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Microwave-assisted synthesis of 8-mercapto-3-methyl-7-alkyl xanthines—an improved method

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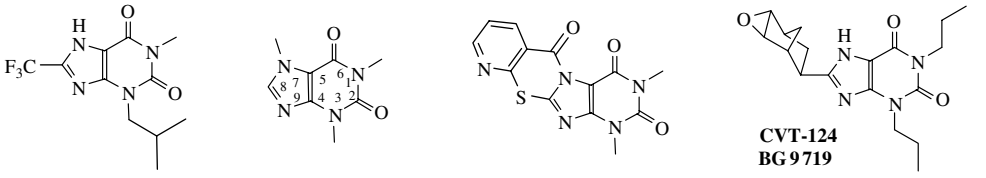
Abstract—A microwave-assisted synthetic method to prepare novel 8-mercapto-3-methyl-7-alkyl xanthine compounds is reported. Compared to conventional synthetic route, the new method significantly shortened synthetic steps and reaction time.

Recently, the design and synthesis of drug-like libraries has shifted in focus to heterocyclic cores.[1] Xanthines have been an important class of biologically active structures. Their activities have ranged from antagonists of adenosine receptors (such as caffeine), to phosphodiesterase (PDE) inhibitors to DNA intercalating agents (Fig. 1).[2] Xanthine-based structures for new drug leads have been explored in various therapeutic areas.[2] However, 8-mercaptoxanthines and the structures derived from them have not been well studied. 8-Mercaptoxanthines have been used as the intermediates for new purine-based heterocyclic ring systems, such as purinobenzothiazines and pyridothiazonopurines.[3] Analogues of this class have shown antitumor activity (Fig. 1).

We are interested in 3,7-di-substituted analogues of 8-mercaptoxanthines. Literature survey has shown that 8-mercaptoxanthine structures can be made from the condensation of 5,6-diaminouracil with thiourea at 210 °C.[4] Such harsh reaction condition and the low yield make this reaction not fit into our parallel synthesis platform. Also 5,6-diaminouracils are unstable due to oxidative dimerization in the presence of oxygen.[5] 1,3,7-Substituted 8-mercaptoxanthines can also be synthesized from the condensation of 1,3-di-substituted-6-hydroxylaminouracil with isothiocyanates.[6] However, this reaction can only be applied to nitrophenyl isothiocyanates. Therefore, the application scope of this reaction is limited. To date, the most favored and efficient method to synthesize 8-mercaptoxanthines is from their corresponding 8-bromo-, 8-chloro-, and 8-oxo-xanthines.[7] We have designed a synthetic sequence for the synthesis of 8-mercaptoxanthines based on the literature conditions (Scheme 1).

Starting with 6-aminouracil **1**, 5-nitrosation of **1** in acetic acid with $NaNO_2$ produced 5-nitroso-uracil **2**. Reduction of the nitroso group with sodium dithionite gave 5,6-diamino-uracil **3**. Formylation of **3** with formic



PDE Inhibitor **Caffeine** **Anticancer Agent** **A1 receptor antagonist**

Figure 1. Biologically active xanthine analogues.

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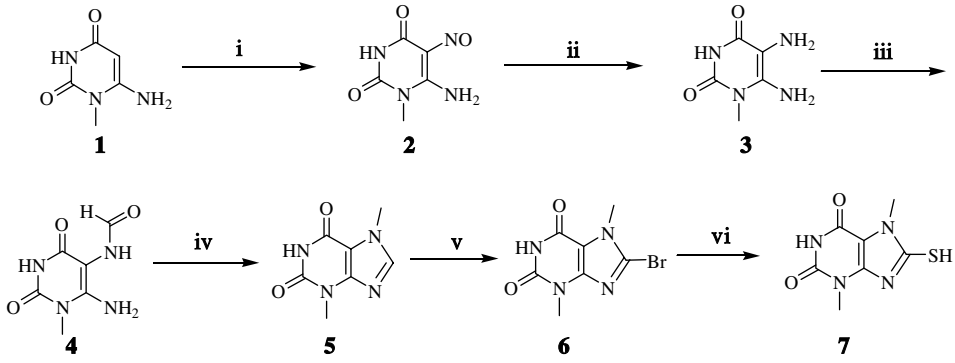
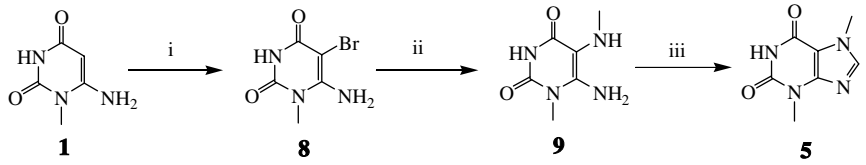


Scheme 1. Reagents: (i) $NaNO_2$, H_2O/HOAc; (ii) $Na_2S_2O_4$, H_2O/NH_3; (iii) formic acid; (iv) dimethylsulfate, NaOH; (v) Br_2, NaOAc, HOAc; (vi) KSBn, EtOH.

