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Poly Ethylene Glycols (PEG) and Micelles as Efficient Catalysts for the Oxidation of Xanthine Derivatives under Conventional and Non-Conventional Conditions

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Abstract

Oxidation of Xanthine alkaloid have been studied with various one and two electron oxidizing agents using PEGs and micelle forming surfactants. The reaction is too sluggish in solution phase, but moderately fast in presence of PEGs and micelles. 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: Oxidation, Xanthine Alkaloids, One and Two Electron Oxidizing Agents, Poly Ethylene Glycols (PEG), Micelle Forming Surfactants, Catalysts, Microwave Irradiations

1. Introduction

Xanthine alkaloids (xanthines) are purine bases, found in body tissues and fluids and in some plants. They are probably the most widely known and used alkaloids, being constituents of popular daily beverages tea and coffee. Xanthine alkaloids include: Caffeine, Theobromine, Pentoxifylline, Theophylline, Aminophylline, Dimenhydrinate, Dyphylline, 1-Methyl-3-isobutylxanthine, Xanthinol Niacinate, Uric Acid, Xanthine.

Xanthine is an intermediate found in the degradation of adenosine mono phosphate (AMP) to uric acid, being formed by oxidation of hypoxanthine. Caffeine, theophylline, and theobromine alkaloids are methylated xanthine derivatives; they differ only in the number and position of methyl substituents around the xanthine ring system. Caffeine alkaloid is a central nervous system (CNS) stimulant. It is also a diuretic and is used in combination with analgesics. Theophylline and theobromine are minor alkaloids of tea; theobromine also occurs in cocoa. Caffeine, theobromine, and theophylline and their derivatives are used in medicine for their bronchodilator effects [1]. Uric acid is an oxidation product of xanthine and hypoxanthine, formed via xanthine oxidase enzyme; it is the final oxidation product of catabolism of purines which originate from food. A decrease in pH, as it occurs in inflamed tissues, facilitates the formation of uric acid crystals, which are the initial cause of gout. Furthermore, xanthine is sparingly soluble in water, and metabolic abnormalities can occasionally lead to its precipitation as aggregates, although xanthine "stones" are quite rare [2]. The N-methyl derivatives of xanthine (see **Table 1**), including theophylline (3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione), theobromine (3,7-dihydro-3,7-dimethyl-1H-purine-2,6-dione), and caffeine (3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione), are alkaloids that are widely distributed in plant products and beverages and are known to have many physiological effects, such as gastric acid secretion, diuresis, and stimulation of the central nervous system [3]. Besides, these compounds are considered to be risk factors for asthma, kidney malfunction and cardiovascular diseases [4].

Solvents play essential roles in chemical processes not only serving to put reactants into contact by dissolution but also affecting rates, chemo-, regio- and stereo-selectivity of the reactions. Until most recently, organic solvents were the most common and perhaps the only choices of solvents among chemists. The most used organic solvents comprise hydrocarbons (including halogenated and aromatic hydrocarbons), ethers and alcohols. Despite the usefulness and importance of these compounds in-

Table 1. NMR and Mass Spectral data for selected reaction products.

Entry	Substrates	Product	Spectral data	
			m/z	^{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 acid	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)

