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Synthesis of Xanthine Derivatives by Ring Closure Reaction

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Ring closure of the imidazole ring is a key step in the synthesis of xanthine and other purine derivatives. A microwave-assisted procedure involving triethyl orthoformate is presented. High yields are achieved even on a gram scale, while reaction times are considerably shortened compared to conventional heating conditions.

Key Words: Microwave-assisted synthesis, Xanthines, Purines, Imidazole ring closure.

INTRODUCTION

The plant alkaloid caffeine, 1,3,7-trimethylxanthine, is the most frequently used psycho-stimulant drug worldwide. It exerts its effects by the blockade of adenosine receptors in the brain[1]. Theophylline, 1,3-dimethylxanthine, which is also naturally occurring, is therapeutically applied as an antiasthmatic drug. A large number of derivatives and analogs of caffeine and theophylline have been synthesized and pharmacologically investigated[2,3]. Some xanthine derivatives (**Scheme-I**), including denbufylline and pentoxifylline, are potent phosphodiesterase inhibitors[4-6]. The latter is clinically used for the treatment of peripheral vascular disease[6]. Other xanthine derivatives, such as lisofylline, are experimental antiinflammatory drugs[7]. Further, xanthine derivatives are currently in pre-clinical or clinical development as novel drugs for various indications and many xanthine derivatives have become important pharmacological tools[8]. It is, thus justified to claim that the xanthine scaffold belongs to the so-called 'privileged structures'[9] in medicinal chemistry and drug development.

A key step in the classical synthetic route towards xanthines is the ring closure of the imidazole ring, which leads to the purine ring system. The classical Traube synthesis of 8-unsubstituted xanthine derivatives comprises

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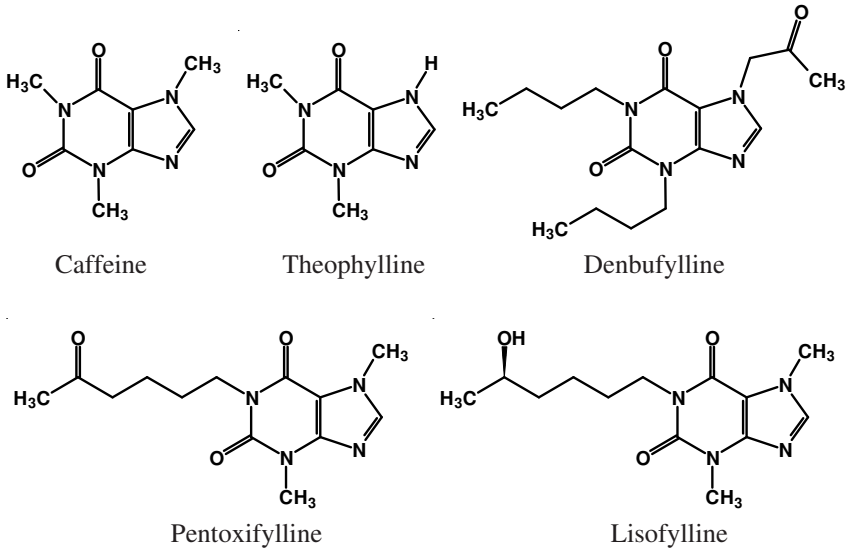
the reaction of a 5,6-diaminouracil derivative with formic acid in a two step procedure, involving tedious workup of the intermediate formamide[10,11].



Scheme-I: Examples of some xanthine drugs

As an alternative, a very efficient ring-closure reaction was first described by Grundmann and Kreutzberger[12]. The reaction of 1,3-dimethyl-4,5-diaminouracil with 1,3,5-triazine led to very pure theophylline in quantitative yield after a reaction time of less than 1 min. Although this finding appeared to be very encouraging, its applicability is limited since 1,3,5-triazine is not a readily accessible reagent.

Another ring closure procedure is the reaction of 5,6-diaminouracils with triethyl orthoformate, which is easily accessible and requires no special precautions in handling, as it is relatively stable towards hydrolysis. A disadvantage of this method are long reaction times of up to several hours[13,14]. Poor solubility of the precursors in triethyl orthoformate appears to be one of the problems. The present study was aimed at developing a fast, easy and general method for imidazole ring formation.

EXPERIMENTAL

All microwave reactions were carried out in 10 mL sealed glass tubes in a focused mono-mode microwave oven (Discover by CEM Corporation, Matthews, NC). Maximum power levels, target temperatures and reaction times are given. All commercially available reagents and solvents were used without further purification. Petroleum ether with a boiling point of

40-60 °C was used, if not otherwise noted. The melting points were measured by a Wepa 'apotec' melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were performed on a Bruker Avance 500 MHz spectrometer. The chemical shifts of the remaining protons of the deuterated solvent served as internal standard. Mass spectra were recorded on a MS-50 spectrometer at the Chemical Institute, University of Bonn.

