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The first synthesis of the ketene dithioacetals from sugar lactones: a convenient access to 3-ulosonic acids

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Abstract:

Isomeric 2-deoxy aldonolactones undergo Horner-Emmons reactions with 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]1,3-dithiane, to give the corresponding ketene dithioacetals, which are the key intermediates in the synthesis of 3-deoxy-2-keto-aldonic acids.

Keywords: Homologation; Ketene; Thioacetals; Lactones

Construction of ketene dithioacetals, firstly prepared by Freund,[1] has become a convenient methodology for the one-carbon homologation of carbonyl derivatives.[2,3] In particular, the utility of ketene dithioacetals as intermediates in the synthesis of aldehydes,[4-6] carboxylic acids[7,8] and esters,[9] has attracted considerable attention. Ketene dithioacetals are readily available from carbonyl compounds *via* the reaction with the carbanionic species generated from substituted dithioacetals in the Peterson,[10,11] Wittig,[12] or Horner-Emmons[13,14] olefination process. However, the formation of ketene dithioacetals fails when the ketones involved in the reaction have particularly acidic α-hydrogens. Such a limitation has been disclosed recently by Deslongchamps,[15] who studied the reaction of some ketones (cyclopentanone, 4-*t*-butylcyclohexanone, acetophenone and others) with phosphonate dithioacetal **A** (Fig.1). This difficulty could be overcome applying a new phosphonate **B**,

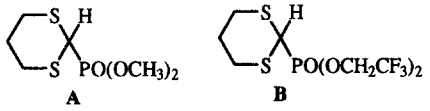

Fig. 1

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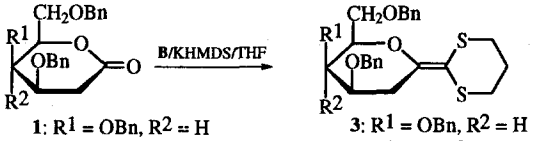
recently reported by Mikołajczyk.[16] Reaction of the above mentioned ketones with phosphonate **B** produced the expected ketene dithioacetals.[15] This result was considered in terms of an electron withdrawing character of trifluoroethyl substituent which stabilises the phosphonate anion **B**[15] and accelerates the elimination step of the Horner-Emmons reaction.[17]

Encouraged by these results we envisioned the formation of ketene dithioacetals from sugar lactones and phosphonate **B**. To our knowledge, no information on such a reaction using lactones are available in the literature. It was therefore decided to explore the scope of ketene dithioacetals methodology in relation to this class of compounds.

Two lactones **1** and **2** [18] were subjected to reaction with phosphonate **B** (Scheme 1). In a typical procedure, a solution of potassium bis(trimethylsilyl)amide (2.0 equiv.) in toluene (Fluka) was added dropwise to **B** (2.0 equiv.) dissolved in anhydrous THF (5 mL/mmol) at -78 °C under argon. The resulting mixture was stirred at this temperature for 1 h, and then solution of appropriate hexono-1,5-lactone in 1.5-2 mL of THF/mmol was added dropwise. The reaction mixture was stirred 3 h while the temperature was allowed to rise to ~0 °C. The reaction mixture was then neutralized with trifluoroacetic acid, and the crude product was purified by flash chromatography.



1: R^1 = OBn, R^2 = H
2: R^1 = H, R^2 = OBn

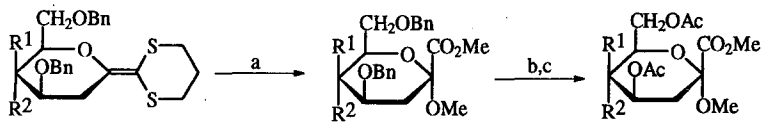
3: R^1 = OBn, R^2 = H
4: R^1 = H, R^2 = OBn

Scheme 1

We found that the reaction was clearly successful, and furnished the desired ketene dithioacetals **3** and **4** in 72 and 62%, respectively.[1] These high yields promoted a further study aimed at the

[1] Compound **3**: yield 72%, m.p. 69-70 °C, $[\alpha]_D$ +51.9° (c, 1.19 in $CHCl_3$); HR-MS (LSIMS) calcd for $C_{31}H_{34}O_4S_2$ $[M+Na]^+$ 557.1796 found 557.1823; ^1H NMR (500 MHz, $CDCl_3$): δ 2.08-2.14(m, 2H, H-2'ax, H-2'eq), 2.63(dd, 1H, H-3ax), 2.71-2.85(m, 4H, H-1'ax, H-1'eq, H-3'ax, H-3'eq), 3.30(ddd, 1H, H-3eq), 3.64(ddd, 1H, H-4), 3.73(m, 2H, H-7a, H-7b), 3.83(td, 1H, H-6), 3.93(bs, 1H, H-5), 4.46-4.94(3×ABq, 3×2H, $C\underline{H}_2Ph$), 7.22-7.40(m, 15H, Ar); $J_{3ax,4}$ 11.8, $J_{3eq,4}$ 5.1, $J_{3eq,5}$ 0.9, $J_{3ax,3eq}$ 14.2, $J_{4,5}$ 2.15 Hz; ^{13}C NMR (500 MHz, $CDCl_3$): δ 25.5(C-2'), 28.0(C-3), 29.6(C-3'), 30.3(C-1'), 68.8(C-7), 70.4(Bn), 72.5(C-5), 73.5(Bn), 74.1(Bn), 76.7(C-4), 78.7(C-6), 105.6(C-1), 127.3-128.4 and 138.1-138.6(Ar), 150.3(C-2).
Compound **4**: yield 62%, m.p. 40-42 °C, $[\alpha]_D$ +44.9° (c, 1.08 in $CHCl_3$); HR-MS (LSIMS) calcd for $C_{31}H_{34}O_4S_2$ $[M]^+$ 534.1899 found 534.1889; ^1H NMR (500 MHz, $CDCl_3$): δ 2.09-2.14(m, 2H, H-2'ax, H-2'eq), 2.47(dd, 1H, H-3ax), 2.73-2.84(m, 4H, H-1'ax,

