

Experiment 17: multi-step synthesis: Benzocaine

Objectives

The purpose of this experiment is to provide an example of how a multi-step synthesis can be used to prepare an organic compound, which is present in several consumer products.

Introduction

Benzocaine, ethyl 4-aminobenzoate, is found in medications used to ease the pain of wounds, burns and sunburn. It is also used in suppositories for hemorrhoid sufferers. A quick look around the shelves of any drug store would reveal the wide use of this compound in such products as Solarcaine[®], Lanacaine[®] and Anivy[®]. Benzocaine may be prepared from 4-nitrotoluene by the following five-step synthesis shown in Figure 17.1

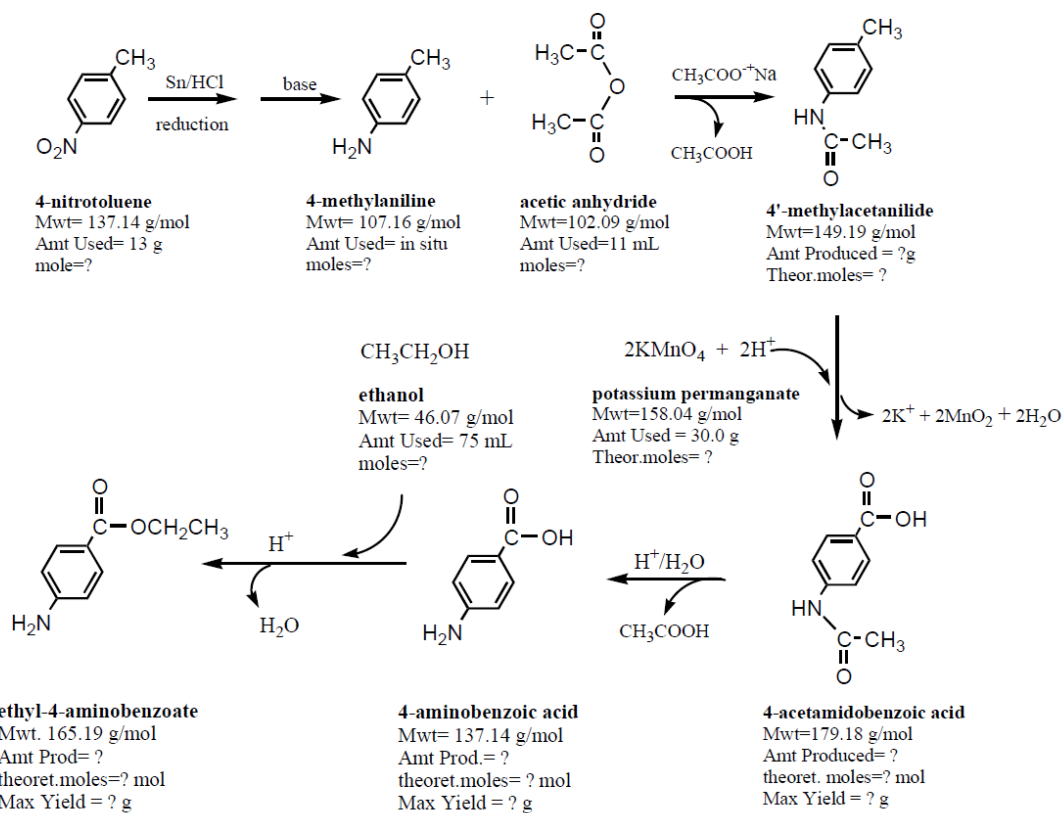


Figure 17.1 Overall reaction for the formation of benzocaine from *p*-nitrotoluene.

One problem with a synthesis of this type is that the overall yield of the final product is often quite low. For example, if a 50% yield is obtained in each of the five steps shown in the above reaction scheme, the overall yield will be $0.50 \times 0.50 \times 0.50 \times 0.50 = 0.03125$, or just over 3%. This should give you an indication of why synthetic organic chemists sometimes appear to be obsessed with obtaining the maximum percentage yield from a given reaction.

