Synthesis of C-8 alkyl xanthines by pentaamminecobalt(III) complex

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ABSTRACT

Alkyl xanthines underwent selective homolytic aromatic substitution at C-8 position with alkyl groups of pentaamminecobalt(III) complex. In this process of synthesis, we used monoalkyl hydrazines as the radical source in aqueous ammonia solution. Evidence supporting coordination of the alkyl hydrazine to pentaamminecobalt(III) complex by radical trapping was in good agreement with literature. The products were characterized using GC-MS and ^1H, ^{14}N and ^{59}Co NMR spectroscopy.

Keywords: Alkyl Hydrazine; Radical Alkylation; Caffeine; Homolytic Aromatic Substitution; Pentaamminecobalt(III)

1. INTRODUCTION

Alkyl xanthines belong to purine group of molecules and are of interest due to their therapeutic value. A number of xanthines are used as adenosine receptor antagonists to treat neurodegenerative diseases in humans [1]. Several xanthines are known to inhibit cells at the G2 checkpoint in the cell cycle, thereby making cells more sensitive to DNA damage [2]. Xanthines, such as caffeine, theophylline, theobromine (see **Figure 1**) and its derivatives have been used for antihyperuraemic therapy, inhibition of monoamine oxidase B [3], besides serving as anticancer agents. Xanthines are known to enhance affinity for certain receptors selectively as well. This has led to an interest in synthesizing substituted alkyl xanthines.

Aqueous organometallic chemistry and its catalysis have attracted much interest, partly due to the reduced requirement for organic solvents [4]. Many organocobalt(III) complexes are sensitive to oxygen or moisture. Hydrolysis of a cobalt(III)-carbon bond is dependent on the nature of the ligand and requires mild conditions. Alkylcobalt(III) complex acts as a potential radical sour-

ce, e.g. in organic synthesis [5] such as oxidation, reduction, thermolysis, photolysis and sonolysis. Homolytic aromatic substitution is a well-known method for the preparation of 8-substituted xanthines. Previously, 8-methylcaffeine was known to be prepared by irradiation of a mixture of caffeine and *tert*-butyl peracetate with ultraviolet light [6]. Similarly, 8-(1-adamantyl) caffeine and 8-cyclohexyl caffeine were obtained by employing photochemically prepared radicals [7] while other 8-alkyl xanthines were known to be synthesized by reaction with solvent-derived alkyl radicals using benzoyl peroxide as a radical initiator [8].

Till date, no studies have been focused on Cobalt catalysed synthesis of C-8 alkyl xanthines. In this study, an attempt was made to synthesize and purify C-8 substituted alkyl xanthines.

2. MATERIAL AND METHODS

Concentrated aqueous NH_3 (5 mL) was added to a solution of Co $(NO_3)_2 \cdot 6H_2O$ (30 mg, 0.1 mmol), the monoalkyl hydrazine (2.0 mmol), and methyl xanthine (1.0 mmol) in H_2O (10 mL). The mixture was stirred for 8 - 10 h at room temperature in presence of atmospheric dioxygen. The reaction was monitored by GC-MS after extraction into CH_2Cl_2. Following completion, the product was extracted into CH_2Cl_2 (25 mL) and the solvent was removed by rotary evaporation. The resulting solid was dissolved in a 2:3 mixture of ethoxyacetate, *n*-hexane (5 mL) and purified by column chromatography using silica gel (mesh, 11, 3.5 cm) and a 2:3 mixture of ethoxyacetate and *n*-hexane as eluent. The pure compounds were isolated and further characterized by GC-MS, ^1H NMR and elemental analysis (*See* **Figure 2**).