transformation of **3** and **4** to the 3-ulosonic acids which are important constituents of cellular and bacterial membranes.[19,20] Unfortunately, none of the known methodologies used for the oxidative hydrolysis of ketene dithioacetals provides directly a hydroxy carboxylic acids in one step.[21] Looking for the best conditions for the conversion of ketenes **3** and **4** we first attempted the reaction with NBS (two equiv.) and methanol in CH_2Cl_2 at rt (the conditions employed for oxidation of sulfides to sulfoxides[22]). We were delighted to find that the reaction resulted in clean and stereoselective formation of desired α–methyl 3-ulosonates **5** and **6** (Scheme 2), isolated in ~80% yield as the sole products.[2]



3: R^1 = OBn, R^2 = H
4: R^1 = H, R^2 = OBn
5: R^1 = OBn, R^2 = H
6: R^1 = H, R^2 = OBn
7: R^1 = OAc, R^2 = H
8: R^1 = H, R^2 = OAc

Scheme 2. Reagents and conditions: (a) NBS-MeOH, CH_2Cl_2, rt; (b) H_2/Pd-C, EtOH; (c) Ac_2O-Py.

In summary, we believe that our studies demonstrate not only a successful construction of ketene dithioacetals from sugar lactones, but also provide a general, versatile two-steps route to the glycosides of 3-deoxy-2-ulosonic acids. Further detailed studies on this subject will be presented in due course.

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H-1'eq, H-3'ax, H-3'eq), 3.32(ddd, 1H, H-3eq), 3.67-3.76(m, 3H, H-4, H-5, H-6), 3.77(dd, 1H, H-7a), 3.81(dd, 1H, H-7b), 4.54-4.82(3×ABq, 3×2H, C$\underline{H}_2$Ph), 7.15-7.40(m, 15H, Ar); $J_{3ax,4}$ 8.8, $J_{3eq,4}$ 4.8, $J_{3ax,3eq}$ 14.7, $J_{7a,6}$ 3.5, $J_{7b,6}$ 2.4, $J_{7a,7b}$ 11.3 Hz; ^{13}C NMR (500 MHz, $CDCl_3$): δ 25.5(C-2'), 29.7(C-3), 30.4(C-3'), 30.5(C-1'), 68.9(C-7), 71.2(Bn), 73.5(C-5), 74.1(Bn), 77.4(Bn), 78.2(C-4), 79.3(C-6), 105.6(C-1), 127.5-128.4 and 138.1-138.3(Ar), 150.2(C-2).

[2] In a typical run, a solution of **3** or **4** (0.5 mmol) in CH_2Cl_2 (5 mL) was treated with methanol (1 mL) and NBS (178 mg, 1 mmol). The mixture was stirred at rt until the reaction was complete (~0.5 h), and then was filtered through a short column of silica gel and evaporated. The residue was purified by chromatography on silica to give the desired esters.

Spectroscopic data for methyl (methyl 4,5,7-tri-*O*-benzyl-3-deoxy-α-D-*lyxo*-hept-2-ulopyranosid)onate (**5**): $[\alpha]_D$ +23.0° (c, 0.92 in $CHCl_3$); HR-MS (LSIMS) calcd for $C_{30}H_{34}O_7$ $[M+Na]^+$ 529.2202 found 529.2200; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.20-2.30(m, 2H, H-3ax, H-3eq), 3.22(s, 3H, OMe), 3.64-3.77(m, 3H, H-6, H-7a, H-7b), 3.79(s, 3H, CO_2Me), 3.90(bs, 1H, H-5), 3.93(ddd, 1H, H-4), 4.41-4.95(3×ABq, 3×2H, C$\underline{H}_2$Ph), 7.22-7.35(m, 15H, Ar).

Spectroscopic data for methyl (methyl 4,5,7-tri-*O*-benzyl-3-deoxy-α-D-*arabino*-hept-2-ulopyranosid)onate (**6**): $[\alpha]_D$ +41.3° (c, 1.16 in $CHCl_3$); (lit. $[\alpha]_D$ +36.5° (c, 2.0 in $CHCl_3$) [23]); HR-MS (LSIMS) calcd for $C_{30}H_{34}O_7$ $[M+Na]^+$ 529.2202 found 529.2189; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.76(dd, 1H, H-3_{ax}), 2.52(dd, 1H, H-3_{eq}), 3.24(s, 3H, OMe), 3.54-3.80(m, 4H, H-5, H-6, H-7a, H-7b), 3.81(s, 3H, CO_2Me), 4.02(ddd, 1H, H-4), 4.50-4.90(3×ABq, 3×2H, C$\underline{H}_2$Ph), 7.15-7.40(m, 15H, Ar); $J_{3ax,4}$ 11.2, $J_{3eq,4}$ 5.1, $J_{3ax,3eq}$ 13.0, $J_{4,5}$ 8.4 Hz.

Compounds **5** and **6** after hydrogenolysis (H_2/Pd-C) and acetylation were transformed into α-methoxy esters **7** [24,25] and **8** [26] identical by the NMR data with those synthesized by a previously elaborated methodology.

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