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AN INEXPENSIVE, EFFICIENT SYNTHESIS OF 1-METHYLXANTHINE

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Abstract: 1-Methylxanthine has been prepared in 20% overall yield via a reproducible six-step sequence.

Methylxanthines comprise an important class of pharmacologically active compounds,1 of which caffeine (1), theophylline (2), and theobromine (3) are the most widely employed as therapeutic agents.

As part of a program aimed at the development of novel pulmonary stimulant agents, we required a substantial quantity of 1-methylxanthine (10), a primary urinary metabolite2 and analytical standard.3 Although it is commercially available,4 its very high cost (over $200/gram) prompted us to investigate an efficient synthesis. After a significant and lengthy development effort, we have succeeded in refining, and in some instances significantly
modifying, a sparsely-detailed, 80-year-old German synthesis\textsuperscript{5} to a
degree wherein reproducible and quite acceptable yields of 1-
methylxanthine are obtained. The sequence is depicted in the
Scheme.

Direct $N_1$-methylation of xanthine is impossible due to compe-
tition from the other two nitrogen atoms,\textsuperscript{6} thus, construction of
the xanthine ring system subsequent to methylation is necessary.
The synthesis of pyrimidine rings via condensation of the appro-
priate urea derivative with ethyl cyanoacetate or diethyl malonate
is the classic approach.\textsuperscript{7} Methylisourea hydrochloride (5) was
obtained in high yield via treatment of anhydrous cyanamide (4)\textsuperscript{8}
with methanolic hydrogen chloride gas.\textsuperscript{9} Condensation of 5 with
ethyl cyanoacetate in refluxing sodium methoxide/methanol for 20
hours afforded pyrimidine 6. Contrary to the original report, this
extended reaction time was necessary to achieve acceptable yields.

The key methylation step, when carried out with dimethyl sulfate
in aqueous base as reported, occurred in a disappointing 11\% yield.
Although this reagent is widely employed for alkylation of both
purine and pyrimidine bases, reported yields are often quite low,\textsuperscript{10}
and although the starting material could be recycled, we sought a
more efficient procedure for this transformation. After dozens of
experiments, it was determined that trimethyl phosphate\textsuperscript{11} afforded
the highest and most reproducible yields. Specifically, a slurry
of pyrimidine 6 in dimethylformamide was deprotonated with sodium
hydride and the anion solution treated with three equivalents of
trimethyl phosphate. Simple filtration provided the 1-methyl
pyrimidine 7 in 76\% yield and in a high state of purity.
SYNTHESIS OF 1-METHYLXANTHINE

SCHEME

a: MeOH, HCl; b: NaOMe, EtO₂CCH₂CN; c: NaH, (MeO)₃PO;
d: NaNO₂, HOAc; e: (NH₄)₂S; f: HCONH₂, HCl
Nitrosation of 7 in acetic acid afforded the deep blue nitroso derivative 8 which, being unstable, was immediately reduced with a minimal amount of 37% ammonium sulfide\textsuperscript{12} to give the penultimate, fluffy-white 4,5-diamino pyrimidine derivative 9 in 60% yield after recrystallization.

Engelmann completed the synthesis by reaction of 9 with formamide followed by heating the resulting solid amide with a flame; however, we found that closure of the imidazole ring could be accomplished via refluxing 6 in acidic formamide for 12 hours.\textsuperscript{13} Furthermore, if concentrated hydrochloric acid was employed as the proton source, the quantity of water introduced proved sufficient to simultaneously hydrolyze the enol ether functionality (the original report executed this transformation as an additional, separate step).

Conclusion

In summary, we have outlined a reproducible, efficient synthesis of 1-methylxanthine. The overall yield of 20% cannot be compared to the original report, which contained no such data. However, our sequence is two steps shorter and effects the critical methylation step in seven times the yield of the reported method. We are currently attempting to adapt this procedure to a variety of 1-alkyl xanthine analogs.

