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SOLVENT-FREE SYNTHESIS OF THIO-ALKYLXANTHINES FROM ALKYLXANTHINES USING MICROWAVE IRRADIATION

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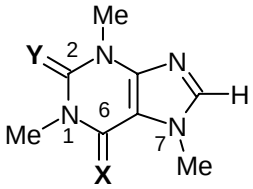
Abstract-An expeditious, solvent-free procedure for the conversion of the xanthine bases theophylline, 8-methyltheophylline, caffeine, and theobromine to the corresponding 6-thio and 2,6-dithio derivatives using Lawesson's reagent under microwave irradiation is proposed.

The synthesis of 1,3-disubstituted 6-thioxanthines has received considerable attention on account of their biological activity.[1~4] The usual approach involves the transformation of the 6-oxo group into its 6-thio analogue with phosphorus pentasulfide in pyridine.[5] On the other hand, non-enolizable 1,3,7-trialkylxanthines such as caffeine (**1a**) fail to react and yield 6-thiocaffeine (**1b**) under the same conditions,[6] and has been directly synthesized from **1a** using various reagents and/or conditions,[7] or by an indirect approach.[6,8] The synthesis of 2,6-dithio-alkylxanthines has been less deeply studied because replacing the 2-oxygen atom of alkylxanthines with sulfur is more difficult. In fact, 2,6-dithiotheophylline (**2c**) has been prepared from 2-thiotheophylline (**2b**), previously obtained from 4,5-diamino-1,3-dimethyl-2-thiouracil using Traube's method.[9] Only three instances of direct synthesis of 2,6-dithio-alkylxanthine have so far been reported.[7b,7c,10] Most of these procedures, however, require a long time and drastic reaction conditions, in addition to the use of dry solvents; also, they occasionally afford modest yields.



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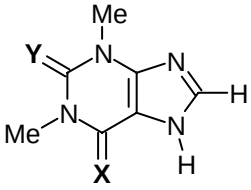

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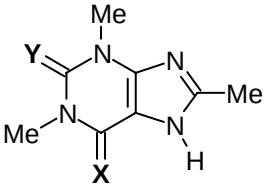

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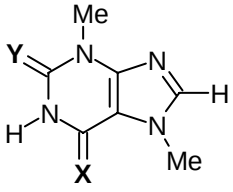

4

a, X=Y=O
b, X=S, Y=O
c, X=Y=S

Lawesson's reagent has been used for the conversion of a wide variety of carbonyl compounds to their thiocarbonyl analogues.[11] However, this method usually requires an excess of reagent, a long reaction time, a dry hydrocarbon solvent at a high temperature, and generates unwanted side products.[12]

The chemical potential of microwaves for efficient transformation of functional groups under solvent-free conditions has aroused much interest lately.[13] Recently, thioketons, thioesters, thiolactones and thioamides have been prepared by reaction of their oxo analogues with Lawesson's reagent under microwave irradiation conditions.[14]

In this paper, we report the synthesis of 6-thiocaffeine (**1b**), 6-thiotheophylline (**2b**), 8-methyl-6-thiotheophylline (**3b**), 6-thiotheobromine (**4b**), 2,6-thiocaffeine (**1c**), 2,6-dithiotheophylline (**2c**), 8-methyl-2,6-dithiotheophylline (**3c**) and 2,6-dithiotheobromine (**4c**) by reaction of the corresponding xanthine bases with Lawesson's reagent under microwave irradiation. All reactions were carried out under atmospheric pressure in a focused microwave reactor[15] in the absence of solvent. The reaction conditions were optimized to obtain the best possible yield (Table 1).

The reaction of 1 mmol of alkylxanthine with 0.5 mmol of Lawesson's reagent (Entries *1*, *3*, *5* and *7*, Table 1) yielded 6-thio derivatives selectively. When the reaction was conducted at a 1:1.1 substrate-reagent mmol ratio (Entries *2*, *4*, *6* and *8*, Table 1), 2,6-dithioxanthines were obtained almost quantitatively. It should be noted that, although this procedure resulted in decreased reactivity of the oxygen atom at position 2, thionation at positions 6 and 2 only occurred if the mole ratio of Lawesson's reagent to xanthines was increased from 0.5:1 to 1.1:1.