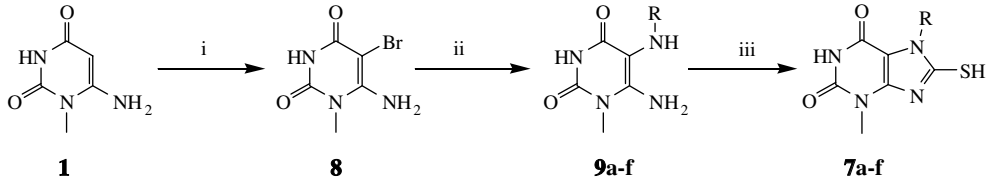


Scheme 2. Reagents and conditions: (i) Br_2, $NaHCO_3$, MeOH; (ii) $MeNH_2/H_2O$, 70 °C, 4 h; (iii) triethylorthoformate, reflux, 8 h.

acid afforded **4**, which was cyclized and methylated at 7-position to give xanthine **5**.[8] Bromination at the 8-position of xanthine **5** with bromine and sodium acetate in acetic acid at 60 °C for about 1 h led to the formation of 8-bromoxanthine **6**.[9]

Potassium benzylthiolate reacted with **6** at 120 °C to give 8-mercaptoxanthines 7. This reaction sequence has produced 8-mercaptoxanthines in a satisfactory yield, but it is relatively long. Also it is still problematic to get access to 7-substituted analogues using this method. Compared to the synthesis of other substituted xanthines, only limited studies have been done for 7-substituted analogues. Besides the S_N2 substitution at 7-NH of xanthines (Scheme 1), there is another synthetic method to synthesize 7-substituted xanthines (Scheme 2).[2b]

Bromination of 6-aminouracil 1 at 5-position afforded 5-bromo-uracil **8**, and which was transformed into 5,6-diamino-uracil **9** via replacement of bromide by methylamine under reflux.[2b,10] Compound **9** can be smoothly cyclized into xanthine **5** using triethylorthoformate under reflux. The resulting xanthines **5** can be converted to 8-mercapto-xanthines **7** following Scheme 1 procedure. However, the overall sequence of the method has not been shortened. Also, except methylamine, there are no other alkylamines and aromatic amines being tested. Therefore, the reaction conditions need to be further elaborated for the various amines. Considering that the reactions need extensive heating, we expect microwave irradiation will facilitate the transformation. The advantages of microwave-assisted synthesis have already been widely recognized and have been designed as one efficient parallel synthesis platform.[11] Also we are systematically studying the reaction conditions of various heterocyclic scaffolds in MW conditions. We used CEM microwave reactor Explorer to conduct our MW reactions (Scheme 3). Replacement of bromide with various alkylamines proceeds smoothly at 120 °C for 10 min (Table 1, **9a**–**f**). Conversion of 5-bromo-uracil **8** to **9** is complete without trace of starting material **8** being detected using analytical LC–MS in this MW condition (Table 1). After simple precipitation at acidic condition and wash by ethanol, diethyl ether, and water, compound **9** was used in next step reaction without further purification. The purities of **9** are determined by ^1H NMR and TLC plate. For alkylamines, the reaction is not significantly affected by different alkyl groups. After studying the MW conditions for the synthesis of **9**, we focused our effort on optimizing the microwave conditions from **9** to **7** (Scheme 3). Literature survey showed that 5,6-diamines can be transformed to 8-mercapto-xanthines in one step reaction using thioureas, carbon disulfide, and potassium ethylxanthate.[4,12,13] However, all the reported reactions were run using 5,6-diamino-uracils with no substitution at 5-position of 5,6-diamino-



Scheme 3. Reagents and conditions: (i) Br_2, $NaHCO_3$, MeOH; (ii) RNH_2, MW, 120 °C, 10 min; (iii) EtOC(O)SK, MW, 120 °C, 10 min.