5,6-Diamino-1,3-dialkyluracils[10]: In 60 mL of 12.5 % aq. ammonia solution, 20 mmol of the corresponding 1,3-dialkyl-6-amino-5-nitrosouracil[10] was dissolved. The solution was kept at 50-60 °C and $Na_2S_2O_4$ (*ca.* 9 g) was added upon stirring until the originally deeply coloured solution had almost decolourized. After cooling to room temperature, *ca.* 100 mL of brine was added and the solution was extracted four times, each time with 100 mL of CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered and concentrated. Compound **3** was dissolved in CH_2Cl_2, precipitated by adding petroleum ether, filtered under reduced pressure and washed with petroleum ether. Compound **4** was purified by column chromatography on silica gel (eluent:CH_2Cl_2:ethanol = 9:1). The product-containing fractions were concentrated and treated as described for compound **3**. The isolated diaminouracils were dried and stored in a vacuum desiccator at room temperature.

5,6-Diamino-1,3-diethyluracil (3): Yield: 3.2 g (80 %); m.p. 103-104 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (t, 3H, *J* = 7.25 Hz, CH_3), 1.29 (t, *J* = 7.25 Hz, 3H, CH_3), 2.26 (br. s, 2H, NH_2), 3.92 (q, *J* = 7.25 Hz, 2H, CH_2), 3.96 (q, *J* = 7.25 Hz, 2H, CH_2), 4.92 (s, 2H, NH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2 (CH_3), 13.5 (CH_3), 36.6 (CH_2), 38.2 (CH_2), 95.7 (C5), 148.5 (C6), 149.9 (C2), 161.4 (C4); EIMS (m/z, %) 198 (M^+, 100).

5,6-Diamino-1,3-dibutyluracil (4): Yield: 2.6 g (51 %); m.p. 93 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, 3H, *J* = 7.6 Hz, CH_3), 0.95 (t, *J* = 7.25 Hz, 3H, CH_3), 1.33 (m, 2H, CH_2), 1.38 (m, 2H, CH_2), 1.56 (m, 2H, CH_2), 1.64 (m, 2H, CH_2), 2.28 (br. s, 2H, NH_2), 3.83 (t, *J* = 7.9 Hz, 2H, NCH_2), 3.89 (t, *J* = 7.6 Hz, 2H, NCH_2), 4.87 (s, 2H, NH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7 (CH_3), 13.8 (CH_3), 20.1 (CH_2), 20.2 (CH_2), 30.1 (CH_2), 30.4 (CH_2), 41.4 (CH_2), 43.1 (CH_2), 95.7 (C5), 148.5 (C6), 150.3 (C6), 161.6 (C4); EIMS (m/z, %) 54 (M^+, 100).

1,3-Dialkylxanthines 1 and 2: A mixture of 1 g of 5,6-diamino-1,3-dialkyluracil (5 mmol of **3** or 4 mmol of **4**, respectively) and triethyl orthoformate (6 mL) was subjected to microwave irradiation for 5 min (120 W, 160 °C) in a 10 mL pressure tube, with stirring. The resulting yellow suspension was diluted with 50 mL of 2 N aq. HCl solution. After the addition of brine, the aqueous suspension was extracted three times with dichloromethane (100 mL each). The united organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The products were

dissolved in CH_2Cl_2, precipitated by adding petrol ether, filtered off, washed with petroleum ether (10 mL) and dried at 70 ºC.

1,3-Diethylxanthine (1): Yield: 0.79 g colourless crystals (76 %); m.p. 221 ºC (Lit.[15] 212 ºC). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.28 (t, 3H, *J* = 7.1 Hz, CH_3), 1.36 (t, *J* = 7.35 Hz, 3H, CH_3), 4.15 (q, 2H, *J* = 7.1 Hz, CH_2), 4.21 (q, 2H, *J* = 7.1 Hz, CH_2), 7.81 (d, 1H, *J* = 1.6 Hz, C_8H), 12.77 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3 (CH_3), 13.4 (CH_3), 37.0 (CH_2), 39.0 (CH_2), 107.1 (C5), 140.3, 148.5, 150.5, 156.1; EIMS (m/z, %) 208 (M^+, 100).

1,3-Dibutylxanthine (2): Yield: 0.85 g colourless crystals (80 %); m.p. 186-187 °C (Lit.[10] 189 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.94 (t, 3H, *J* = 7.55 Hz, CH_3), 0.95 (t, *J* = 7.25 Hz, 3H, CH_3), 1.38 (m, 2H, CH_2), 1.40 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 1.75 (m, 2H, CH_2), 4.08 (m, 2H, NCH_2), 4.13 (m, 2H, NCH_2), 7.78 (d, 1H, *J* = 1.3 Hz, C_8H), 13.00 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7 (CH_3), 13.8 (CH_3), 20.0 (CH_2), 20.2 (CH_2), 30.1 (CH_2), 30.1 (CH_2), 41.6 (CH_2), 43.8 (CH_2), 107.0 (C5), 140.3, 148.8, 150.3, 156.3; EIMS (m/z, %) 264 (M^+, 100).