3. RESULTS AND DISCUSSION

The 8-alkyl xanthines have been synthesized and characterized using GC-MS and ^1H NMR. Further elemental analysis of the isolated compounds was done which were
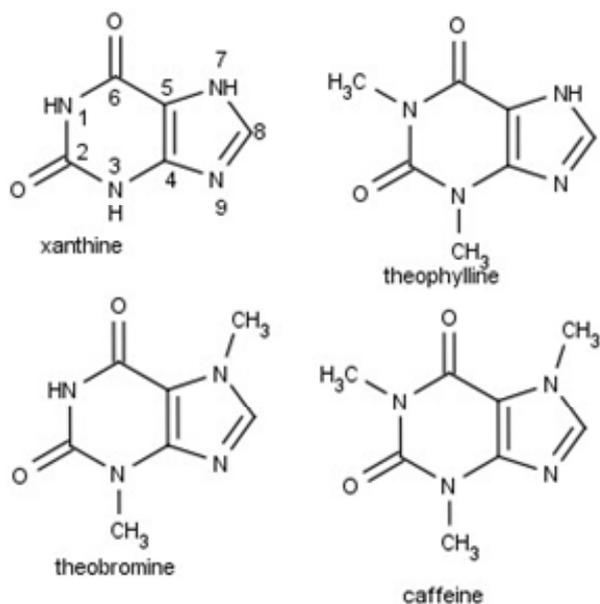
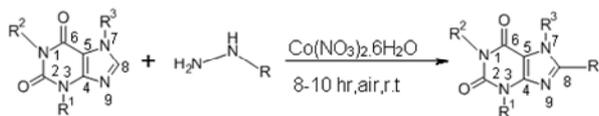**Figure 1.** Structures of xanthine and its derivatives.

Figure 2. Preparation of C-8 substituted alkyl xanthines.

in agreement with respect to molecular structures. While the following seven compounds synthesized, *viz.* 8-tert-butyl caffeine, 8-tertbutyl theophylline, 8-tertbutyl-3-isobutyl-1-methyl-theophylline,8-isopropyl -3- isobutyl-1-methyl theophylline, 8-isopropyl caffeine,8-isopropyl theophylline and 8-isopropyl theobromine; had a conversion of 60% - 90% (*See* **Table 1**). These were further used to study their effect in cancer cell lines. However, two compounds, *viz.* 8-ethyl caffeine and 8-ethy tertbutyl theobromine were not considered due to their insolubility in aqeous solution. Although we tried to synthesize many compounds, we wereable to get good yields for secondary and tertiary alkly hydrazines which have predominantly yielded 8-substituted alkly xanthines

The reaction of monoalkyl hydrazines with cobalt (III) in aqueous ammonia in the presence of atmospheric oxygen was analysed by ^{14}N and ^{59}Co NMR. A solution of 0.1 M $Co(NO_3)_2$ in 4 M NH_3 provided a ^{59}Co NMR signal at 8759 ppm (line width at half height, $\Delta\upsilon\frac{1}{2}$ = 11.2 kHz), which was assigned to the diamagnetic $[(NH_3)_5CoOOCo(NH_3)_5]^{4+}$ and is in agreement with the literature [11]. Addition of a stoichiometric amount of a methyl hydrazine (or another alkyl hydrazine) to the solution resulted in immediate disappearance of the ^{59}Co NMR signal. Rapid gas evolution (presumably O_2) together with the disappearance of $[(NH_3)_5CoOOCo(NH_3)_5]^{4+}$ was consistent with methyl hydrazine displacing the co-

ordinated dioxygen to give a cobalt(III) compound. This was oxidized slowly to the $[Co(NH_3)_5 (CH_3)]^{2+}$ cation which was evident by the appearance of a ^{59}Co signal at 7370 ppm ($\Delta\upsilon\frac{1}{2}$ = 13.2 kHz) (**Figure 3**) [9].

Magnetic susceptibility measurements in solution following Evans method [10] using *tert*-butanol with ^{1}H NMR detection showed that a solution of 0.1 M $Co(NO_3)_2$ in 4 M NH_3 was essentially diamagnetic and consistent with formation of the $[(NH_3)_5CoOOCo(NH_3)_5]^{4+}$ cation. Addition of a stoichiometric amount of methyl hydrazine resulted in a paramagnetic species. This was consistent with the disappearance of the ^{59}Co NMR signal. Coordination of dioxygen to yield diamagnetic cobalt(III) complexes, as indicated by the ^{59}Co NMR signals, was conceivable indicating that dioxygen oxidizes the alkyl hydrazine *via* simultaneous coordination to the cobalt ion. Although many cobalt-dioxygen complexes are known to form in aqueous solution [11], to our knowledge, there are no reports on cobalt coordination compounds with both alkyl hydrazines and dioxygen ligands. Nevertheless, in view of many studies on cobalt-dioxygen complex formation with nitrogen donor ligands [12], it appears plausible that such species may form as intermediates. The ^{1}H NMR spectra of the reaction mixtures showed that oxidation, e.g. of ethyl hydrazine gives a $[Co(NH_3)_5(CH_2CH_3)]^{2+}$ cation prior to xanthine alkylation. The ethyl ^{1}H NMR resonance signals of the ethyl hydrazine gradually decreased and instead, two new resonances at 3.90 and 3.97 ppm appeared. These were assigned to the $[Co(NH_3)_5(CH_2CH_3)]^{2+}$ cation by comparison with data for the isolated coordination compound [12].