Experimental Section

Methylisourea Hydrochloride (5) was prepared in 82% yield from anhydrous cyanamide\textsuperscript{7} via a published procedure.\textsuperscript{8}
4-Imino-2-methoxy-6-oxodihydropyrimidine (6). To a 5 L, single-necked flask, fitted with a magnetic stirring bar, was added methanol (2 L), followed by sodium (120 g, 5.0 mol) in small pieces with good cooling. To the clear solution was added methylisourea HCl (5, 250 g, 2.26 mol) in methanol (1.5 L), causing NaCl to precipitate. Ethyl cyanoacetate (272 g, 2.41 mol) was then introduced, and the yellow mixture was refluxed under nitrogen for 20 hr, becoming deep red. The mixture was cooled, filtered, evaporated, and the residue dissolved in hot water (1 L). This solution was treated with decolorizing carbon, filtered, and glacial acetic acid was added slowly until the solution became acidic (ca. 25%), causing the crude product to precipitate. Filtration and recrystallization from water (600 mL) afforded pure product (226 g, 71%) as light brown needles: mp 226-8°C (lit.8 214-6°C); NMR (DMSO-d$_6$) δ 6.35 (s, 1H, NH), 4.75 (s, 2H, CH$_2$), 3.80 (s, 3H, OCH$_3$), 2.50 (s, 1H, =NH); TLC (silica gel; 25% MeOH/75% EtOAc) $R_f$ 0.49.

4-Imino-2-methoxy-1-methyl-6-oxodihydropyrimidine (7). To a 50-mL, three-necked flask, fitted with a magnetic stirring bar and nitrogen inlet, was charged sodium hydride (80% dispersion, 216 mg, 7.2 mmol) which was washed with three 5-mL portions of hexane. A slurry of 4-imino-2-methoxy-6-oxodihydropyrimidine (6, 1.0 g, 7.1 mmol) in DMF (25 mL) was added. With the expulsion of hydrogen gas the starting material went into solution. Trimethyl phosphate (2.98 g, 21.3 mmol) was introduced and the solution stirred at room temperature for 15 hr. The product which precipitated was removed
by vacuum filtration and dried under vacuum (0.84 g, 76%) to afford
white needles: mp 214-215°C (lit.\(^8\) 206-8°C); NMR (DMSO-\(d_6\)) \(\delta\) 6.35
(s, 1H, NH) 4.75 (s, 2H, CH\(_2\)), 3.80 (s, 3H, OCH\(_3\)), 3.08 (s, 3H,
CH\(_3\)), 2.50 (s, 1H, =NH); TLC (silica gel; 25% MeOH/75% EtOAc)
R\(_f\) 0.60.

4-Imino-5-isonitroso-2-methoxy-1-methyl-6-oxydihydropyrimidine
(8). In a 125 mL, single-necked flask, 4-imino-2-methoxy-1-methyl-
6-oxydihydropyrimidine (7, 8.5 g, 54.8 mmol) was dissolved in hot
water (85 mL). Sodium nitrite (4.2 g, 61 mmol) was then introduced
with stirring, followed by glacial acetic acid (15 mL). The vivid
purple product which immediately precipitated was filtered and
dried under full vacuum until the color changed from purple to
blue, denoting the loss of water (ca. 6 hr; 8.78 g, 87%):
mp 135°C [d] (lit.\(^8\) 145°C [d]). The material was carried on
immediately to the next step.

4,5-Diamino-2-methoxy-1-methyl-6-oxydihydropyrimidine (9). In a
125 mL, single-necked flask, fitted with a magnetic stirring bar,
4-imino-5-isonitroso-2-methoxy-1-methyl-6-oxydihydropyrimidine (8,
6.6 g, 36 mmol) was added to 37% ammonium sulfide (30 mL, 0.16
mol). The mixture was stirred for 1 hr in an ice bath, whereupon
the yellow product was isolated via vacuum filtration and
recrystallized from water (100 mL), leaving white fluffy crystals
(5.3 g, 87%): mp 150-152°C (lit.\(^8\) 160°C); NMR (DMSO-\(d_6\)) \(\delta\) 5.62 (s,
2H, NH\(_2\)), 3.80 (s, 3H, OCH\(_3\)), 3.18 (s, 2H, NH\(_2\)), 3.08 (s, 3H, CH\(_3\)).

1-Methylxanthine (10). To a 125 mL flask was added formamide (35
mL), 6N hydrochloric acid (3.5 mL), and 4,5-diamino-2-methoxy-1-
methyl-6-oxydihydropyrimidine (9, 1.0 g, 31 mmol). The orange solution was refluxed for 12 hr, allowed to cool to room temperature, diluted with an equal amount of water, and refrigerated for 15 hr. The light yellow, crystalline product was isolated via filtration and dried under vacuum (2.2 g, 42%). Purification to analytical standards was effected via recrystallization from water, including treatment with decolorizing carbon, to afford snow-white crystals which were identical spectroscopically and chromatographically to an authentic sample. 4

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References

4. Sigma Chemical Co., St Louis; cat. no. M 0645.
8. Rather than being purchased (at high cost), anhydrous cyanamide was prepared via ether extraction from a 50% aqueous solution. The ethereal solution was treated with anhydrous magnesium sulfate, filtered, and evaporated to dryness, leaving pure cyanamide as a clear, colorless oil.


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