

# Synthesis of caffeine from theobromine: Bringing back an old experiment in a new setting

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## ABSTRACT

Caffeine is one of the most widely consumed, naturally occurring, mild, and central nervous system stimulants. Its synthesis, by the *N*-methylation ( $S_N2$  substitution) of theobromine is described as an experiment for the undergraduate organic chemistry laboratory. The *N*-methylation of theobromine is rapid and efficient and its progress is monitored by TLC using authentic standards. The undergraduate student also is able to observe the effect of temperature on the rate of the *N*-methylation reaction.

**KEYWORDS:** caffeine, theobromine, undergraduate organic chemistry laboratory, thin layer chromatography, microscale organic reaction

## Resumen (Síntesis de la cafeína a partir de la teobromina: retomando un experimento remoto bajo una nueva perspectiva)

La cafeína es uno de los productos más consumido, concurrente en la naturaleza, afeble y estimulante del sistema nervioso central. Su síntesis, mediante la *N*-metilación (sustitución  $S_N2$ ) de la teobromina se describe como un experimento de laboratorio de química orgánica para nivel licenciatura. La *N*-metilación de la teobromina es rápida y eficiente, y su progreso es monitoreado por Cromatografía en Capa Fina (TLC, por sus siglas en inglés) comparándose con estándares comerciales. El estudiante de licenciatura también será capaz de observar el efecto de la temperatura sobre la velocidad de la reacción de la *N*-metilación.

**Palabras clave:** cafeína, teobromina, laboratorio de química orgánica de licenciatura, cromatografía de capa fina, reacción orgánica en microescala

## Introduction

Caffeine (a methylxanthine) is a well-known compound that occurs in coffee, tea, kola nuts, mate leaves, guarana paste, cocoa beans, and other related natural products. Caffeine and theobromine (from *Theobroma cacao*; *theo* = god, and *broma* = food; thus, *food of the gods*) are the two most abundant methylxanthines in chocolate, both of which have received considerable attention in the food and nutrition fields, in part because of the physiological effects which they elicit (Brown, 2004). Surprisingly, given the widespread use and occurrence of caffeine, there are relatively few reported syntheses thereof described in the literature, and a significant number of these methods date back to the late 19<sup>th</sup> and the beginning of the 20<sup>th</sup> century. In 1895 Emil Fisher (Nobel Prize in Chemistry, 1902) described the first synthesis of caffeine from uric acid (Kunz, 2002, and citations therein).

Subsequently, Fisher reported the synthesis of caffeine by *N*-methylation of theobromine with  $\text{CH}_3\text{I}$  in the presence of NaOH as the base (Fischer, 1898). Later, Biltz and Damm described the *N*-methylation of theobromine using dimethyl sulphate (Blitz, 1917). More recent syntheses of caffeine from theobromine describe the use of dimethyl sulfate in the presence of alumina impregnated with KF in acetonitrile (Yamawaki, 1981).

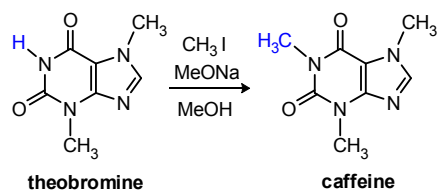
Caffeine has been an important focus in many undergraduate experimental laboratory protocols, *e.g.*, in analytical chemistry experiments (Singh, 1998; Pawliszyn, 1997; Hill, 1988; Van Atta, 1979; Ferguson, 1998; DiNunzio, 1985; Delaney, 1985; Beckers, 2004; Leacock, 2011; Bergen, 2000; Fenk, 2010; Menguy, 2009; Harmon, 2012; Pavlik, 1973) and isolation from natural (Onami, 1996; Murray, 1995; Hampp, 1996; Mitchell, 1974; Schaber, 2012; Adam, 1996) or commercial products (Neuzil, 1990; Moye, 1972; Hall-Laswick, 1972; Williams, 1992). Surprisingly, however, laboratory experimental procedures for the synthesis of caffeine are quite limited. In 1973, Pavia reported the synthesis of caffeine by methylation of theobromine with dimethyl sulphate (Pavia, 1973), a procedure not suitable for the undergraduate laboratory given the toxicity (carcinogenicity and mutagenicity), volatility (inhalation hazard), and