Table 1. Microwave-assisted synthesis of 8-mercaptoxanthines

Product	Group	Purity (%)	Yield (%)	
		Isolated	Conversion (LC–MS)[a]	Isolated
9a	*n*Bu	>95[b]	100	79
9b	Bn	>95[b]	100	75
9c	$PhCH_2CH_2$	>95[b]	100	81
9d	*p*-F–$PhCH_2CH_2$	>95[b]	100	78
9e	*o*-$PyCH_2$	>95[b]	100	71
9f	*m*-$PyCH_2$	>95[b]	100	75
9g	Ph	—	0	0
9h	*p*-OMe–Ph	—	0	0
7a	*n*Bu	100[a]	83	76
7b	Bn	98[a]	81	73
7c	$PhCH_2CH_2$	100[a]	93	88
7d	*p*-F–$PhCH_2CH_2$	100[a]	100	97
7e	*o*-$PyCH_2$	96[a]	95	90
7f	*m*-$PyCH_2$	100[a]	81	73

[a] Gradient MeCN in H_2O 0–100% (0.1% FA), 10 min.
[b] Determined by ^1H NMR spectra.

uracils. There is also no report on the synthesis of 7-substituted 8-mercaptoxanthines with the corresponding substitutions at either the 5- or 6-position of 5,6-diaminouracils. Compared to thiourea and carbon disulfide, potassium ethylxanthate gave highest yields in relatively milder reaction conditions. Therefore, we chose potassium ethylxanthate to synthesize the final products **7**.[14]

Condensation of potassium ethylxanthate with 5,6-diamino uracils **9** was proceeded smoothly to produce 8-mercaptoxanthines **7** under microwave irradiation at 120 °C for 10 min (Table 1, **7a**–**f**). This reaction can tolerate the steric hinderance caused by 7-substitutions. Therefore, this protocol offered a general microwave-assisted method to get access to 8-mercapto-7-alkylxanthines. However, application of anilines to replace bromide of **8** failed to produce the desired diaminouracil products **9** (Table 1, **9g** and **9h**). We have tried to increase MW irradiation times from 10 to 30 min, and temperature from 120 to 140 °C, and these changes did not improve the results.

In summary, we have developed a microwave-assisted general method to synthesize novel 8-mercapto-7-alkylxanthines. The method is the shortest sequence in all published procedures for 8-mercaptoxanthines. This is also the first published procedure for 7-alkylated 8-mercaptoxanthines except 7-methyl analogues and will have broad application to explore these kinds of compounds for therapeutic utilities.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.095.

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14. *General procedure for Scheme 3*: All reactions were performed in oven-dried glassware unless otherwise noted. Reagents were purchased from commercial suppliers and used without further purification. Reactions were carried out on CEM Explorer Microwave Synthesizer. NMR spectra were recorded on a Varian Mercury 400 (^1H NMR at 400 MHz) spectrometer in DMSO-d_6 using residual solvent peaks as internal standard 2.49 (DMSO-d_6) ppm. Chemical shifts are given in parts per million and coupling constants, *J*, are given in hertz. Mass spectra were obtained on Thermo-Finnigan LCQ Advantage MAX spectrometer.

Synthesis of 6-amino-5-bromo-1-methyluracil (**8**): To a suspension of 6-amino-1-methyluracil (7.06 g, 50 mmol), sodium bicarbonate (4.2 g, 50 mmol) in methanol (50 mL) was added bromine (2.57 mL, 50 mmol) under vigorous stirring at 0 °C during 0.5 h. The mixture was stirred at room temperature for 2 h. After it was stirred at room temperature for 2 h, the solution was cooled to 4 °C, and the white precipitate was collected by filtration. The white solid was stirred in water (100 mL) at 4 °C, filtered, washed with cold water, and dried under high vacuum over calcium sulfate. The off-white solid (11.0 g, yield 100%) was characterized by HPLC/MS and ^{1}H NMR as pure product. MS (*m*/*z*): $C_5H_6BrN_3O_2$ calcd 219.0; found $[M+H]^+ = 220.1$, 222.1; $[M-H]^- = 218.0$, 219.9. ^{1}H NMR (DMSO-d_6, δ): 10.89 (s, 1H), 7.03 (s, 2H), 3.26 (s, 3H).

