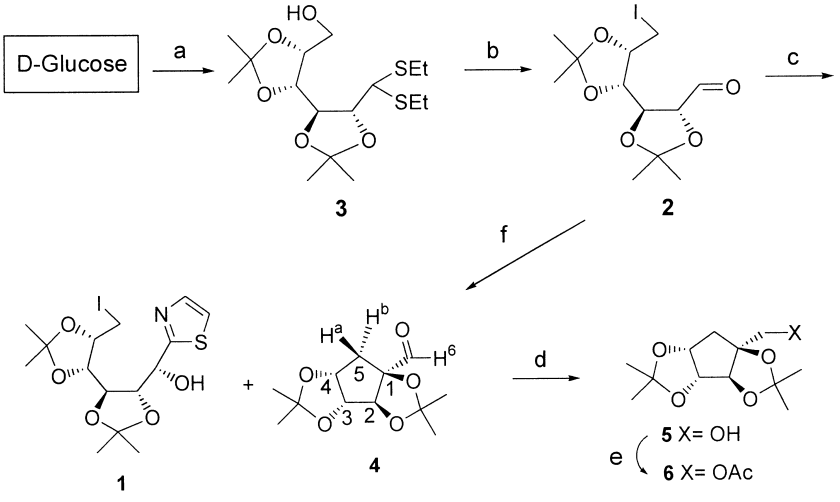
Abstract

The base-mediated intramolecular alkylation of 6-deoxy-6-iodo-2,3:4,5-di-*O*-isopropylidene-D-glucose (**2**) leading to the polyfunctionalized cyclopentane **4** is described.

In the course of a project under progress in our laboratory we needed alcohol **1** (Scheme 1). For this purpose we prepared aldehyde **2**[1] from D-glucose via compound **3**[2] (Scheme 1) and submitted it to Dondoni's one-carbon homologation by using the thiazole–carbonyl coupling.[3] In the usual conditions,[4] after complete reaction, in addition to the expected product **1**[1] (60% yield), we isolated a less polar compound **4**[1,5] (7% yield) (Scheme 1). The structure of this product (only one



Scheme 1. Synthesis and intramolecular alkylation of α-alkoxy aldehyde **2**. Reagents: (a) Ref. 2; (b) i. Ph_3P, I_2, toluene (73%); ii. HgO, $HgCl_2$, acetone, H_2O (85%); (c) 2-TST, CH_2Cl_2, rt (**1**: 60%, **4**: 7%); (d) $NaBH_4$, MeOH (85%); (e) Ac_2O, py (93%); (f) DBU CH_2Cl_2, rt (**4**: 75%)