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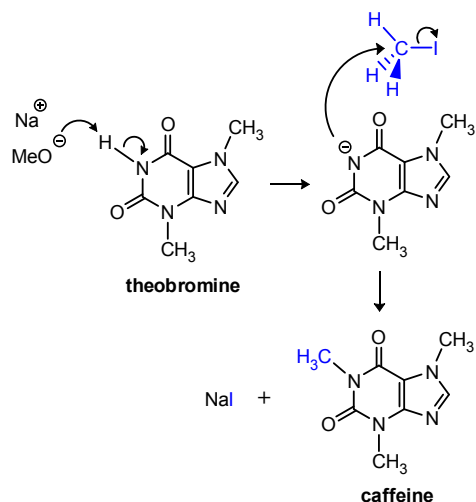
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**Scheme 1.** Caffeine synthesis from theobromine.



**Scheme 2.** Reaction mechanism: *N*-Methylation of theobromine occurs via  $S_N2$ .

environmentally hazardous nature [It has even been considered as a potential chemical weapon of war! (Rippey, 2005)] of this substance. Since then, no other undergraduate laboratory experiment about synthesis of caffeine has been reported.

Herein we report a modification of the Pavia's synthesis procedure. The *N*-alkylation of theobromine using methyl iodide in methanolic sodium methoxide solution allows an efficient and rapid synthesis of caffeine (Scheme 1 and Scheme 2). The reaction goes to completion at room temperature in 90 min, or in 40 min at 60 °C, and the product is free of contaminants giving 90% of yield (similar to the Fischer's procedure). This experiment is multifaceted and can be used to instruct the students in the bimolecular nucleophilic substitution reactions (microscale organic techniques), the effect of temperature on reaction rates, evaluation of the progress of a reaction by thin layer chromatography, and compound identification by melting points and mixed melting points with authentic materials.

### Instructor's preparation guide

The main focus of this paper is the synthesis of caffeine from theobromine, but this may be complemented by extraction of the required theobromine from cocoa powder using previously published procedures (Pavia, 1973). TLC plates with a fluorescent indicator are necessary. Dichloromethane was used as the preferred solvent (chloroform gave the same result, but is less desirable because of its greater toxicity). It is

recommended that the teacher handles methyl iodide, this step has to be done under the fume hood. Gloves, goggles and a face mask are mandatory. The standard solutions of theobromine and caffeine will be prepared by the teacher. Since each group will use a very small amount of each of these solutions, a few millilitres can accommodate many students. To prepare stock solutions of theobromine and caffeine theobromine (Sigma-Aldrich), add 0.2 g of the standard to approximately 50 mL of methylene chloride.

### Objectives

- To synthesize caffeine from the theobromine by  $S_N2$  (microscale technique).
- To monitor a chemical reaction by TLC.
- To identify the effect of temperature on the reaction rate.
- To identify the product by determining the melting point and comparing this value with the authentic standard.

### Reagents and equipment

#### Reagents

Theobromine (Sigma-Aldrich), caffeine (Sigma-Aldrich), methanol, sodium methoxide, dichloromethane, anhydrous sodium sulphate, and methyl iodide.

#### Equipment

Rotavapor, short wave (254 nm) UV lamp, microscale equipment, lab coat, latex gloves, goggles, hot plate-magnetic stirrer, bucket with reflux pumps, small magnetic bar, tweezers or forceps, capillary tubes, TLC plates, TLC developing chamber, 50 mL beaker, büchner funnel and büchner flask, test tube, glass rod, 1 mL pipette, rubber pipette filler, pasteur pipette and bulb, glass funnel, cotton, filter paper, scissors, spatula, scoopula, rubber tubing (~80 cm long), ring stand, thermometer, sand container (metal or glass), clamp, and a pencil.

### Student experimental protocol

Synthesis of caffeine was carried out in a microscale apparatus. Students were divided into two groups. Group 1 performed the synthesis at room temperature (Method 1) while group 2 effected the reaction at 50-60°C (Method 2). Reaction was followed by TLC and compared with standards of caffeine and theobromine. Group 1 followed the course of the reaction every 30 minutes while group 2 monitored the progress of the reaction at 40 min (total heating time).

#### a) Method 1. Reaction at room temperature

In a 5 mL round-bottom flask (equipped with a magnetic bar), suspend 0.05 g of theobromine in 1.5 mL of MeOH. Note that theobromine is not dissolved in methanol. Add 0.03 g of NaOMe and shake gently for one minute by using a plate magnetic stirrer. Assure that theobromine has dissolved completely. Note that the solution turns yellow. Add

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