Lab 6A • 05/02/12

Synthesis of benzocaine

The mechanism is a classic Fischer esterification. We have two main starting materials: p-aminobenzoic acid, and then ethanol as a solvent, but also a reagent. You have sulfuric acid that you're using as an acid catalyst. You reflux it for half an hour or so, and you end up with the ethyl ester. This is benzocaine for it's common name. It's more technical name would be ethyl p-aminobenzoate. [lab directions – sodium carbonate to neutralize both original starting material and excess sulfuric acid; stronger base not used to avoid saponification]

[Consider this: aside from whatever toxicity the compound may or may not have, you are non-PhD chemists in a non-pharmaceutical lab using non-pharmaceutical grade chemicals do no substantive purification of your product once you make it.]

What is roughly the shape of a nerve cell, and how do two nerve cells communicate? If want to simplify, I might draw something that looks like this. It's an astrocyte; there the myelin, the phospholipid layer that's the sheath of this kind of nerve cell. Then there's another nerve cell that's next to it. How does an electrical signal get generated? Nerve cells are electrical signals. To generate that electrical signal, you have to create a potential, a difference in charge, the desire of electrons to flow; that makes the signal. The way that the body does that, one of the ways it can do it, is by moving sodium or potassium ions, which have a certain fixed size, and they pass very carefully through these things called sodium channels; [they actually pass through different channels because they're differ ion sizes]. For example, example sodium ions can flow into a channel or flow out of a channel. If you make an imbalance of the ions, you generate a charge, which that's that signal that gets sent along the nerve cell. What if you block the sodium channel? That's what benzocaine does. In other words, it prevents an electrical signal being generated. It's not that the cell doesn't get damaged, it's just once it fires, it gets stuck in that position; the electrical signal never resets. It's like a circuit breaker that's tripped on or off, depending on how you want to tell that story. Eventually, that compound breaks down in the body; the sodium channel is able to open up again. Any of you who've ever had dental work and get [analgesic] shots like that, sodium channels get blocked, they stay blocked for a while until the compound decomposes. As it slowly decomposes, that's when you start feeling things tingling and the pain slowly starts to come back again, because the electrical signal finally can flow. The pain-mitigating action of the various caines – lidocaine, benzocaine, cocaine – they all operate, in the pain-killing sense, as sodium channel blockers.

Electrical signals in nerve cells can be generated by the movement of sodium ions through channels in the cell membrane. Benzocaine blocks the sodium channel[s], preventing, you could say, the circuit from being reset, which means no ion flow, preventing the generation of a signal, which in this case we're talking about pain. [In between the two nerve cells, there is this gap], the synapse. At that synapse, what goes on? It's not that we have a spark that crosses that gap; we have a chemical message that's sent across that gap, using what are called neurotransmitters. Neurotransmitters are chemicals that activate a reception site on what's called a receptor that only acknowledges the presence of that chemical if there's a good enough physical or chemical fit. There's quite a broad variety of receptors – there are nicotinamide receptors which are sensitive to nicotine; those kinds of receptors are found in muscles throughout the body, which is why nicotine is so addictive. It's not just smoking itself that's addictive, but it's the fact that it's used as a neurotransmitter throughout the body that, if you start ingesting extra, your body gets used to it; when you stop, it says: hey, what'd you do with that? That's why people get hook on cigarettes. Besides those, there are opiod receptors, which are often exploited for pain [mitigation]; morphine and compounds like that are used on those circuits. You have seratonin-related receptors – that's one of the biggies, that regulates mood, sleep, eating patterns, the rhythms of life; if you mess with that, it causes all kind of strange effects. There are amphetamine receptors, cannabinoid receptors. Different kinds of neurotransmitters can have what's call an agonist or an antagonist effect – in other words, it activates that system or it deactivates that system. [phytochemistry]

Reverse synthesis problems

Our first problem said take just one molecule and somehow make this unsaturated, bicyclic ketone. The point of this problem was to be able to recognize that it would likely be the product of an aldol condensation. Why? Because we do have that alpha,beta unsaturation to a carbonyl; that's the classic way to recognize that we have an aldol condensation. Once we recognize that we have an aldol condensation, how do we back up? Remember that all of these alpha reactions happen through an alpha position. The carbonyl that ends up in the product is the carbonyl that used to be part of the enolate. That means, specifically, where I've indicated there, that is the alpha position that reacts. How does it react? It attacks another carbonyl, which is what ends up at the beta position. When it first gets attacked, you could end up with an alcohol; that's the beta-hydroxyketone or aldehyde, but then it could dehydrate, which is how we end up with the alpha,beta-unsaturated ketone or aldehyde. What you do is simply cut through the carbon-carbon double bond [and] open it up. The alpha side of it, that's just going to be empty, cause that's where the hydrogen was; the beta side of it, that's where the carbonyl goes, so that means the correct answer would be this.

