

Catalytic Oxidation of Certain Xanthine Alkaloid Compounds under Conventional and Non-Conventional Conditions

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Abstract: Oxidation of Xanthine alkaloids such as Xanthine (XAN), hypoxanthine (HXAN), caffeine ¹(CAF), theophylline (TPL), theobromine (TBR), have been undertaken by Ru(III) in acetonitrile medium. The reaction is too sluggish in solution phase, but moderately fast in presence of Poly ethylene glycols (PEG) such as PEG-200, 300,400&600. PEG bound Ru(III) [H-(OCH₂-CH₂)_n-O-RuCl₂(H₂O)₃(CH₃CN)₂] is considered to be more reactive than Ru(III) and thus accelerate the reaction rates. However, the reactions are dramatically enhanced under microwave irradiations. Present protocol has several advantages, such as solvent-free conditions, during work-up, fast reaction times, high yields, eco-friendly operational and experimental simplicity, readily available additives as catalysts.

Keywords: Xanthine Alkaloids, One and two electron Oxidizing Agents, Poly Ethylene Glycols (PEGs), Microwave Irradiations

I. Introduction

Transition metal atoms have one s, three p, and five d orbitals that possess geometrical and energetic features suitable for bonding with the ligands. It is well known that the physical and chemical properties of transition metal materials depend on the size and shape. Platinum-group metal ions are special class of transition metal ions which have been used as catalysts in redox reactions for the past several decades. The uses of such platinum-group metal catalysts reveal mechanistic details of redox reactions, providing great advantages in the interpretation of reaction. Hence, studies on the use of platinum-group metal ions either alone or in binary mixtures as catalysts in many redox reactions have been gaining interest. All second and third-row transition metals form exclusively low spin complexes, whereas Ruthenium is special in the stability of adjacent oxidation states, especially Ru(II), Ru(III) (as in the parent RuCl₃·xH₂O) and Ru(IV). Ruthenium, the heavier homologue of iron, has been of great significance in coordination chemistry because of the fascinating electron transfer and energy transfer properties displayed by the complexes of this metal. Ruthenium and its chloro complexes particularly in the (+3) oxidation state have evinced a great deal of interest in recent years because of their use in homogeneous catalysis for catalyzing a wide varieties of redox and hydrogenation reactions. Ruthenium(III)chloride and its EDTA complexes have recently been successfully employed as catalysts in the oxidation of allyl alcohol, ascorbic acid, and cyclohexanol.

Recently Vinod Kumar et al studied the catalytic applications of Ru (III), Os (VIII), Pd (II), and Pt (IV) species metal ions oxidative conversion of folic acid (FA) to pterin-6-carboxylic acid, p-aminobenzoic acid and glutamic acid by sodium N-bromo-p-toluenesulfonamide (bromamine-T; BAT) in alkaline medium. It is customary to measure the efficiency of a catalyst by the number of reusable cycles. Similarly, the value of a new solvent medium basically depends on its environmental impact, the ease with which it could be recycled, and solvent properties viz.,

low vapor pressure, non-flammability and high polarity for solubilization. In performing the majority of organic transformations, solvents also play an important role in mixing the ingredients to make the system homogeneous and allow molecular interactions to be more efficient. Polyethylene glycol (PEG) is a condensation polymer of ethylene oxide and water with the general formula $[H(OCH_2-CH_2)_n-OH]$, where n is the average number of repeating oxyethylene groups typically from 4 to about 180. The low molecular weight members from $n=2$ to $n=4$ are diethylene glycol, triethylene glycol and tetraethylene glycol respectively, which are produced as pure compounds. The wide range of chain lengths provides identical physical and chemical properties for the proper application selections directly or indirectly in the field of chemical and biological sciences. In recent past Polyethylene glycols (PEG) have been used as catalysts, catalyst supports and also have been found to be an inexpensive, non-toxic, environmentally friendly reaction medium, which avoid the use of acid or base catalysts. A perusal recent literature shows a broad spectrum of uses of PEGs in chemical sciences including PEG mediated/catalyzed oxidations. Even though the use of Ru (III) as non toxic and homogeneous catalyst has been reported by several workers in acidic and alkaline media, nearly no work has been done to reveal the mode of catalyzed reaction in PEG medium. Nevertheless, there are few reports on the Oxidation reactions conducted in PEG-200 and PEG-400. Moreover PEG can be recovered after completion of the reactions and recycled/reused in another batch. Inspired by the striking features of PEG the author wants to use it as a catalyst by avoiding the use of acid in the present study viz., Ru(III) triggered oxidation of certain xanthine alkaloid compounds.