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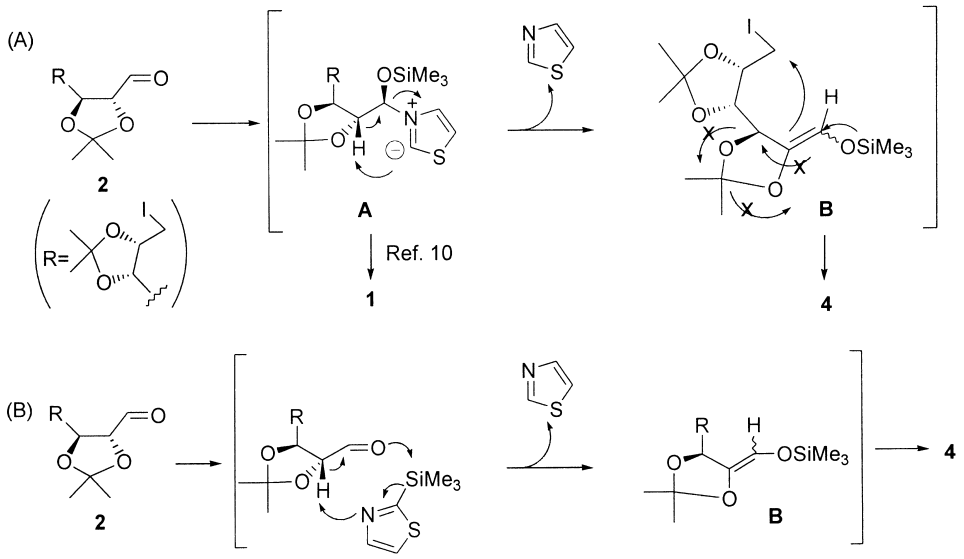
diastereomer was detected and isolated to which the *anti* relative configuration at the new stereocenter was assigned based on literature precedent[3]) was assigned based on the full spectroscopic and analytical data. In agreement with this, in the ^{1}H NMR (^{13}C NMR) spectra of **4** we observed an aldehydic proton at 9.73 ppm as a singlet (198.4 ppm for H-*C*O) and two significant protons at 2.50 ppm (dd, $J_{5a,5b}=15.2$ Hz, $J_{4,5b}=2.9$ Hz, 1H, H5b) and 2.17 ppm (dd, $J_{5a,5b}=15.2$ Hz, $J_{4,5a}=6.2$ Hz, 1H, H5a) (C5: 39.9 ppm) forming the AB part of an ABX system with a proton at 4.91 ppm (td, $J_{4,5b}=2.9$ Hz, $J_{4,5a}=6.2$ Hz, 1H, H4). In the IR spectrum no carbonyl band absorption was observed, the carbonyl function being in the hydrated form, a common and well known fact in α-alkoxy aldehydes. The absolute configuration at C-1 was easily assigned as *R* by NOE NMR measurements. These data, along with the elemental analysis coupled to the MS spectrum [$C_{12}H_{18}O_5$: 243 ($M+1^+$, 19), 227 (M^+–15, 64), 43 (100)], clearly pointed out that product **4** was the cyclopentane resulting from the intramolecular α-alkylation of the α-alkoxy aldehyde **2**.

Additional proof for structure determination was obtained upon reduction of compound **4** with sodium borohydride (to give alcohol **5**)[1] and acetylation leading to product **6**[1] (Scheme 1).

This reactivity was completely unexpected and unprecedented. As is well known, the base-mediated alkylation of aldehydes is hampered by crotonization or polymerization due to the aldol-like competitive reaction. A series of aldehyde derivatives (imines, hydrazones, oximes or enamines) have been used for this purpose.[6] In fact, a search for the α-alkylation of the α-alkoxy aldehydes gave a limited number of examples.[7] In addition, a recent synthesis of chiral α-alkyl, α-trifluoromethyl α-alkoxy aldehydes used an indirect approach from ketones,[8a] and an elegant synthesis of spirocyclopentenenones from α-alkoxy aldehydes in furanose templates was only possible through enamine intermediates.[8b] This is in sharp contrast with the α-alkoxy ketones which have proved to be excellent intermediates for aldol reactions via the enol borinates.[9]

In Scheme 2 we show a tentative proposal in order to explain the results that we have observed. We have hypothesized an intramolecular (A) mechanism where the presumed intermediate **A**, after proton abstraction gives the trimethylsilyl enol ether **B**, the real precursor for the intramolecular alkylation. Note that intermediate **A** should also yield the major product (**1**) in this reaction.[10]



Scheme 2. Possible mechanisms for the intramolecular alkylation of α-alkoxy aldehyde **2**

Alternatively (B), the intermolecular 2-(trimethylsilyl)thiazole (2-TST) mediated abstraction of the α-proton in compound **2** should also afford the reactive intermediate **B** leading to compound **4**.