The second problem, you were told that you needed to specifically take two molecules and somehow produce an unsaturated, cyclic compound. If we made a cyclic compound, it's a Robinson annulation. How could we figure that out? The most obvious thing that looks like it happened was an aldol condensation, so let's do the same thing that we did up above – break apart the aldol. Remember that it's the carbonyl that survived that was the enolate; it's going to be the alpha position of that enolate that reacted. The position that got attacked was a carbonyl. But now look at the relative position of both of those carbonyls – alpha, delta. We have a delta-carbonyl carbonyl compound, which means that this could have been the product of a Michael addition.

It turns out we have two choices, in theory, about how we could have broken this molecule apart to have been made by a Michael addition. To figure that out, we're going to break a bond at the alpha,beta position. We could do it from the alpha,beta position for the top carbonyl, or we could take the opposite perspective – we could saw that the bottom carbonyl compound, maybe for this first step, is the portion of the compound that did make the carbonyl. Relative to the bottom carbonyl, we could also cut between the alpha and the beta [positions]. So here are our two versions of that: cut at the top, and that will get us acetone plus this unsaturated aldehyde. If I cut the other bond instead, then I get propanal, plus an unsaturated ketone. My instinct would tell me that that second way might be the better way in real life, because you would have a more easily-formed enolate – the enolate would more likely form from the aldehyde even if both were in solution, and then we have the conjugated ketone that could be attacked, squishier ion liking to react with squishier ion. This part was aldol; this part was the Michael. Again, aldol plus a Michael gives us Robinson.

Next problem, you weren't told how many molecules, you were just shown a product. This is a beta-ketoester, which means what kind of reaction was likely here? Claisen. Watch out for two carbonyl near it other like that. It has to be a beta carbonyl, it can't just be any two-carbonyl compound. How do we pull this apart retrosynthetically? You know that it's the alpha position of one ester that attacks the carbonyl of the other. The alpha position, then, is directly connected to the next carbonyl, and the carbonyl that gets attacked is the one that does not end up as the ester. The whole point of a Claisen condensation is the alpha [position] attacks, opens up the carbonyl, the carbonyl collapses, and kicks something out. There's the part that was an ester that was attacked, so when we pull this apart, we're going to have two esters, which is, of course, what goes into a Claisen condensation. But here's one point: the overall product is an ethyl ester, so to prevent any kind of transesterification, when you pulled it apart, both the portion that stays an ester and the portion that was an ester must both be ethyl esters.

[complication of multiple alkylation in malonic ester synthesis] Any of the problems you see here related to the malonic ester synthesis, all of your products are going to be modified acetic acids. If you remember, the malonic ester itself is two carbonyls separated by one carbon. One of the carbonyls leaves because of decarboxylation, so if end up with one carbon and a carbonyl that's an acid, that's acetic acid. If you're going to be making a functionalized acetic acid, then the other carbons here are going to be from an alkyl halide or a sulfonate that could have been used during the reaction. We'll start out with diethyl malonate. First, we react with base. Since malonate is an acidic enough compound, we could get away with using ethoxide. Why ethoxide? Because you avoid any kind of transesterification. Theoretically, if we had any base that we carefully added to this compound, as long as the base was strong enough, you should be able to avoid transesterification if that proton really is acidic compared to the base. To be safe, we use ethoxide. Once you deprotonate, you alkylate. Since we found how many carbons we need in our alkyl halide, just stick a halogen onto the end of it, and this is primary, which is what we need, so it can be attacked; Sn2 occurs. Afterwards, we can saponify. Saponification would be better because we do have a double bond, and if you prolongly expose that double bond to acid and water, theoretically you could hydrate it. To help prevent that, saponification would be a better route. Of course, if you saponify, you end up with a salt. In order to decarboxylate, we then need to put it back at least under slightly acidic conditions. So, without water, if I just show acid and heat, then we can avoid hydrating the alkene, we reprotonate the salt, and we get decarboxylation.

Next one, you're told that some kind of ketone reacts in order to make a carboxylic acid; that is the haloform reaction. Haloform takes a methyl ketone – it first turns it into a salt, and then, on reacidifcation, we get the carboxylic acid.

Final problem – two molecules reacting to make this part aldehyde-part ketone. If we look at this, we see that it is a delta-carbonyl carbonyl compound; that's again the signature of a Michael addition. We again, therefore, have two ways we can chop this up; again, we would break the bond at the alpha,beta position to move backwards to the starting materials. On the lefthand side, I could break the alpha,beta bond there; on the righthand side, I could break the alpha,beta bond. For the lefthand version, that's gonna get us ethanal plus an unsaturated ketone; on the righthand version, it's going to get us butenal plus acetone. [cis trans cannot be determined because we don't know the stereochem formed]

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Na_2CO_3 – use to neutralize excess H_2SO_4 as well as unreacted starting material.

NaOH is not used since there is a small chance that even @ room temperature there might be saponification. Also, the only products of carbonate reacting with acid are CO_2 and H_2O.