For the past several years, our group has focused its attention in designing synthetic protocols using a variety of eco friendly materials such as Poly ethylene glycols and unconventional energy sources (such as microwave irradiation and ultrasound) to enhance Vilsmeier–Haack (VH) and Hunsdiecker reactions. Dramatic rate accelerations followed by an increase in the product yield were observed in all these reactions. Encouraged by the striking features and applications of PEGs and microwave irradiation in chemical processes and organic synthesis, coupled with zeal to employ atom economy eco-friendly reagents, the author proposes to take up Oxidation of certain biologically important compounds such as xanthine(XAN), hypoxanthine(HXAN), caffeine (CAF), theophylline (TPL), theobromine (TBR), using Ru(III). The proposed work is taken up different stages (a) to conduct the reactions under and microwave conditions to save energy (b) to conduct the reactions in a mortar by grinding with a pestle under solvent-free conditions or by using microwave irradiation under solid phase conditions.

II. Material And Methods

All chemicals used were of analytical grade. Doubly distilled water (distilled over alkaline $KMnO_4$ and acid dichromate in an all glass apparatus) was used whenever required. Acetonitrile and other solvents were HPLC grade and used as such throughout the work.

Xanthine (XAN), hypoxanthine(HXAN), caffeine (CAF), theophylline (TPL), theobromine (TBR), Ru(III) were prepared according the method of Corey as cited in literature

Typical experimental procedure for oxidation of xanthine alkaloids: A neat mixture of xanthine alkaloid (1.0 mmol) dissolved in acetonitrile and Ru(III) (1.2 mmol) were placed in a 50ml R.B. flask and refluxed for several hours till the reaction is completed as ascertained by TLC. After completion of the reaction, the contents were extracted with dichloromethane (2 - 25 ml) and washed with water (40 ml). The reactions were too sluggish even under reflux conditions. The dichloromethane layer was separated and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (SiO_2 , ethyl acetate–hexane 1:2) to afford the end product. Main product of oxidation was characterized as uric acid derivative from IR, NMR and Mass spectroscopic studies.

Table no 1: NMR and Mass spectral data for selected reaction Products

Entry	Substrates	Product	m/z	Spectral Data
				¹ H NMR
1	Caffeine	1,3,7-Try methyl uric acid	210	δ 3.35(N-CH ₃); δ 3.41(N-CH ₃) δ 3.73(N-CH ₃); δ 13.49(O-H)
2	Theobromine	3,7-Dimethyl uric acid	196	δ 9.45(N-H); δ 3.24(N-CH ₃) δ 3.73(N-CH ₃); δ 13.49(O-H)
3	Theophyllene	1,3-Dimethyl uric acid	196	δ 3.35(N-CH ₃); δ 3.41(N-CH ₃) δ 13.43(O-H); δ 13.92(N-H)
4	Xanthine	Uric cid	168	δ 13.91(N-H); δ 9.48(N-H) δ 13.41(O-H); δ 15.53(N-H)
5	Hypoxanthine	Uric acid	168	δ 13.91(N-H); δ 9.48(N-H) δ 13.41(O-H); δ 15.53(N-H)

Typical experimental procedure for PEG mediated oxidation of xanthine alkaloids: A neat mixture of xanthine alkaloid (1.0 mmol) dissolved in acetonitrile, PEG and Ru(III) (1.2 mmol) were placed in a 50ml R.B. flask and refluxed for several hours till the reaction is completed as ascertained by TLC. The reactions times decreased in presence of PEGs. After completion of the reaction, the contents were treated according the above procedure to pure product of oxidation. (Scheme 1)

Typical experimental procedure for Microwave irradiated (MWI) oxidation of xanthine alkaloids: A neat mixture of xanthine alkaloid (1.0 mmol) dissolved in acetonitrile, PEG and Ru(III) (1.2 mmol) were placed in a 50ml R.B. flask. The reaction mixture was inserted in a silica gel bath and placed in a laboratory microwave oven and irradiated (700W) three times for three to five minutes with a period of 20 seconds time intervals. After completion of the reaction, the contents were treated according the above procedure to pure product of oxidation.(Scheme 1)

