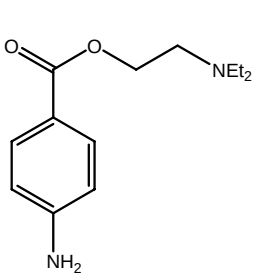
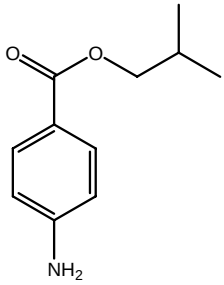
The Synthesis of Lidocaine

Introduction

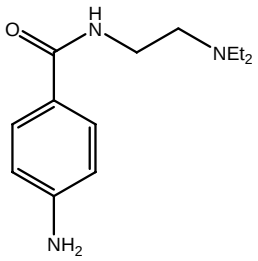
Lidocaine (trade names *Lidothesin, Xylocain, Anestacon*) is an important member of Class 1b drugs used as local anesthetics. Procaine, Isocaine, Procainamide, Tocainide, and Mexiletine are other members of this family of compounds. All of them have an amine functional group in common, which appears to be essential for enzyme binding. Most of these drugs are commercially available as the more stable hydrochloride salts, because many free amines are easily oxidized in air.



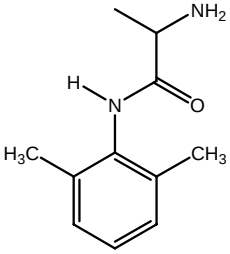
Procaine



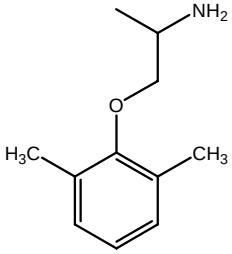
Isocaine



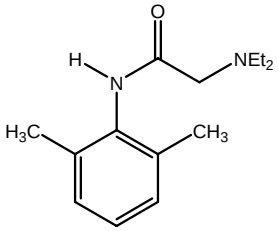
Procainamide



Tocainide



Mexiletine



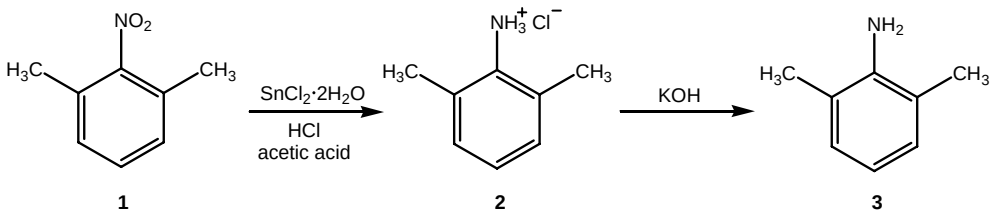
Lidocaine

Lidocaine was first synthesized and patented by a Swedish pharmaceutical company (Astra) in 1948. Lidocaine itself is a sodium channel blocker (class 1B antiarrhythmic) that causes a depression of rapidly depolarizing tissue. It can be used as a local anesthetic and as an antiarrhythmic after heart attacks. It has also found use in asthma therapy (dispensed in nebulizers). It is usually not habit forming and shows relatively mild side reactions, and therefore is suitable for long-term use. It can be found today in many over-the-counter topical pain relievers.

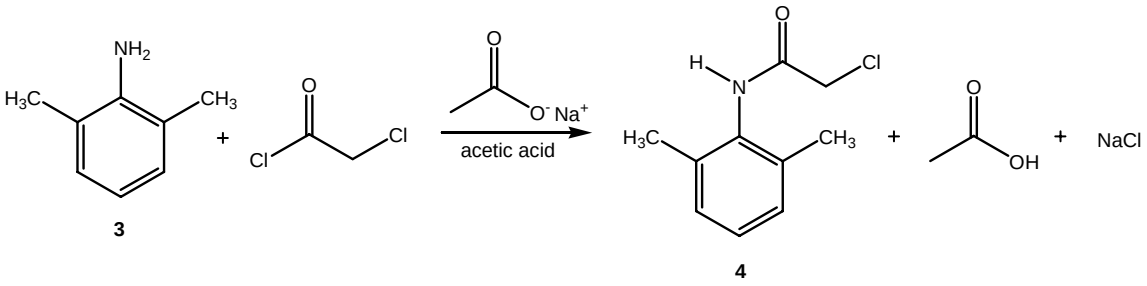
Synthetic Strategy

Lidocaine will be prepared via a three-step linear synthesis starting from 2,6-dimethylnitrobenzene.