Microwave assisted synthesis of 6-amino-1-methyl-5-alkylaminouracil (**9a**–**f**): An oven dried 10 mL microwave reaction tube charged with 6-amino-5-bromo-1-methyluracil **8** (10 mg, 0.5 mmol) and corresponding amine (0.5 mL, 3–4 mmol), was capped and irradiated on CEM Explorer microwave synthesizer. The reactions were held at 120 °C for 10 min to afford an orange to brown solution. After cooling to room temperature, 8 mL of diethyl ether was introduced to lead to solid precipitate that were filtered, washed with small amount of ethyl acetate, diethyl ether, and water, and dried under vacuum to give off-white solid **9a**–**f**. The products were characterized by HPLC–MS, TLC, and ^{1}H NMR. The conversion rate is determined by the disappearance of starting material **8** and purity was calculated by analyzing TLC plate and ^{1}H NMR spectra.

6-Amino-5-(butylamino)-1-methylpyrimidine-2,4(1*H*,3*H*)-dione (**9a**) off-white solid, yield = 79.2%. MS (*m*/*z*): $C_9H_{14}N_4O_2$ calcd 212.1; found $[M+H]^+ = 213.1$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.46 (s, 1H), 6.34 (s, 2H), 3.20 (s, 3H), 2.71 (br s, 1H), 2.59 (t, J = 7.2 Hz, 2H),1.39 (m, J = 7.2 Hz, 2H), 1.28 (m, J = 7.2 Hz, 2H), 0.86 (t, J = 7.2 Hz, 3H).

6-Amino-5-(benzylamino)-1-methylpyrimidine-2,4(1*H*,3*H*)-dione (**9b**) off-white solid, yield = 75%. MS (*m*/*z*): $C_{12}H_{14}N_4O_2$ calcd 246.1; found $[M+H]^+ = 247.1$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (br s, 1H), 7.39 (d, J = 7.2 Hz, 2H), 7.28 (t, J = 7.2 Hz, 2H), 7.20 (t, J = 7.2 Hz, 1H), 6.39 (s, 2H), 3.80 (d, J = 6.4 Hz, 2H), 3.18 (s, 3H), 3.12 (t, J = 6.4 Hz, 1H).

6-Amino-1-methyl-5-(phenethylamino)pyrimidine-2,4(1*H*, 3*H*)-dione (**9c**) off-white solid, yield = 80.8%. MS (*m*/*z*): $C_{13}H_{16}N_4O_2$ calcd 260.1; found $[M+H]^+ = 261.1$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.28–7.14 (m, 6H), 6.27 (s, 2H), 3.18 (s, 3H), 2.84 (m, 3H), 2.72 (t, J = 7.2 Hz, 2H).

6-Amino-5-(4-fluorophenethylamino)-1-methylpyrimidine-2,4(1*H*,3*H*)-dione (**9d**) off-white solid, yield = 78.4%. MS (*m*/*z*): $C_{13}H_{15}FN_4O_2$ calcd 278.1; found $[M+H]^+ = 279.1$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.45 (br, 1H), 7.28–7.05 (m, 4H), 6.25 (s, 2H), 3.17 (s, 3H), 2.99 (t, J = 7.2 Hz, 1H), 2.82 (m, 2H), 2.70 (t, J = 7.2 Hz, 2H).

6-Amino-1-methyl-5-(pyridine-2-ylmethylamino)pyrimidine-2,4(1*H*,3*H*)- dione (**9e**) yellow solid, yield = 70.7%. MS (*m*/*z*): $C_{11}H_{13}N_5O_2$ calcd 247.1; found $[M+H]^+ = 248.1$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H), 8.49 (d, J = 4.8 Hz, 1H), 7.72 (dt, J = 7.2, 2.0 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.23 (dd, 7.2, 2.0 Hz, 1H), 6.60 (s, 2H), 3.90 (d, J = 6.0 Hz, 2H), 3.48 (br s, 1H), 3.19 (s, 3H).

6-Amino-1-methyl-5-(pyridine-3-ylmethylamino)pyrimidine-2,4(1*H*,3*H*)-dione (**9f**) off-white solid, yield = 75.2%. MS (*m*/*z*): $C_{11}H_{13}N_5O_2$ calcd 247.1; found $[M+H]^+ = 248.1$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (br s, 1H), 8.53 (d, J = 2.0 Hz, 1H), 8.41 (dd, J = 4.8, 2.4 Hz, 1H), 7.80 (dt, J = 7.6, 2.0 Hz, 1H), 7.28 (dd, 2.4, 2.0 Hz, 1H), 6.44 (s, 2H), 3.85(d, J = 6.0 Hz, 2H), 3.17 (s, 3H).

