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A Novel Method of Caffeine Synthesis from Uracil

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ABSTRACT

An inexpensive and novel method of caffeine synthesis starting from uracil in six simple steps is described. Uracil **1** is first converted to I, 3-dimethyluracil **2**, followed by nitration, reduction, and cyclization to theophylline and finally methylation of theophylline forms caffeine.

Key Word: Caffeine synthesis.

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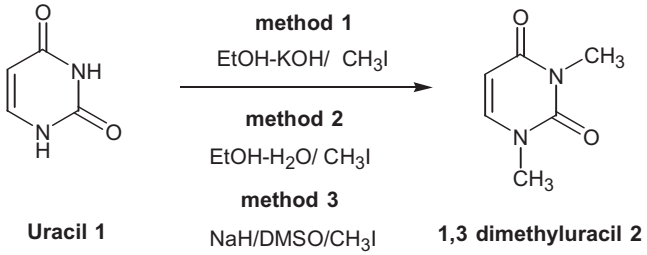
Caffeine **7** (3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione or 1,3,7-trimethylxanthine) is a well-known compound that occurs in nature in coffee, tea, cola nuts, mate' leaves, guarana paste, and other related natural products. It is also obtained as a byproduct in the manufacture of caffeine-free caffeine.[1] This is perhaps one of the reasons that there are only few methods of synthesis described in the literature.[2–7] These methods date back to either late 19th or the beginning to mid-20th century. Some of the early methods (Fischer and Traube's)[2,3] were not aimed directly at the synthesis of caffeine, rather they were based on purine and related derivatives starting from urea or uric acid in several steps. In addition, Fischer's method was used to prove the structure of caffeine and other xanthine derivatives. The other references are some patents in the 50's and 60's.[1] Other than these there are no recent reports in the literature on the direct synthesis of caffeine. In this report, we wish to describe a simple synthesis of caffeine **7** from uracil **1** by *N*-methylation, nitration, reduction, and cyclization reactions (Schs. 1 and 2). Alternative methods for some of the intermediates have also been described. Yields are good to excellent (Table 1) throughout all the steps. The purity of the samples was checked by mixed melting point methods. Wherever possible the IR and NMR were used to prove the structures of the intermediates and caffeine.

The reaction of uracil with excess of methyl iodide with potassium hydroxide and ethanol (Method 1) or in an aqueous ethanol medium (Method 2) resulted in a very poor yield of 1,3-dimethyluracil **2** (Sch. 1 and Table 1)

On the other hand, the presence of a strong base such as sodium hydride in dimethylsulfoxide (DMSO), a nonaqueous solvent facilitates the methylation tremendously (Method 3, Sch. 1). This results in an increased yield of 60% of 1,3-dimethyluracil **2**, compared to Method 1 (10%) or Method 2 (20%).



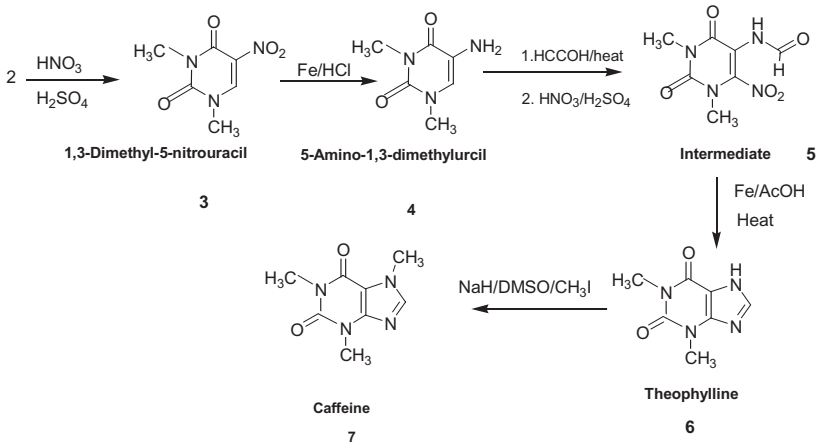
Scheme 1.

Table 1. Synthesis of compounds **1–7**.

Compound	Method	M.p. (°C)[a]	Yield (%)
2	1	119.0–121.5	10
2	2		20
2	3		60
3	Nitration with HNO_3/H_2SO_4	121.0–122.0	64
4		294.0–295.5	70
5			In situ
6		273.0–274.5	75
7	3	234.0–236.5	95

[a]Purity of the samples was checked by mixed melting point methods.