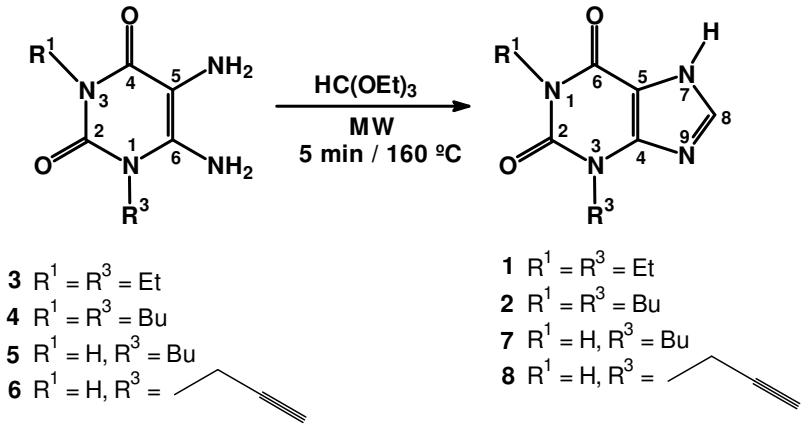
1-Alkylxanthines 7 and 8[13]: A mixture of 1 g of 5,6-diamino-3-alkyluracil (5 mmol of **5**[13] or 5.5 mmol of **6**[13], respectively) and triethyl orthoformate (6 mL) was subjected to microwave irradiation for 5 min (120 W, 160 °C) in a 10 mL pressure tube upon stirring. The products were filtered off, washed with diethyl ether (10 mL) and recrystallized from water.

1-Butylxanthine (7): Yield: 0.88 g colourless crystals (85 %); m.p. 261 °C (Lit.[13] 262 °C). TLC control: comparison with a conventionally prepared sample.

1-Propargylxanthine (8): Yield: 0.94 g colourless crystals (90 %); m.p. 278 °C (Lit.[13] 279 °C). TLC control: comparison with a conventionally prepared sample.

RESULTS AND DISCUSSION

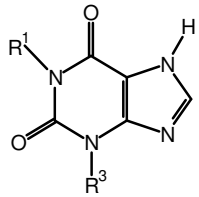
We were especially interested in a facile synthesis of 1,3-diethylxanthine (**1**), which was required as a reaction intermediate in our investigations on the structure-activity relationship of adenosine receptor antagonists and 1,3-dibutylxanthine (**2**) as a precursor to denbufylline. As starting materials the 1,3-dialkyl-5,6-diaminouracils **3** and **4** were prepared as previously described[10]. In order to obtain highly pure compounds separation methods for these air- and temperature-sensitive materials had to be developed. Although the subsequent reactions work well with impure starting materials (containing small quantities of water, inorganic salts or other by-products of the synthesis), highly pure 5,6-diaminouracils were required for the precise determination of the yields.



Scheme-II: Microwave-assisted preparation of xanthine derivatives

Preliminary experiments had shown that 5,6-diamino-1,3-dibutyluracil (**4**) was quite reactive towards triethyl orthoformate under reflux conditions, giving an 80 % yield of 1,3-dibutylxanthine (**2**) after 1 h. Microwave irradiation sped up the reaction considerably: instead of one hour, the reaction could be completed within 5 min with a similar yield. The analogous microwave-assisted reaction with 5,6-diamino-1,3-diethyluracil (**3**) led to the corresponding 1,3-diethylxanthine (**1**) in 76 % yield equally fast.

TABLE-1



Xanthine	R^1	R^3	Reaction time (min)		Yield (%) Method B
			Method A[a]	Method B[a]	
1	Et	Et	n.d.	5	76
2	Bu	Bu	60	5	80
7	Bu	H	300[c]	5	85
8	Propargyl	H	90[c]	5	90

[a]Heating with triethyl orthoformate under reflux.
[b]Heating with triethyl orthoformate at 160 ºC with microwave irradiation.
[c]Taken from the literature[13].

To test the scope of the microwave-assisted method, the reaction of the poorly soluble derivatives 1-butyl-5,6-diamino-uracil (**5**) and 5,6-diamino-1-propargyluracil (**6**) in triethyl orthoformate were also investigated.

Reaction times of 5 h for the preparation of **7** and 1.5 h for **8** have been reported for conventional reaction conditions[13]. After 5 min of microwave irradiation no residual starting material could be detected. The corresponding 8-unsubstituted xanthine derivatives **7** and **8** were isolated in excellent yields of up to 90 % depending on the purity of the employed 5,6-diaminouracils (**Scheme-II**). To test whether this acceleration was only due to the higher temperature applied, a sample of 5,6-diamino-1-propargyluracil (**6**) was mixed with triethyl orthoformate and conventionally heated at 160 °C in a glass pressure tube for 10 min. After workup, most of the starting material could be recovered, while only traces of xanthine **8** were detected by TLC.

Notably, the reactions proceeded smoothly, although the employed quantity of triethyl orthoformate was far too little to dissolve either the starting materials or the products. This greatly facilitated purification and workup, especially when working on a gram scale. Thus, the authors successded in shorten the reaction times in the synthesis of xanthines using triethyl orthoformate by applying microwave energy. This reaction seems to have a broad scope concerning substitution patterns at the 1- and 3-position and is thus an easy and convenient procedure to synthesize 8-unsubstituted xanthine derivatives.

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