Table 1. Solvent-free synthesis of thioxanthine derivatives using microwave irradiation.

Entry	Substrate	Xanthine/LR[a] mole ratio	MW[b] Irradiation Time/power[c]	Product	Yield (%)	mp (ºC)
1	Caffeine, **1a**	1:0.5	6 min / 60 W	**1b**	92	245-246
2	**1a**	1:1.1	6 min / 60 W	**1c**	98	228-230
3	Theophylline, **2a**	1:0.5	10 min / 60 W	**2b**	95	314-316
4	**2a**	1:1.1	10 min / 60 W	**2c**	93	254-256
5	8-Methyltheophylline, **3a**	1:0.5	5 min / 60 W	**3b**	90	289-291
6	**3a**	1:1.1	5 min / 60 W	**3c**	96	249-251
7	Theobromine, **4a**	1:0.5	7 min / 60 W	**4b** + (**4c**)	99	--
8	**4a**	1:1.1	7 min / 60 W	**4c**	92	293-295

a) Lawesson's reagent; b) microwave; c) the temperature of the alumina at the start of irradiation was 120 ºC.

With theobromine (**4a**, Entry *7*) a mixture of 6-thio derivative (**4b**) (60%), 2,6-dithio derivative **4c** (20%) and (**4a**) (20%) was obtained (^{1}H-NMR). This result can be explained assuming that, if 0.4 eq. of Lawesson's reagent are required to yield 20% of **4c** and 0.6 equiv produce 60% of **4b**, 20% of the starting material, **4a**, must be recovered. The obtainment of 2,6-dithio derivatives can be ascribed to an increased reactivity at position 2 in **4a**. This is consistent with the fact that N-1 bears no alkyl substituent, so both the C-6 and the C-2 carbonyl groups are enolizable, and the substitution of the oxygen by a sulfur atom is not so regioselective as in the other alkylxanthines.

In a typical experiment, a mixture of xanthine bases (**1a**, **2a**, **3a** or **4a**) (1 mmol) and Lawesson's reagent (0.5 mmol or 1.1 mmol) was placed in a glass tube and mixed thoroughly with a spatula. The open glass tube was then placed inside a microwave vessel containing alumina (40 g) and exposed to microwave

irradiation at the power and for the time stated in Table 1. After irradiation, the mixture was cooled to rt. For isolation of the products, the reaction mixture was extracted with dichloromethane and filtered off to obtain the corresponding thioxanthines[16] (yields are given in Table 1), which were purified by crystallization or silica gel flash column chromatography (CH_2Cl_2 and CH_2Cl_2/CH_3OH 20:0.5).

In conclusion, we have developed a simple, rapid, highly efficient method for the synthesis of 2-thio- and 2,6-dithio-alkylxanthines from the corresponding oxo derivatives using Lawesson's reagent in a solvent-free microwave-assisted reaction. Further investigation on the synthesis of 6-thiopurine nucleosides is now in progress.

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15. For irradiation, a Prolabo TX-32 microwave oven was used.
16. All products (8-methyldithiotheophylline (**3c**) excepted) are known compounds and were characterized by NMR, IR and UV spectroscopies, EIMS and mp. Data for **3c**: red crystals ($CHCl_3$); mp 249-251 ºC; UV ($CHCl_3$) λ_{max} nm (log ε) 360 (3.87), 304 (4.03), 260 (3.89); IR (KBr) cm^{-1} 3307, 1605, 1111, 1062 ($\nu_{C=S}$); ^{1}H-NMR ($CDCl_3$+CD_3OD) ppm 4.17 (s, 3H, NCH_3), 3.88 (s, 3H, NCH_3), 2.43 (s, 3H, CH_3C8); ^{13}C-NMR ($CDCl_3$+CD_3OD) ppm 173.4, 173.2 (2xC=S), 154.2 (C8), 142.3 (C4), 122.9 (C5), 42.2 (NCH_3), 37.8 (NCH_3), 14.5 (CH_3C8). Anal. Calcd for $C_8H_{10}N_4S_2$: C, 42.46; H, 4.45; N, 24.74; S, 28.33. Found: C, 42.75; H, 4.67; N, 24.22; S, 28.75.