The latter compound disappeared slowly and the formation of 8-ethylcaffeine was observed by the presence of appropriate ^{13}C and ^{1}H resonance signals along with ^{14}N NMR studies. A solution of methyl hydrazine in 6 M NH_3 yielded a broad ^{14}N signal (−299 ppm); addition of a 25 M solution of $Co(NO_3)_2$ yielded signals correlating with -NH-NH_2 (−262 ppm, −331 ppm). Thus we observe that the oxidation of hydrazine with cobalt(III) takes place prior to alkylation of the alkylated xanthine.

This interpretation implies coordination of the alkyl hydrazine to cobalt(III) and is supported by the fact that methyl and ethyl hydrazine have been demonstrated to act as unidentate or bidentate bridging ligands towards cobalt(III) [13,14]. The rapid exchange reactions studied in alkylcobalt(III) complexes allow detection of alkyl radical released during the decomposition in aqueous solution. For example, in the case of pentaammine methylcobalt(III) complex $[Co(NH_3)_2 (CH_3)(NO_3)_2]$ the methyl radical can be trapped by α-phenyl-*N-tert*-butyl-nitrone (PBN) with the appearance of a (^{14}N): 16.89 G signal, and furthermore, on addition of caffeine, there were no signals observed due to a methyl adduct of PBN.

Table 1. The % conversion of C-8 substituted alkyl xanthines.