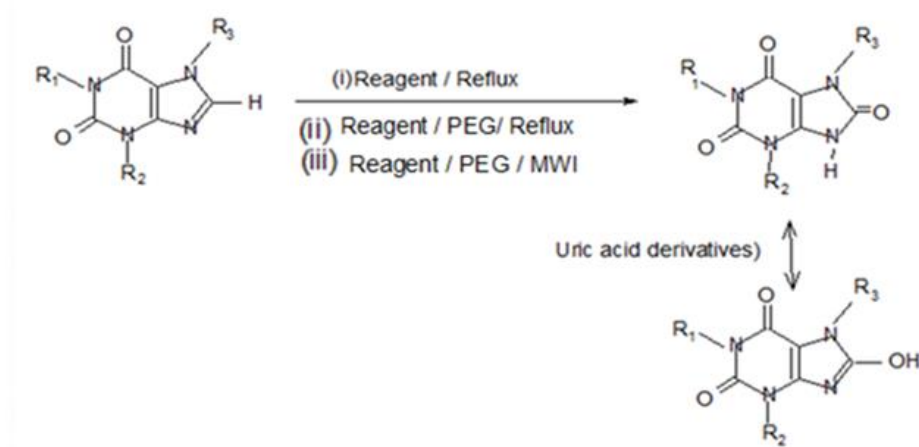


Figure no 1: Oxidation of Xanthine(s) Reaction

- Scheme-1: Reagent = Ru(III)
- Substrate = Xanthine, Hypoxanthine, Caffeine, Theophylline, and Theobromine
- PEGs- PEG -200, PEG -300, PEG -400 and PEG – 600

III. Results

Oxidation reactions with xanthine alkaloids were too sluggish in acetonitrile media even under reflux conditions with longer reaction times. However, PEG mediated reactions are underwent with moderate progress, which could be seen from the data presented in tables 2(A)&2(B) and figures 2& 3. These data also depict that nature of Oxidizing agent had significant effect on the rate of oxidation. The structural variation of PEG had influence on the rate of oxidation.

Table 2: Oxidation of Caffeine and its related compounds in presence of Ru(III) and various Polyethylene Glycols

Table no 2A: Under Solution Phase conditions, Temp: 80^oC-90^oC

Entry	1a	1b	1c	1d	1e
Substrate	CAF	TPL	TBR	HXAN	XAN

ENTRY	PEG-200		PEG-300		PEG-400		PEG-600	
	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)
1a	7.00	75	8.00	73	8.30	72	9.00	70
1b	7.30	74	8.30	73	8.30	72	8.30	70
1c	8.00	72	8.30	70	9.00	70	8.30	70
1d	8.30	72	9.00	70	9.00	70	8.00	68
1e	9.30	70	9.30	68	9.30	68	8.00	65

Table no 2 (B): Under Microwave Irradiation

ENTRY	PEG-200		PEG-300		PEG-400		PEG-600	
	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)
1a	180	80	200	75	180	72	150	70
1b	200	78	210	73	180	72	150	70
1c	200	78	210	70	180	72	150	68
1d	240	72	250	68	200	68	180	68
1e	240	70	250	65	200	65	180	65

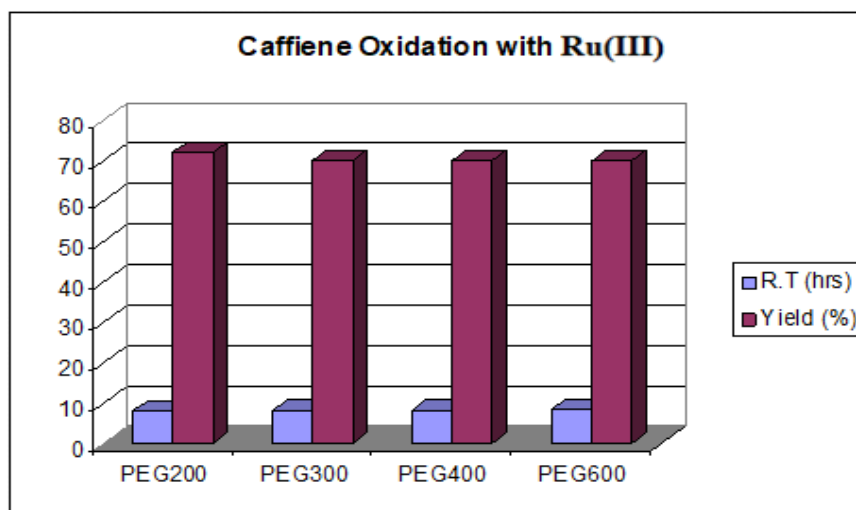


Figure no 2: Effect of Structure of PEG on Ru(III) Oxidation of Caffeine Under solution Phase