Let us now consider the overall strategy that we shall employ.

By comparing our starting material, 4-nitrotoluene, with our penultimate product, 4-aminobenzoic acid, we see that our goal will be to convert a methyl group into a carboxyl group and to reduce a nitro group to an amino group. The final step in the synthesis will then be a simple esterification. However, it is important that the first four steps are carried out in the correct order. For example, if the methyl group is oxidized to a carboxyl group in the first step, the subsequent reduction of the nitro group to an amine would result in the formation of a product containing both an acidic and basic group ($-\text{CO}_2\text{H}$ and $-\text{NH}_2$, respectively). Such a product would be soluble in the acidic reducing mixture (tin and hydrochloric acid) and would also be soluble in base. Thus, isolation of the product from the reaction mixture would be difficult to achieve. The problem cannot be solved by esterifying the carboxyl group before reducing the nitro group because the ester would simply hydrolyze back to a carboxylic acid under the conditions employed in the reduction.

The approach that you will use involves the reduction of the nitro group before the methyl group is oxidized. The reagent used to bring about the reduction is a mixture of tin and hydrochloric acid. After the reduction is complete, the reaction mixture is made basic and the product, 4-methylaniline, is extracted using a process called *steam distillation*. Because 4-methylaniline contains two activating groups, CH_3 and NH_2 , it is very susceptible to oxidation. To prevent oxidation from occurring, the amine is immediately converted to a salt by dissolving it in aqueous acid.

Once 4-nitrotoluene has been converted to 4-methylaniline (in fact 4-methylanilinium chloride), the next step is to oxidize the methyl group. This cannot be done directly, however, as the highly activated aromatic ring would be destroyed under the conditions employed. Instead, the highly activating amino group is acetylated to give an acetamido group, $\text{CH}_3-(\text{C}=\text{O})-\text{NH}-$, which is much less activating. The product of this reaction, 4'-methylacetanilide, is then

oxidized to 4-acetamidobenzoic acid under approximately neutral conditions. The acetamido group is then hydrolyzed back to an amino group and the resulting 4-aminobenzoic acid is esterified to give the desired product.

(i) The reduction of 4-nitrotoluene

The reduction of nitro compounds is the principal³ method of preparing primary aromatic amines. This reduction can be achieved through the use of hydrogen and a suitable catalyst, or by using a metal/acid combination such as tin and hydrochloric acid. A variety of nitrogen compounds is formed as the reduction proceeds, but under the conditions used in this experiment none of the intermediates can be isolated. The actual product of the reduction is the double salt, $(C_6H_5NH_3)_2SnCl_6$, and the free amine is liberated by treating this double salt with base. This treatment also has the added advantage that it renders any tin salts soluble through the formation of stannate ions (SnO_3^{2-}). The amine is extracted from the reaction mixture by steam distillation. (See "Steam Distillation" on pp. 117-119 of *The Organic Chem Lab Survival Manual* or pp.208-212 in 3rd ed.). You will employ a set-up similar to the one shown in Figure 57 (Fig.106 in 3rd ed.), except that, instead of a three-necked flask, you will use a single-necked flask and a Claisen adapter. As we have previously explained, 4-methylaniline is very susceptible to air-oxidation, thus it is immediately converted to a salt through the addition of hydrochloric acid.

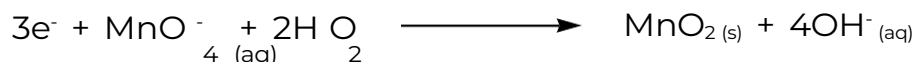
(ii) The acetylation of 4-methylaniline

This step is relatively straightforward and requires no detailed explanation.