Product	R^1	R^2	R^3	R	Conversion	Expected yeild mmol	Isolated Yeild g/mmol
8-ethylcaffeine	CH_3	CH_3	CH_3	Et	20%	0.16	10 mg/0.045 mmol
8-*tert*-butyl-3-isobutyl-1-methyl xanthine	CH_3	iBu	H	tBu	85%	0.85	110 mg/0.39 mmol
8-*tert*-butylcaffeine	CH_3	CH_3	CH_3	tBu	55%	0.35	54 mg/0.2 mmol
8-*tert*-butyl theophylline	CH_3	CH_3	H	tBu	95%	0.49	102 mg/0.43 mmol
8-*tert*-butyl theobromine	H	CH_3	CH_3	tBu	15%	0.1	16 mg/0.17 mmol
8-isopropyl -3-isobutyl-1-methyl xanthine	CH_3	iBu	H	iPr	70%	0.7	20 mg/0.75 mmol
8-isopropyl caffeine	CH_3	CH_3	CH_3	iPr	58%	0.6	40 mg/0.16 mmol
8-isopropyl theophylline	CH_3	CH_3	H	iPr	67%	0.67	35 mg/0.15 mmol
8-isopropyl theobromine	H	CH_3	CH_3	iPr	90%	0.9	30 mg/0.15 mmol
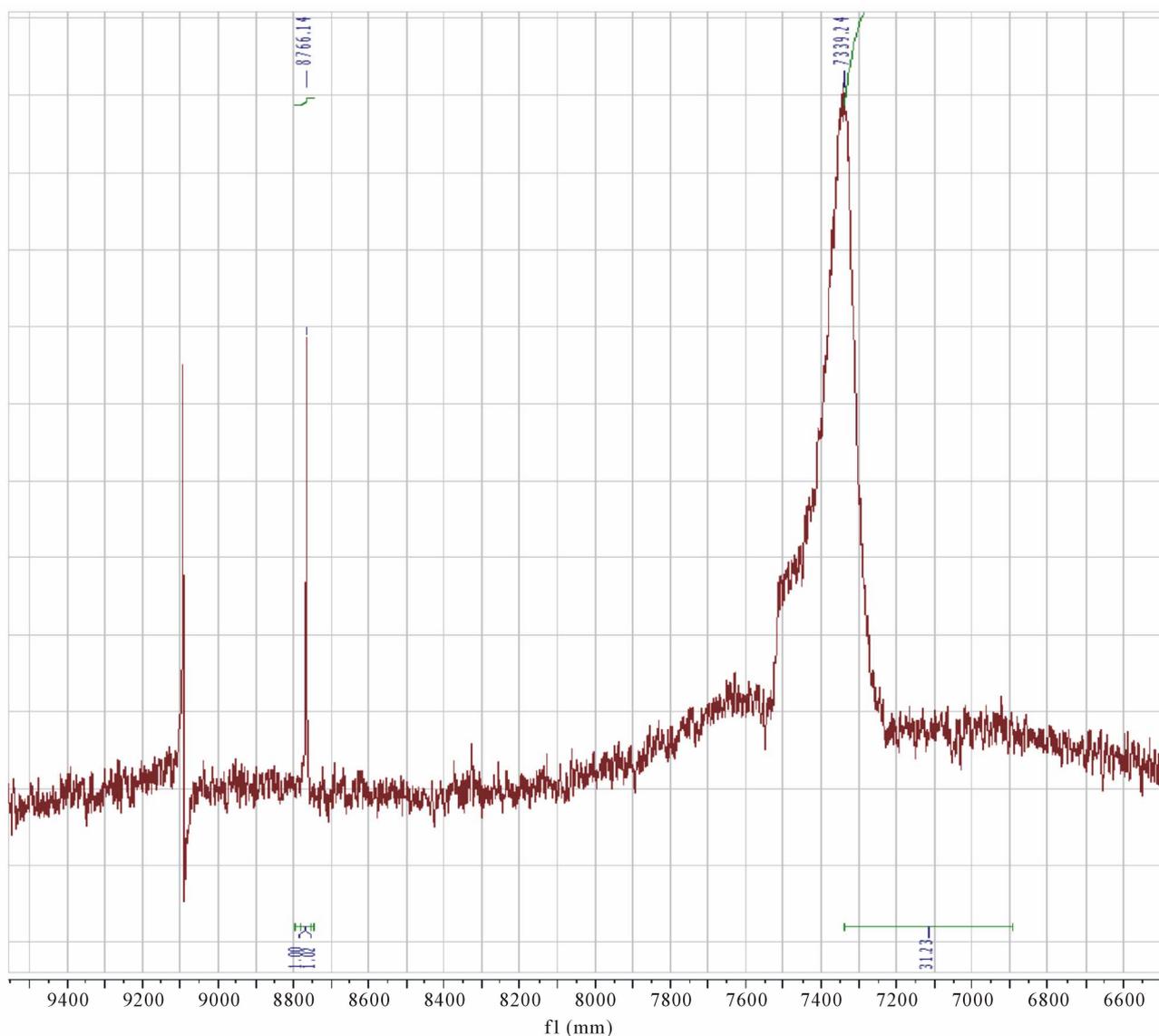
Figure 3. ^{59}Co NMR signal at δ = 8759 ppm [(NH$_3$)$_5$CoOOCo(NH$_3$)$_5$]$^{4+}$ cation, and δ = 7370 ppm [Co(NH$_3$)$_5$(CH$_3$)]$^{2+}$ cation in DMSO-d6.

4. CONCLUSION

We report that cobalt(III) in aqueous ammonia solution serves as a catalyst for obtaining new carbon-carbon bonds by homolytic aromatic substitution. The amminecobalt(III)-promoted aerial oxidation of alkyl hydrazines afforded alkyl radicals, and some primary alkyl radicals were trapped by pentaamminecobalt(III) to form alkyl cobalt(III) cations [15]. However, these compounds are labile and decomposed to return alkyl radicals. It has been previously shown that the $[Co(NH_3)_5(CH_3)]^{2+}$ cation acts as a methylating agent toward the C-8 atom of purine nucleotides [16-18]. We have applied a number of alkyl radicals for the preparation of C-8 substituted alkyl xanthines. We were unable to obtain evidence of a cobalt(III) species with both an alkyl hydrazine ligand and a peroxo ligand. However, this does not exclude the possibility of such a species existing as a reactive intermediate. It may be speculated that a cobalt(III) species with both an alkyl hydrazine ligand and a peroxo ligand is very short-lived due to rapid oxidation of alkylhydrazine.

5. ACKNOWLEDGEMENTS

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