Nitration of 1,3-dimethyluracil **2**, using dinitrogen tetroxide similar to the method reported for cyclooctene[8] was very time consuming, and resulted in extremely poor yield for compound **3** (<10%, the method is not described). Conventional nitration using a nitrating mixture of fuming nitric acid and sulfuric acid produces 64% yield of **3**. The reaction was rapid and isolation of the compound was very easy. The nitro group in compound **3** was reduced using iron and hydrochloric acid in tetrahydrofuran (THF) to produce 5-amino-1,3-dimethyluracil **4**.



Scheme 2.

Heating compound **4** with formic acid generated in situ, the formamide derivative of compound **4** (not shown). Nitration of the formamide derivative introduces a nitro group in position 6 of uracil to produce compound **5** as a light yellow colored solid **(**see Sch. 2).

Reduction and intramolecular heterocyclization of compound **5** was simultaneously carried out with iron and acetic acid to produce theophylline (75%) **6**. Theophylline was purified by flash chromatography on silicagel using ethyl acetate as the solvent. The final step of the synthesis involves *N*-methylation at position 7 of theophylline using method **3** to produce caffeine **7**. Mixed melting point, IR, and NMR confirmed the identities of the compounds **2–6**, and caffeine **7**.

In conclusion, caffeine **7** can be synthesized by a fast efficient, simple, and novel method starting from the inexpensive uracil **1**. Most of the intermediates as well as caffeine were produced in good to high yields under mild conditions. The IR and NMR of the intermediates and the final product matched with the literature spectra.[9,10]

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian 200 MHz FT-NMR spectrometer. Tetramethylsilane (TMS) was used an internal standard. $CDCl_3$ and deuterated acetone were used as solvents for NMR. IR spectra were recorded on Perkin–Elmer Paragon 500 FT-IR spectrometer using nujol mull. Fisher–John melting point apparatus was used to determine the melting points. Flash chromatography was performed on silica gel column using ethyl acetate as the solvent. Thin layer chromatography (TLC) was performed on silica gel plate using ethyl acetate as the solvent. Completeness of all the reactions was determined by following the reaction on TLC plate using ethyl acetate as the solvent. All reagents and solvents were of high purity grade purchased from Aldrich Chemical Company.

1,3-Dimethyluracil: 2

Method 1. Uracil[2,4-(1H,3H)-pyrimidinedione] (6.4 g, 0.057 mol) was dissolved in an aqueous solution of potassium hydroxide (80 mL, 1.5 M). A solution of methyl iodide (CH_3I) (16.4 g, 0.146 mol) in ethanol (80 mL) was added slowly. The solution was refluxed for 4 h. The product was extracted with toluene (100 mL). Zero point eight one gram

(0.0051 mol) (10% yield) was recovered. The compound was purified by sublimation. M.p.: 119.5–121.5°C (Lit.[1] 119–122°C).

Method 2. Similar to Method 1, however, in place of aqueous potassium hydroxide, ethanolic potassium hydroxide was used. This method yielded 20% (1.62 g, 0.0102 mol) of the product **2**.

Method 3. A solution of uracil **1** (6.0 g, 0.053 mol) in DMSO (300 mL) was stirred overnight at room temperature. Four equivalents of sodium hydride (5.1 g, 0.21 mol) were added carefully to the solution of uracil. Five equivalents (37.6 g, 0.265 mol) methyl iodide was added slowly over a period of 10 min. The mixture was stirred for another 40 min and diluted with 100 mL of water to remove excess of hydride. The solution was then acidified with conc. HCl to pH 1–2. The product was then extracted with methylene chloride and washed with saturated bicarbonate solution until neutral. Eight point six grams of 1,3-dimethyl-uracil **3** (61%) was isolated after removing the dichloromethane. ^{1}H NMR of the compound shows the following peaks. δ ($CDCl_3$): 3.29 (s, 3H), 3.37 (s, 3H), 5.65 (d, $J = 15$ Hz, 1H, HC=), 7.1 (d, $J = 15$ Hz, 1H, HC=).

1,3-Dimethyl-5-nitrouracil: 3

Compound **2** (0.80 g, 0.0057 mol) was added carefully to an equal volume of a mixture of fuming nitric and conc. sulfuric acid (1.2 mL) and stirred for 30 min at room temperature. The solution was then refluxed for an hour and added carefully to ice cold water (ca. 3 mL). The light yellow colored crystals of compound **3** were filtered, washed with ice cold water. The percent of the product was 64 (0.68 g, 0.00356 mol). M.p.: 121–122°C. (Lit.[9] 121–122°C). IR (mull): ν/cm^{-1} 1720, 1675.