Microwave Assisted synthesis of 8-mercapto-3-methyl-7-alkylxanthine (**7a**–**f**): The mixture of corresponding 6-amino-1-methyl-5-alkylaminouracil (**9a**–**f**, 0.2 mmol) and potassium ethyl xanthate (256 mg, 1.6 mmol) in anhydrous DMF (2 mL) was capped and irradiated on CEM Explorer microwave synthesizer. The reactions were held at 120 °C for 10 min to afford a yellow to brown solution. After cooling to room temperature, the solvent was evaporated under vacuum. The residue was stirred with 5 mL of water in an ice-water bath to give a clear solution that was acidified with 2 N HCl solution to pH = 4–5. The resulting precipitate was filtered, washed with cold water, small amount of ethanol, and diethyl ether, and dried under vacuum to give off-white or pink solid **7a**–**f**. The products were characterized by HPLC–MS and ^{1}H NMR. The conversion rate and purity were calculated by analyzing UV spectra of final reaction mixtures and isolated products by HPLC on an automated Gilson system using a gradient of 0% MeCN to 100% MeCN in H_2O (0.1% FA) over 10 min on a C18 column (4.6 × 50 mm).

7-Butyl-8-mercapto-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (**7a**) off-white solid, yield = 75.9%. MS (*m*/*z*): $C_{10}H_{14}N_4O_2S$ calcd 254.1; found $[M+H]^+ = 255.1$; $[M-H]^- = 253.1$. Retention time: 5.12 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.29 (s, 1H), 4.17 (t, J = 7.4 Hz, 2H), 3.28 (s, 3H), 1.65 (m, J = 7.4 Hz, 2H), 1.27 (m, J = 7.4 Hz, 2H), 0.88 (t, J = 7.4 Hz, 3H).

7-Benzyl-8-mercapto-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (**7b**) off-white solid, yield = 72.9%. MS (*m*/*z*): $C_{13}H_{12}N_4O_2S$ calcd 288.1; found $[M+H]^+ = 289.1$; $[M-H]^- = 287.1$. Retention time: 5.48 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.29 (s, 1H), 7.39 (d, J = 7.2 Hz, 2H), 7.32–7.22 (m, 3H), 5.40 (s, 2H), 3.29 (s, 3H).

8-Mercapto-3-methyl-7-phenethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (**7c**) off-white solid, yield = 87.8%. MS (*m*/*z*): $C_{14}H_{14}N_4O_2S$ calcd 302.1; found $[M+H]^+ = 303.1$; $[M-H]^- = 301.1$. Retention time: 5.77 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.35 (s, 1H), 7.33–7.20 (m, 5H), 4.37 (m, 2H), 3.30 (s, 3H), 2.95 (m, 2H).

7-(4-Fluorophenethyl)-8-mercapto-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (**7d**) off-white solid, yield = 96.8%. MS (*m*/*z*): $C_{14}H_{13}FN_4O_2S$ calcd 320.1; found $[M+H]^+ = 321.1$; $[M-H]^- = 319.2$. Retention time: 6.01 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.34 (s, 1H), 7.26 (m, 2H), 7.12 (m, 2H), 4.36 (m, 2H), 3.29 (s, 3H), 2.95 (m, 2H).

8-Mercapto-3-methyl-7-(pyridine-2-ylmethyl)-1*H*-purine-2,6(3*H*,7*H*)-dione (**7e**) pink solid, yield = 89.7%. MS (*m*/*z*): $C_{12}H_{11}N_5O_2S$ calcd 289.1; found $[M+H]^+ = 290.1$; $[M-H]^- = 288.0$. Retention time: 4.27 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.29 (s, 1H), 8.47 (m, 1H), 7.72 (dt, J = 7.6, 2.0 Hz, 1H), 7.25 (m, 1H), 7.06 (d, 7.6 Hz, 1H), 5.50 (s, 2H), 3.37 (s, 3H, overlapped with H_2O signal).

8-Mercapto-3-methyl-7-(pyridine-3-ylmethyl)-1*H*-purine-2,6(3*H*,7*H*)-dione (**7f**) off-white solid, yield = 73.4%. MS (*m*/*z*): $C_{12}H_{11}N_5O_2S$ calcd 289.1; found $[M+H]^+ = 290.1$; $[M-H]^- = 288.0$. Retention time: 3.49 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.34 (s, 1H), 8.63 (d, J = 1.6 Hz, 1H), 8.47 (dd, J = 4.8, 1.6 Hz, 1H), 7.80 (dt, J = 8.0, 2.0 Hz, 1H), 7.35 (ddd, 8.0, 4.8, 0.8 Hz, 1H), 5.43 (s, 2H), 3.29 (s, 3H).