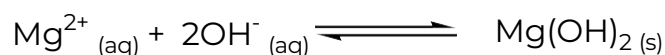
(iii) The oxidation of 4'-methylacetanilide

Although alkanes and aromatic hydrocarbons are generally very resistant to oxidation, the carbon attached to the aromatic ring of an alkylaromatic hydrocarbon is sufficiently activated to be quite easily oxidized. While it is occasionally possible to obtain other oxidation products, an alkyl group is normally cleaved between the α - and β -carbons to give the corresponding aromatic carboxylic acid. In the oxidation of a methyl group, the partially oxidized intermediates, the alcohol and the aldehyde, are more easily oxidized than the methyl group, so that only under rather special conditions is it possible to stop the oxidation and isolate these intermediates. Thus, benzoic acid or some other aromatic acid is the usual product.

The use of chromium (VI) as an agent for oxidizing the side chain of an aromatic hydrocarbon requires elevated temperatures and acidic conditions. However, the permanganate ion can bring about such oxidations at about 80-90° C in an almost neutral solution. The permanganate ion is reduced to manganese(IV) oxide and, as we see from the half-equation,



the reaction mixture becomes increasingly basic as the oxidation proceeds. In order to prevent the base-promoted hydrolysis of the acetamido group, magnesium sulfate is added to the reaction mixture so that the hydroxide ion is removed as the sparingly soluble magnesium hydroxide.



The oxidation is slow; in part because the starting material is not very soluble, when the reaction is complete, a large amount of solid manganese (IV) oxide and some unreacted permanganate ions are present. These substances may be reduced to water-soluble manganese (II) ions through the addition of an acidic solution of sodium hydrogen sulfite.

The acidification also serves to convert the product from the soluble potassium salt to the less soluble carboxylic acid and the latter then crystallizes out of solution.

(iv) The hydrolysis of 4-acetamidobenzoic acid

The hydrolysis of an amide group is generally performed under acidic conditions. At elevated temperatures it is possible that, with the presence of the electron-withdrawing carboxyl group in the para position, some nucleophilic displacement could occur. Once produced, the free amine could also undergo some air oxidation.

The product of this reaction is an amino acid. In basic solutions, the amino acid will be converted to the water-soluble carboxylate salt, while in acidic solutions it will be present as the water-soluble amine salt (see Figure 17.2). Thus, care must be taken in adjusting the pH of the final solution so that 4-aminobenzoic acid itself is precipitated.

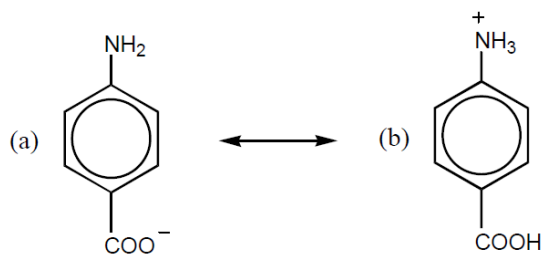
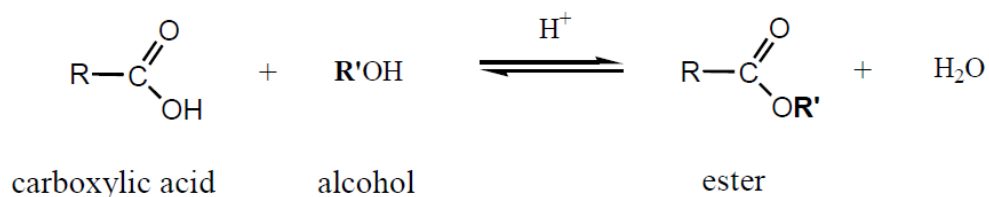


Figure 17.2 4-Aminobenzoic acid in its anionic form (a) and in its protonated form (b).

(v) The esterification of 4-aminobenzoic acid

The acid catalyzed esterification of a carboxylic acid is an equilibrium reaction that usually requires either a large excess of one of the reactants (usually the alcohol) or the removal of one of the products (usually water) for a good yield of ester to be obtained.



As the product of our reaction is quite soluble in ethanol, some of the latter must be removed from the reaction mixture before the product can be isolated.