



Synthesizing a Polysubstituted Benzene Derivative

Transcript

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Dr. Jessie Key: Hello again, Dr. Jessie Key here. In this video, you'll be exploring two examples where complex polysubstituted benzene derivatives are synthesized from benzene.

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Dr. Jessie Key: In our first example, we will plan a synthesis of 1-chloro-4-isopropyl-2-nitrobenzene from the starting material benzene. There are many ways you could approach this problem, including strategies that could be classified as either 'forward' or 'retro' synthesis. Forward synthesis places emphasis on going forward from the starting material one step at a time until you reach the final desired product.

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Dr. Jessie Key: Retrosynthesis is the opposite where you focus on the final product and work backwards one step at a time until you reach the starting material. I find that both strategies have merit and some people prefer one over another. But usually the way my mind works, I often end up using some combination of the two.

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Dr. Jessie Key: Let me walk you through how I would approach this. First, I look at the functional groups present in the final product and classify them according to both their directing effects and their activation/deactivation effects. At carbon 1, there's a chloro group, which is weakly deactivating and ortho/para directing – it could be added by chlorination.

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Dr. Jessie Key: At carbon 2, there's a nitro group, which is strongly deactivating and meta directing - it could be added by nitration. Finally, at carbon 4, there's an isopropyl group, which is weakly activating and ortho/para directing – it could be added by Friedel-Crafts alkylation. Next, I would look for the relative position of each group.

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Dr. Jessie Key: The chloro group is ortho to the nitro and para to the isopropyl. The nitro group is ortho to the chloro group and meta to the isopropyl. The isopropyl group is para to the chloro group and meta to the nitro group.

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Dr. Jessie Key: Now with this information in hand, I can plan my synthetic route: Knowing that Friedel-Crafts alkylations do not work with strongly deactivating groups present, this suggests that nitration should be a later step or the last step in the synthesis. So I'll focus on first placing the isopropyl or chloro groups onto the ring. The best order for doing this would probably be to first put the ortho/para directing isopropyl group on the ring because its steric bulk would give a higher yield of the para chlorination product in the subsequent step.

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Dr. Jessie Key: With the chloro group in place, it can direct the nitro group to the correct position ortho to the chloro group. So my synthesis would start with benzene undergoing a Friedel-Crafts alkylation reaction with 2-chloropropane in the presence of aluminum trichloride. This gives isopropylbenzene as an intermediate.

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Dr. Jessie Key: Next chlorination occurs with chlorine, Cl₂ and aluminum trichloride, which gives 1-chloro-4-isopropylbenzene as an intermediate. The final step is nitration, using nitric acid and sulfuric acid to give the desired 1-chloro-4-isopropyl-2-nitrobenzene. In our second example, let's see how we can synthesize 1-bromo-3-ethylbenzene from benzene.

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Dr. Jessie Key: Feel free to pause and give this a try on your own, and when you are comfortable, we can go through it together. Welcome back! Again, let's analyze the substituents present in the desired final product and classify based on the activating, deactivating and directing effects.

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Dr. Jessie Key: The ethyl group is a weak activator and ortho/para-directing, and could be added to the ring by Friedel-Crafts alkylation, while the bromo group is a weak deactivator, that is also ortho/para-directing, and could be added by bromination. Given this information, it does not immediately make sense how the two substituents can be positioned relatively meta to each other. We will need to look at this from a broader retrosynthetic viewpoint - how else can we get to the final product?

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Dr. Jessie Key: The ethyl group could be obtained by Clemmensen reduction of acetophenone! The ketone of acetophenone would be a moderate deactivator and meta-directing. With this knowledge, it now becomes clear that we can obtain the meta arrangement of the two substituents by first performing a Friedel-Crafts Acylation with ethanoyl chloride and aluminum trichloride to generate acetophenone.

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Dr. Jessie Key: Bromination can then be performed with bromine and iron tribromide to give meta substitution of the bromine with 3-bromoacetophenone. Finally, Clemmensen reduction can be performed with zinc-mercury amalgam, hydrochloric acid, and heat to get the desired product: 1-bromo-3-ethylbenzene.