5-Amino-1,3-dimethyluracil: 4

Zero point five gram (0.0027 mol) of **3** was dissolved in enough THF to form a 2 M solution. Equal volume 1 M HCl was added followed by 10 equiv. of (1.52 g) of active iron powder. The solution was refluxed for 30 min. The reduced product was extracted into methylene chloride after neutralizing with saturated bicarbonate solution. A 70% yield (0.30 g) of the reduced product **4** was formed. After purification of the product by

flash chromatography on silica gel using ethyl acetate, the product was identified by IR and NMR. IR (mull): ν/cm^{-1} split peak at 3300 from NH_2 stretch, 1600 overlapped C=O. NMR: δ $CDCl_3$ 1.61 (s, 2H), 3.4 (s, 3H), 3.6 (s, 3H), 5.32 (s, 1H). M.p.: 294.0–295.5°C. (Lit.[9] 295°C).

Formylation and Nitration of Compound 4

One hundred milligrams (0.00065 mol) of compound **4** was dissolved in excess of formic acid and refluxed overnight to formylate the amino group. After bicarbonate workup with saturated $NaHCO_3$ solution 100 mg of the product was formed (not shown in the scheme). The 100 mg of the crude product was nitrated with (1.2 mL) an equal volume of a mixture of fuming nitric and conc. sulfuric acid (1.2 mL). The mixture was heated under reflux for an hour. It was added to ice cold water (5 mL). A 100-mg of a light yellow-colored compound **5** was formed in 54% yield.

Theophylline 6 (3,7-Dihydro-1,3-dimethyl-1H-purine-2,6-dione)

The intramolecular cyclization of compound **5** was carried out by using iron and acetic acid. Two milliliters of glacial acetic acid and 10 equiv. of iron powder (0.30 g) were mixed with 100 mg of compound **5**. The mixture was refluxed for 30 min. The mixture was washed with water and neutralized with saturated bicarbonate solution. The product was extracted with a 1:1 mixture of ethyl acetate and dichloromethane. After evaporating the solvent the crude product was purified using flash chromatography on silica gel with ethyl acetate. Seventy-five percent yield (69 mg) of theophylline **6** was recovered. M.p.: 273.0–274.5°C. The purity was further confirmed by mixed melting point using standard theophylline (Lit.[1] 270–274°C). IR and NMR confirmed the identity of the product. IR (mull): ν/cm^{-1} 3400 (W), 1725, 1665. NMR δ $CDCl_3$: 3.45 (s, 3H), 3.75 (s, 3H), 5.6 (s, 1H), 9 (s, 1H).

Caffeine 7 (3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione)

The *N*-methylation of theophylline was carried out in a similar manner to *N*-methylation of uracil method **3**, described above for compound **2**. Five grams (0.029 mol) of theophylline **6** and (20.6 g, 0.145 mol)

methyl iodide was dissolved in 300 mL DMSO. The solution was stirred at room temperature for 24 h. Four equivalents of NaH (2.7 g, 0.116 mol) were added carefully to the DMSO solution. After the addition of NaH the color of the solution turns from yellow to turbid white. Approximately after 45 min the solution turns yellow again. The mixture was diluted with equal volumes of water, and neutralized with dilute HCl. The product was extracted into methylene chloride. Caffeine was further purified by flash chromatography on silica gel using ethyl acetate. A (5.4 g) 95% of the product was recovered. M.p.: 234.0–236.5°C sublimes (Lit.[1] 238°C). The IR and NMR peaks match well with the literature values.[9,10] IR (mull): ν/cm^{-1} 1710 and 1660. NMR δ (CD_3COCD_3): 3.56 (s, 3H), 3.78 (s, 3H), 4.28 (s, 3H), 8.10 (s, 1H).

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REFERENCES

1. *The Merck Index*, 12th Ed.; Merck & Co., Inc.: Whitehouse Station, NJ, 1996; 268 pp.
2. Fischer, A. Ber. **1895**, *28*, 2473, 3135.
3. Traube, S. Ber. **1900**, *33*, 3035.
4. Gepner, B.; Kreps, L. J. Gen. Chem. USSR **1946**, *16*, 179.
5. Finar, I.L. *Organic Chemistry*, 2nd Ed.; John Wiley & Sons Inc.: New York, 1959; 700–704.
6. Brederick, H.; Schuh, Hv.; Martini, A.S. Chem. Ber. **1950**, *83*, 201–211.
7. Brederick, H.; Gotsmann, U. Ber. **1962**, *95*, 1902–1909.
8. Seifert, W.K. Organic Synthesis **1988**, *6*, 837.
9. *The Aldrich Library of FT-IR Spectra*, 1st Ed.; Charles J. Pouchert, Ed.; Aldrich Chemical Co.: Milwaukee, 1985.
10. *The Aldrich Library of FT-NMR Spectra*, 1st Ed.; Charles J. Pouchert, Jacquelyn, Behnke, Eds.; Aldrich Chemical Co.: Milwaukee, 1993.

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