2014

Experiment #2 - Acetylation of Betulin (2014)

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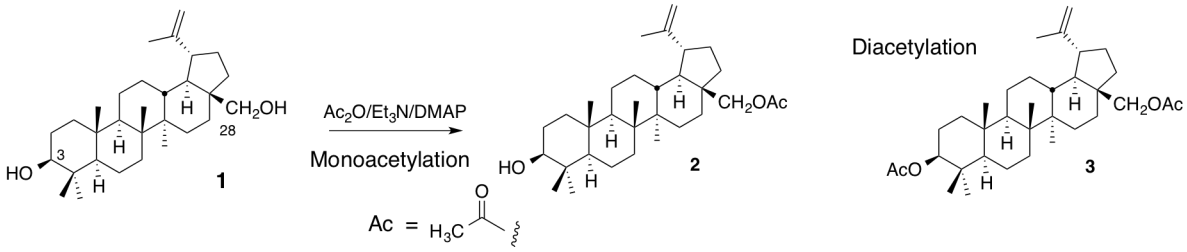
In the second lab we will be attempting the monoacetylation of betulin to produce the 28-acetylbetulin **2** (Scheme below, and also in the general synthetic outline slide distributed at our first betulin group meeting). The original procedure, given at the bottom, called for the reaction to go overnight (18 hr) at room temperature (rt). To speed things up, we will reflux for one hour. One potential pitfall with these acceleration methods is that the 3,28-diacetate of betulin **3** may form in significant quantities. This by-product was a minor contaminant following the original procedure.



First, write out the procedure you will follow by adapting the original procedure to the experiment you will do, scaled to 2 g of betulin. We will be replacing pyridine with a less foul-smelling basic amine, triethylamine (replacement will be one to one on a molar basis), and you will reflux for one hr, monitoring the reaction by TLC (use the same solvent system you found was best when running the TLC on betulin isolation). Last year we also attempted a microwave procedure, but this did not work as well.

For those of you who did not get pure betulin from the extraction, start by recrystallizing the crude product as described in the previous procedure: "If need be, the betulin can be recrystallized from methanol/chloroform, 1:1 (MeOH/$CHCl_3$)." The betulin for this procedure, however, need not be perfectly pure since the desired monoacetate will be isolated, and hence purified, by flash chromatography.

The work-up of the reaction is done by an extraction procedure using a separatory funnel. This is a basic technique in organic chemistry used to purify compounds on the basis of relative solubility in immiscible solvents (such as water and dichloromethane), and we will go over this in our pre-lab lecture. To prepare for this, please watch the following video: http://www.youtube.com/watch?v=vcwfhDhLiQU

The monoacetate can be easily purified by flash chromatography[1] using a pre-packed silica gel column (RediSep, 12 g silica gel), using a syringe barrel with a plunger to push the solvent through.. Use a solvent system to elute the desired monoacetate as indicated in the oriringal procedure, or use TLC to find a solvent system that best separates the monoacetate form the diacetate, with the Rf of the monacetate falling between 0.2 – 0.4 (see footnote).

Answer these questions BEFORE coming to lab – have them written out

1) What is the structure of DMAP (4-dimethylaminopyridine)?
2) What is the structure of acetic anhydride?
3) What is the mechanism of this reaction, including the role of DMAP?
4) What is brine, and why is brine used to extract the organic solvent?
5) What is the partition coefficient "P"?

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1 Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925

6) In the extraction of dichloromethane with aqueous solutions, which is the bottom layer and which is the top layer? What about with chlorobenzene? (Look up the densities of these organic solvents and compare them to water).

Original Procedure: *JOC* **2002**, *67*, 2864

The yield of this reaction varied with the scale (60-72%), with highest yields obtained at smaller scales (200 mg of 5). In a larger-scale reaction, to a solution of betulin (4 g, 9.04 mmol), 4-(dimethylamino) pyridine (DMAP, 0.4 g, 1% w/w), and pyridine (6 mL, 25.2 mmol) in CH_2Cl_2 (36 mL) was added acetic anhydride (0.90 mL, 9.53 mmol), and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was washed with 10% aqueous HCl, water, saturated aqueous $NaHCO_3$ solution, and then saturated brine and then dried (Na_2SO_4). Removal of the solvent in vacuo and flash chromatography of the crude product on silica gel (85:15 hexanes: EtOAc) afforded 8 (2.59 g, 60%) as a white solid, accompanied by 3,28-diacetate10f (290 mg, 6%) and recovered betulin (651.9 mg, 16%): mp 217-219 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72 (s, 3H), 0.79 (s, 3H), 0.93 (s, 3H), 0.94 (s, 3H), 0.99 (s, 3H), 1.64 (s, 3H), 2.04 (s, 3H), 2.41 (ddd, J) 6.0, 11.2, 11.2 Hz, 1H), 3.15 (dd, J) 5.2, 11.6 Hz, 1H), 3.82 (d, J) 11.2 Hz, 1H), 4.21 (dd, J) 1.2, 11.2 Hz, 1H), 4.55 (br s, 1H), 4.65 (d, J) 1.6 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.7, 15.3, 15.95, 16.04, 18.2, 19.0, 20.7, 21.0, 25.1, 27.0, 27.3, 27.9, 29.5, 29.7, 34.1, 34.5, 37.1, 37.5, 38.6, 38.8, 40.8, 42.6, 46.2, 47.6, 48.7, 50.3, 55.2, 62.7, 78.9, 109.8, 150.1, 171.6.

NOTE:
1) If performed properly, the flash chromatography will give pure monoacetate **2** and diacetate **3**. Record an NMR spectrum of each, and save both compounds - be sure to calculate the yield for each.

2) For a YouTube video on traditional flash chromatography:
https://www.youtube.com/watch?v=fF1gXUvyGb4

3) One stain that works for monitoring betulin, as well as the mono- and di-acetate is the standard ethanolic vanillin with H_2SO_4