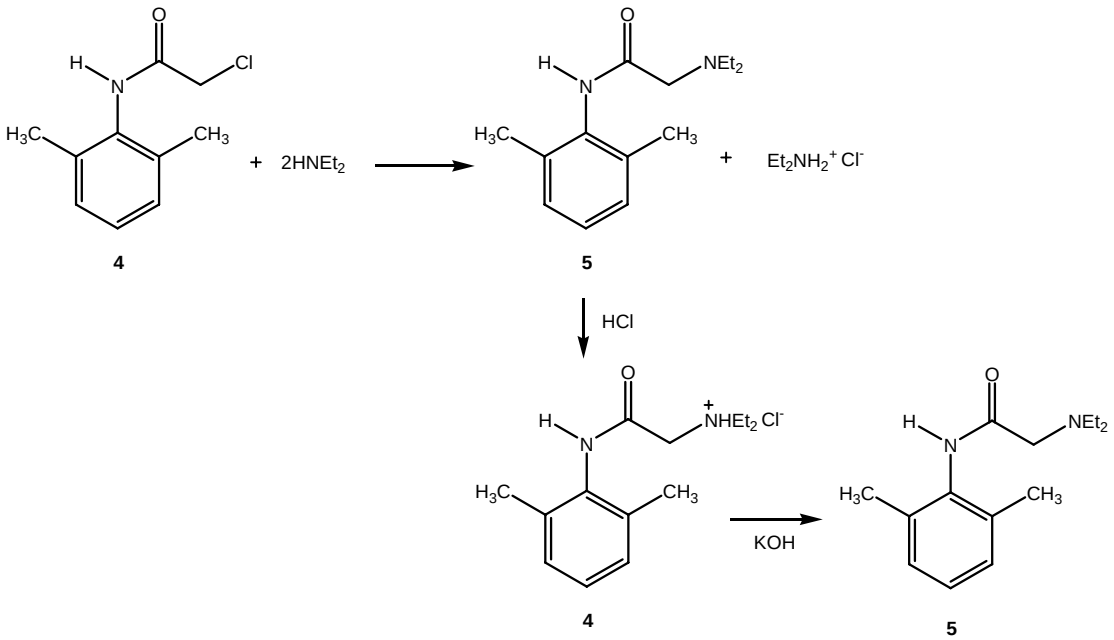
The reduction of 2,6-dimethylnitrobenzene **1** with three equivalents of stannous chloride ($SnCl_2$) yields the ammonium salt **2**. It is very important that the reaction mixture is strongly acidic during this reaction because the reduction of nitrobenzene using different reducing reagents and conditions can afford a variety of functional groups: nitroso, hydroxylamine (zinc dust, pH 4), azoxy (sodium arsenite), azo (zinc, weakly basic), or hydrazo (zinc, strongly basic). In industrial settings, often iron or tin with hydrochloric acid is used instead of stannous chloride because iron and tin are cheaper, but the reduction takes much longer. In the workup portion of the reaction, the ammonium salt **2** is reacted with an aqueous potassium hydroxide solution, liberating the free 2,6-dimethylaniline **3** in an acid-base reaction.



The reaction of **3** with the bifunctional α-chloroacetyl chloride leads to α-chloro-2,6-dimethylacetanilide **4**. A slight excess of the acid chloride is used to ensure the complete conversion of the amine to the amide. The formation of the amide is a result of the significantly higher reactivity (~10^6 times) of the acyl chloride over the alkyl chloride. The addition of sodium acetate solution avoids the formation of HCl which would protonate unreacted **3** causing it to co-precipitate with the desired product **4**.



In the last step, diethylamine performs a nucleophilic substitution (S_N2) on the remaining alkyl chloride. Diethylamine serves both as a nucleophile to form lidocaine **5**, and as acid scavenger, leading to formation of $NH_2Et_2^+$ Cl^- in this reaction. Since diethylamine is not a very strong nucleophile, it is used in excess here to improve the yield and speed up the reaction. The unreacted amine is later removed by extraction with water. The aqueous extraction of lidocaine with acid separates the unreacted chloroanilide **4** and the lidocaine. After addition of a strong base like aqueous potassium hydroxide, crude lidocaine is obtained.



Safety

Glacial acetic acid, concentrated hydrochloric acid and *8 M KOH* are very corrosive. *2,6-dimethylnitrobenzene* and *2,6-dimethylaniline* are highly toxic and suspected carcinogens. *Chloroacetyl chloride* is a lachrymator and should only be handled under the hood. It reacts violently with water. *Diethylamine* is a corrosive and flammable liquid. *Diethyl ether* is highly flammable and therefore has to be kept away from hot surfaces and open flames. Keep all bottles closed if not needed! Avoid any contact of any of these compounds with your skin and eyes and inhalation of the vapors. Flush affected areas with water and rinse it with dilute sodium bicarbonate solution. Wear gloves and work in the hood.