Electrical signals in nerve cells are generated by the movement of ions (sodium) through channels in the cell membrane. Benzocaine blocks the sodium channels, preventing the "circuit" from being reset (no ion flow), preventing the generation of a signal (pain).

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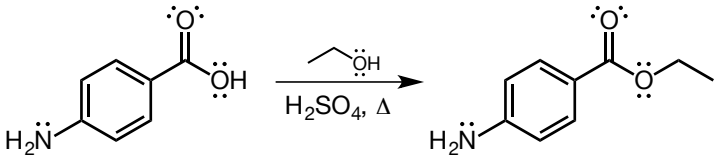

p-aminobenzoic acid benzocaine

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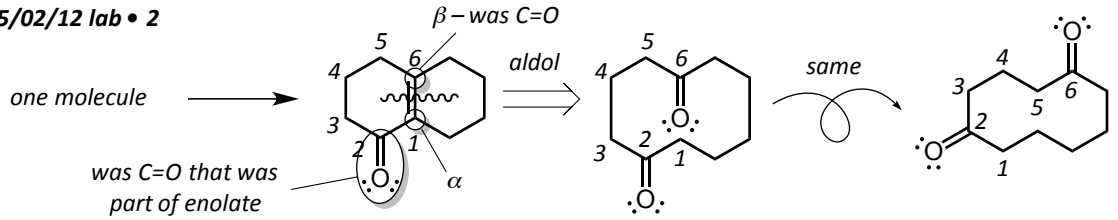

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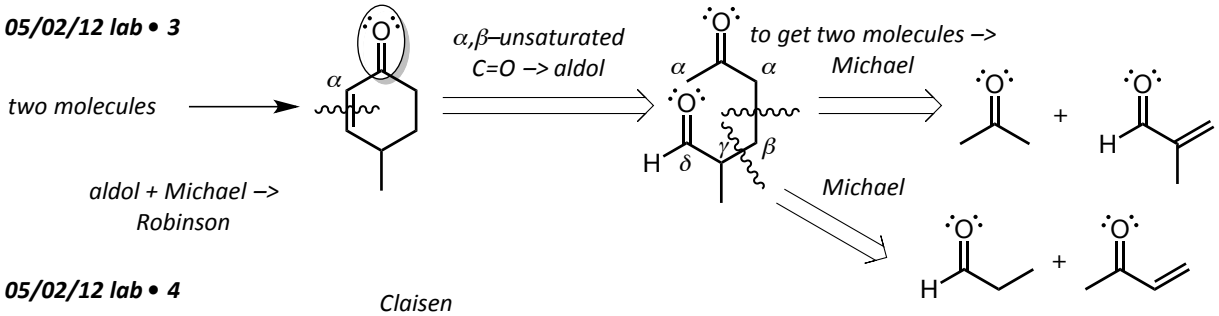

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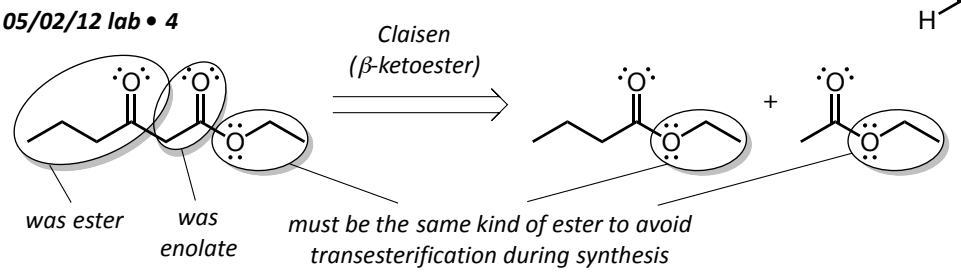

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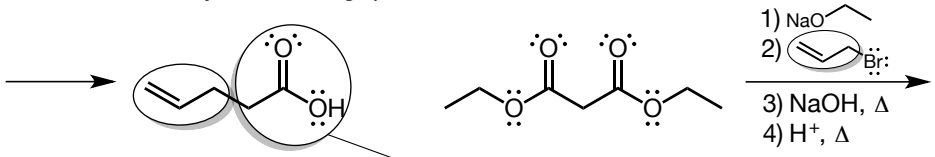

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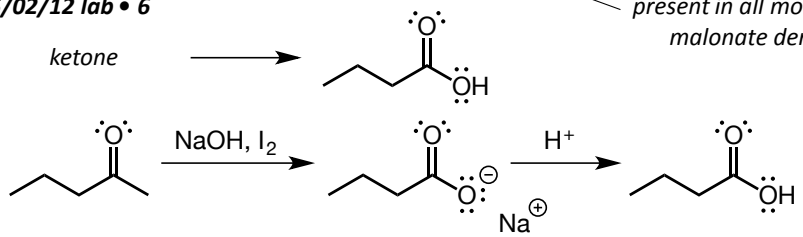

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