In any case, the β-elimination in intermediate **B** (Scheme 2) was not observed, and this is really exceptional, considering the experimental conditions used (at room temperature and with 2-TST as the only reagent in the medium) and comparing with the necessary controlled conditions in order to prevent the β-elimination (low temperature reaction (–78°C), LDA as base, cosolvents such HMPT or DMPU, and highly reactive alkylating agents) in the *intermolecular alkylation* of tartaric acid derivatives, described by Seebach and co-workers.[11] In the present case, the stability of the enolate can also be due to the rigid acetonide skeleton which precludes the optimal geometrical arrangement for the β-elimination to take place.[11]

With these ideas in mind and as an obvious issue, we tested the *direct* alkylation of compound **2** with DBU (1.1 equiv.) as base, in the same experimental conditions. Very interestingly, a rapid reaction ensued (1 h) giving cleanly compound **4** in 75% isolated yield after flash chromatography (Scheme 1).

In summary, we have reported the first example of an intramolecular alkylation in ε-iodo, α-alkoxy aldehydes, by using unusual, extremely simple and mild reaction conditions. These results open the way for new exciting ventures directed to the important synthetic intermolecular alkylation of chiral α-hetereoatom (O or N)-substituted aldehydes, as a strategy for the synthesis of enantiomerically pure quaternary centers[12] containing molecules.[13] Work is now in progress in our laboratory and will be reported in due course.

Acknowledgements

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5. Compound **2** (197 mg, 0.53 mmol) dissolved in dry CH_2Cl_2 (1 mL) was treated with 2-TST (0.094 mL, 0.58 mmol, 1.1 equiv.) at 0°C, under argon. The reaction mixture was warmed and stirred to room temperature for 18 h. The solvent was removed and the residue was treated with Bu_4NF (0.53 mL, 1.1 M in THF) as usual until complete desilylation. The solvent was evaporated, diluted with water and extracted with CH_2Cl_2 several times. The organic layer was dried, filtered and evaporated. Flash chromatography (hexane/ethyl acetate 10%) gave compounds **1** (141.4 mg, 60%) and **4** (9.3 mg, 7%). Compound **4**: oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H, CHO), 4.91 (td, $J=6.2$ Hz, $J=2.9$ Hz, 1H, H4), 4.63 (d, $J=6.2$ Hz, 1H, H3), 4.61 (s, 1H, H2), 2.50 (dd, $J=15.2$ Hz, $J=2.9$ Hz, 1H, H5b), 2.17 (dd, $J=15.2$ Hz, $J=6.2$ Hz, 1H, H5a), 1.52, 1.46, 1.38, 1.31 (s, s, s, s, 12 H, $4\times CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4 (CHO), 113.5, 111.1 [$2\times C(CH_3)_2$], 86.6, 83.6 (C2, C3), 81.2 (C4), 39.9 (C5), 27.5, 26.7, 25.9, 24.7 [$2\times C(CH_3)_2$].
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9. See, for instance: Paterson, I.; Tillyer, R. D. *J. Org. Chem.* **1993**, *58*, 4182.
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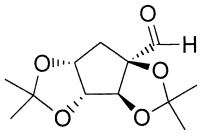
13. Compounds **4**–**6** are densely functionalized, chiral cyclopentane derivatives with some of the structural and functional moieties present in carbocyclic nucleosides of type **C** (Maycock, C. D.; Barros, M. T.; Godinho, L. C. *Tetrahedron Lett.* **1993**, *34*, 7985) and glycosidase inhibitors (trehazolin aglycon) (Kobayashi, Y.; Miyazaki, H.; Shiozaki, M. *J. Org. Chem.* **1994**, *59*, 813).



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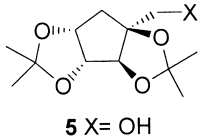
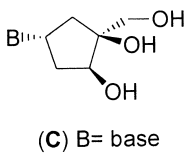
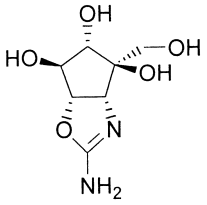


5 X= OH

6 X= OAc



(**C**) B= base



Trehazolin aglycon