Procedure

***Synthesis of 2,6-dimethylaniline* (3)**

Dissolve 15 g of $SnCl_2 \cdot 2H_2O$ in 27 mL of concentrated hydrochloric acid. If necessary, heat the mixture gently. Add this solution in one portion to a solution of 3 mL of 2,6-dimethylnitrobenzene in 34 mL of glacial acetic acid. Swirl the resulting mixture and then allow it to stand for 15 minutes before placing the mixture in an ice bath. Collect the formed precipitate by vacuum filtration. Place the wet precipitate obtained above in a beaker and add 20 mL of water. Neutralize the acidic mixture by carefully adding an 8 M aqueous potassium hydroxide with continuous stirring until basic to litmus. Place the mixture in an ice bath. Upon cooling to room temperature, extract the mixture three times with diethyl ether. Combine the organic layers and wash them twice with water and once with brine. Dry the organic layer over anhydrous potassium carbonate. Decant away from the drying agent and evaporate the diethyl ether from a dry, pre-weighed flask using a rotary evaporator. The oily residue will be your crude product **3**. Obtain and record the following information:

1. crude product description (color, physical state, etc.)
2. crude weight/percent yield

***Synthesis of α-chloro-2,6-dimethylacetanilide* (4)**

Dissolve **3** in 17 mL of glacial acetic acid. Add 1.1 equivalents (based on the moles of **3**) of α-chloroacetyl chloride to this solution. Heat the solution to 40-50 ^{o}C for ten minutes to complete the reaction. Upon cooling, add a solution of ~3.3 g sodium acetate trihydrate in 67 mL water and then place the resulting mixture in an ice bath. Collect the precipitate by vacuum filtration. Rinse the filter cake with copious amounts of water in order to remove the acetic acid. It is important that the product be completely free of acetic acid after this step (why?). The pH of the individual water rinses can be checked with litmus paper to determine if the product is acid free. Allow for the product to air-dry on a watch glass until the next meeting.

There is a reasonable chance that you will not obtain a precipitate as described above. If this is the case, you can try "seeding" using a small sample of authentic product from a classmate. If this does not work, check the TLC to be sure that you have formed product and devise an extractive workup that will separate the unreacted aniline **3** from the desired product **4**. (Make sure you understand how to do this even if you obtain a precipitate in the first place). After the aqueous workup and following removal of solvent, you should obtain a solid. If not, check the TLC, using a sample of authentic product from a classmate as a standard. If the product appears relatively pure, you can continue even though the material is not a solid. Obtain and record the following information:

1. crude product description (color, physical state, etc.)
2. crude weight/percent yield
3. mp (if a solid)

4. TLC analysis
5. IR (check for presence of amide functional group)

***Synthesis of lidocaine; α-(N,N-diethylamino)-2,6-dimethylacetanilide* (5).**

In a round bottom flask, dissolve α-chloro-2,6-dimethylacetanilide **4** in 17 mL of toluene. Before continuing, spot several (4 to 5) TLC plates in advance with this solution of **4**. Provide three lanes and spot the **4** on the "SM" and "CO-SPOT" lanes. You will use these plates to monitor the progress of this reaction. Add three equivalents of diethylamine to the round bottom flask, and reflux the mixture vigorously until the reaction is complete. The amount of time required for complete reaction depends on many factors but it will likely take anywhere from more than a few minutes up to several hours. If the reaction is not complete when your lab period ends, you can stopper the reaction and reflux it for additional time at the next period. Usually a white precipitate forms during the reflux. Upon cooling, transfer the reaction mixture to a separatory funnel and extract the mixture three times with water. Next, extract the organic layer with two portions of 3 M hydrochloric acid. Cool the combined acidic aqueous extracts in an ice bath and then add 8 M aqueous potassium hydroxide slowly until the mixture is strongly basic again. The formation of a thin, dark yellow oily layer on top or a white solid is observed at this point. Place the mixture in an ice bath. Once the mixture is chilled, try to initiate the crystallization of the final product if no solid has formed at this point. Collect the obtained precipitate by filtration using a Büchner funnel. Wash it with twice with water and then press it as dry as possible. Obtain and record the following information:

1. crude product description (color, physical state, etc.)
2. crude weight/percent yield
3. TLC analysis

Recrystallize the crude product from hexanes. Regardless of the final physical state of your product (solid or oil), obtain and record the following:

1. pure product description (color, physical state, etc.)
2. pure product weight/percent yield
3. overall (three-step) percent yield (from starting material **1**)
4. TLC analysis
5. melting point (if a solid)
6. IR
7. ^{1}H and ^{13}C NMR spectra of lidocaine will be given to you.

Turn in a sample of your final product.