

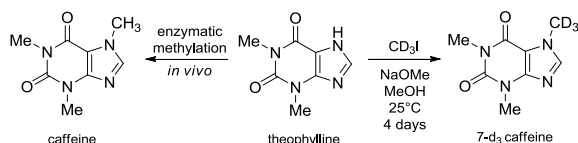


Coffee, Tea, or Chemistry?

Specific practical goals:

- to conduct a nucleophilic substitution reaction
- to adapt experimental conditions from the literature
- to optimize yield based on conditions
- to employ microwave synthesis reactors

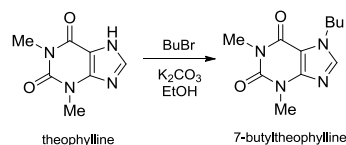
Theophylline (Scheme 1) is a naturally occurring compound found in small amounts in tea leaves. Synthetic theophylline is used medicinally to treat various respiratory conditions (e.g., asthma). In plants and animals, theophylline is converted to caffeine by an enzymatically controlled methylation reaction. Caffeine and theophylline are two of the three most frequently encountered members of the class known as methylxanthine alkaloids (the third being theobromine, found in chocolate).



Scheme 1. Biological and synthetic methylation of theophylline.

Methylxanthine alkaloids are tightly regulated by international sports and racing rules; thus, analytical methods are needed to monitor levels of these substances in race animals and professional athletes. Balssa and Bonnaire (*J Label Compd Radiopharm* **2007**, *50*, 33) have synthesized an ingestible 7-deuteriocaffeine analog (Scheme 1) which can be used as an internal analytical standard for this purpose. In this procedure, a proton on theophylline is removed by base and the resultant anion reacts with deuteriomethyl iodide. The reaction requires four days at room temperature.

The physiological effects of caffeine and theophylline spring from their interaction with various adenosine receptors, and medicinal chemists have explored the activity of non-natural theophylline derivatives that have N-7 substituents other than methyl (Daly et al., *J Med Chem* **1986**, *29*, 1305). Your group's activity is devoted to making the 7-butyl caffeine analog (Scheme 2) using theophylline, 1-bromo-butane (BuBr) as an alkylating agent, potassium carbonate (K_2CO_3) as a base, and ethanol (EtOH) as a solvent.



Scheme 2. Synthetic route to 7-butyltheophylline.

Fortunately, you have available to you state-of-the-art microwave reactors to accelerate the reaction. Your group should propose a set (or more than one set) of experimental conditions to carry out this reaction. As you do, please keep in mind the considerations found in the "Scaling Reactions" and "Microwave-assisted Synthesis" primers. As you consider time and temperature, the results from Balssa and Bonnaire may be a useful starting point.

The HPLCs will be set up to identify theophylline and 7-butyltheophylline, so you can use them as a quick way to estimate the progress of the reaction, and a dedicated set of reagents will be available to your group. Each person should run at least one reaction. Aside from that stipulation, you may run as many or as few as you care to in the lab period.

Safety Information

Theophylline. Toxic if swallowed. Harmful to aquatic life. May be harmful if inhaled. May cause respiratory tract irritation. May be harmful if absorbed through skin. May cause skin irritation. May cause eye irritation.

Sodium carbonate. May be harmful if swallowed. Causes mild skin irritation. Causes serious eye irritation. May be harmful if inhaled. Causes respiratory tract irritation. May be harmful if absorbed through skin.

Bromobutane. Highly flammable liquid and vapor. May be harmful if swallowed. Causes skin irritation. Causes serious eye irritation. May cause respiratory irritation. Toxic to aquatic life with long lasting effects. May be harmful if inhaled. Causes respiratory tract irritation. May be harmful if absorbed through skin.

Ethanol. Highly flammable liquid and vapor. Causes skin and eye irritation. May be harmful if inhaled. Causes respiratory tract irritation. May be harmful if absorbed through skin. Causes skin irritation. Causes eye irritation. May be harmful if swallowed.