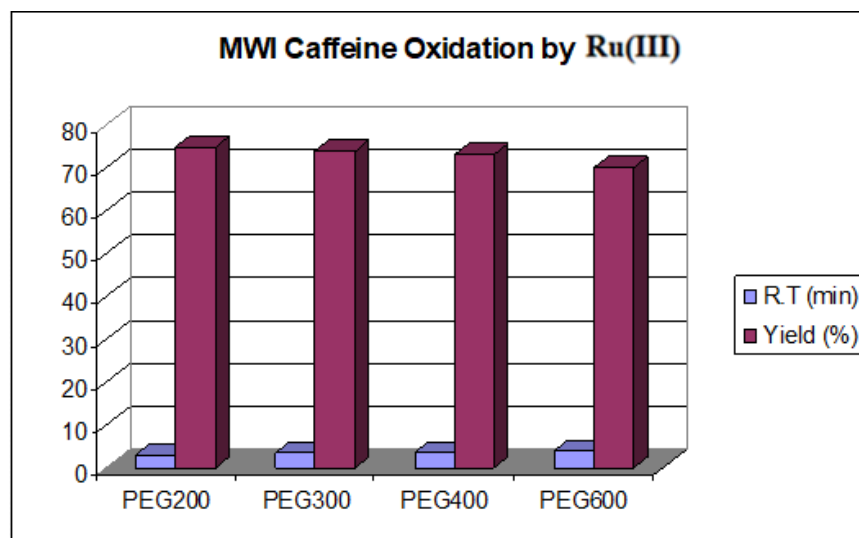


Figure no 3: Effect of Structure of PEG on Ru(III) Oxidation of Caffeine Under Microwave Irradiation

IV. Conclusion

In summary, we have developed a simple and efficient method for oxidation of xanthine alkaloids using PEGs. Xanthine alkaloid oxidation is too sluggish in solution phase but moderately progressed in presence of PEGs. However, the reactions are dramatically enhanced under microwave irradiations. Present protocol has several advantages, particularly solvent-free conditions, during work-up, fast reaction times, high yields, eco-friendly operational and experimental simplicity, readily available additives as catalysts.

References

- [1]. A. Haimov and R. Neumann, "Polyethylene glycol as a non-ionic liquid solvent for polyoxometalate catalyzed aerobic oxidation," *Chemical Communications*, no. 8, pp. 876–877, 2002.
- [2]. N. L. Bauld, "Cation radical cycloadditions and related sigmat-ropic reactions," *Tetrahedron*, vol. 45, no. 17, pp. 5307–5363, 1989.
- [3]. M. Schmittel, "Umpolung of ketones via enol radical cations," in *Topics in Current Chemistry*, vol. 169, pp. 183–230, 1994.
- [4]. M. Schmittel and A. Langels, "A short-lived radical dication as a key intermediate in the rearrangement of a persistent cation: the oxidative cyclization of 2,2-dimesityl-1-(4-N,N-dimethylaminophenyl)ethanol," *Angewandte Chemie*, vol. 36, no. 4, pp. 392–395, 1997.
- [5]. M. Rock and M. Schmittel, "Controlled oxidation of enolates to α -carbonyl radicals and α -carbonyl cations," *Journal of the Chemical Society, Chemical Communications*, no. 23, pp. 1739–1741, 1993.
- [6]. B.B. Snider and T. Kwon, "Oxidative cyclization of δ - and ϵ -unsaturated enol silyl ethers and unsaturated siloxycyclopropanes," *The Journal of Organic Chemistry*, vol. 57, no. 8, pp. 2399–2410, 1992.
- [7]. R. Kumar, P. Chaudhary, S. Nimesh, and R. Chandra, "Polyethylene glycol as a non-ionic liquid solvent for Michael addition reaction of amines to conjugated alkenes," *Green Chemistry*, vol. 8, no. 4, pp. 356–358, 2006.
- [8]. K. Tanemura, T. Suzuki, Y. Nishida, and T. Horaguchi, "Aldol condensation in water using polyethylene glycol 400," *Chemistry Letters*, vol. 34, no. 4, pp. 576–577, 2005.
- [9]. L. Heiss and H. J. Gais, "Polyethylene glycol monomethyl ether-modified pig liver esterase: preparation, characterization and catalysis of enantioselective hydrolysis in water and acylation in organic solvents," *Tetrahedron Letters*, vol. 36, no. 22, pp. 3833–3836, 1995.
- [10]. V. N. Vasudevan and S. V. Rajendra, "Microwave-accelerated Suzuki cross-coupling reaction in polyethylene glycol (PEG)," *Green Chemistry*, no. 3, pp. 146–148, 2001.
- [11]. P. Anastas and J. Warner, "Green Chemistry: Theory and Practice," Oxford University Press, New York, 1998.
- [12]. D. E. Metzler, "Biochemistry: The Chemical Reactions of Living Cells," Academic Press, New York, 1977, p. 882.
- [13]. D. M. Graham, "Caffeine—Its Identity, Dietary Sources, Intake and Biological Effects," *Nutrition Reviews*, Vol. 36, No. 4, 1978, pp. 97–102.
- [14]. J. M. Harris and S. Zalipsky, "Poly(Ethylene Glycol): Chemistry and Biological Applications," ACS Books, Washington DC, 1997. doi:10.1021/bk-1997-0680
- [15]. R. S. Varma, "Microwaves: Theory and Application in Material Processing IV," D. E. Clark, W. H. Sutton and D.A. Lewis, Eds., American Ceramic Society, Westerville, 1997, p. 357.