organic reactions they undoubtedly have high flammability and volatility, their hazardness and toxicity have a detrimental impact on the environment. In recent past this scenario has been substantially changed by environmentally benign substitutes (green solvents) for volatile and toxic organic solvents under the concepts of Green Chemistry and green reaction processes [5,6]. Poly (ethylene glycol) (PEG) [7-9], a biologically acceptable polymer used extensively in drug delivery and in bio conjugates as tools for diagnostics has been used as a solvent medium support for various transformations. In recent times PEG has surpassed even ionic liquids in forefront of research PEG is economically cheap and environmentally safe. To date some of the more important reactions have been carried out and investigated in PEG [7-23]. Besides the use of safer solvents, in recent past increasing attention has also been paid for designing eco friend- ly reactions using environmentally safe and economically cheap reagents to prevent environmental pollutions according to the guidelines given by Paul Anastas and John Warner [5]. Recent reviews and publications [24-27] in the field of solvent-free organic synthesis revealed that organic reactions performed under these conditions are not only simple but also satisfy both economical and environmental demands by replacing the toxic solvents. Solvent free reactions further, have gained much attention because of their enhanced selectivity, mild reaction conditions, and associated ease of manipulation. Apart from solvent free organic synthesis, quite some attention has been paid to develop methodologies using ultrasound and microwaves. Methods developed under sonicated [28-33] and microwave irradiated conditions [34-36] proved to good tools to save energy and reduce reaction times to a greater extent. Considerable efforts were also diverted to use economically cheap and environmentally safe reagents as catalysts to design organic synthesis. A survey of literature reveals that Micelles act as a kind of micro reactors and enhance the rate and selectivity of a variety of chemical and biochemical reactions. A close parallelism between enzymatic reactions and micellar reactions has attracted the attention of several synthetic organic chemists and biochemists [37-40]. Far the past several years, our group has focused its attention in designing synthetic protocols using a variety of eco friendly materials such as micelle-forming surfactants and unconventional energy sources (such as microwave irradiation and ultrasound) to enhance Vilsmeier-Haack (VH) and Hunsdiecker reactions [40-43]. 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, micelles, 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 commonly available laboratory desktop eco friendly reagents such as hydrogen peroxide (H_2O_2), tetra butyl Hydrogen peroxide (TBHP), Potassium peroxy disulfate ($K_2S_2O_8$), Potassium peroxy diphosphate ($K_4P_2O_8$), Sodium perborate ($NaBO_4$), Potassium periodate (KIO_4), Pyridinium chloro chromate (PCC) and Quinolonium chloro chromate (QCC). The proposed work is taken up different stages 1) to conduct the reactions under and microwave conditions to save energy; 2) 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.

2. Experimental Details

2.1. Materials 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.

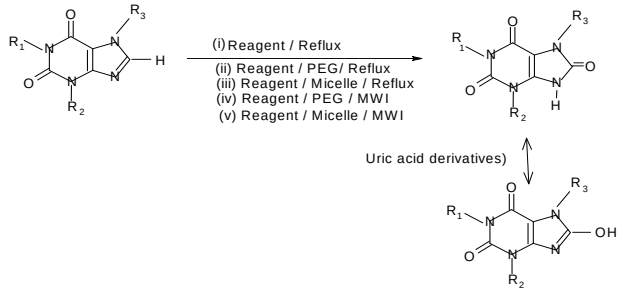
Xanthine (**XAN**), hypoxanthine (**HXAN**), caffeine (**CAF**), theophylline (TPL), theobromine (TBR), hydrogen peroxide(H_2O_2), tetra butyl Hydrogen peroxide (TBHP), Potassium peroxy disulfate ($K_2S_2O_8$), Potassium peroxy diphosphate ($K_4P_2O_8$) and Sodium perborate ($NaBO_4$), and Potassium periodate(KIO_4), were procured from Aldrich or E-Merck. Pyridinium chloro chromate (PCC) and Quinolonium chloro chromate (QCC) were prepared according the method of Corey as cited in literature [44].

2.2. Typical Experimental Procedure for Oxidation of Xanthine Alkaloids

A neat mixture of xanthine alkaloid (1.0 mmol) dissolved in acetonitrile and Reagent (1.2 mmol) were placed in a 50 ml 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 1**).

2.3. Typical Experimental Procedure for PEG/ Micelle Mediated Oxidation of Xanthine Alkaloids

A neat mixture of xanthine alkaloid (1.0 mmol) dissolved in acetonitrile, PEG / micelle forming surfactant and Reagent (1.2 mmol) were placed in a 50 ml 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 treated according the above procedure to pure product of oxidation (**Scheme 1**). The reactions times decreased in presence of PEG/ micelles (**Tables 2** to **5**).



Scheme 1. Reagent = H_2O_2, TBHP, $K_2S_2O_8$, $K_4P_2O_8$, KIO_4, $NaBO_4$, PCC, QCC; Substrate = Xanthine, Hypoxanthine. Caffeine, Theophylline, and Theobromine PEGs-PEG-200, PEG-300, PEG-400 and PEG-600; Micelle-TX-100, SDS, CTAB.

Table 2. Oxidation of caffeine and its related compounds in presence of TX-100 and various oxidizing agents.

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

(a) Under solution phase conditions

ENTRY	TBHP		H_2O_2		$K_2S_2O_8$		$K_4P_2O_8$		PCC		QCC		$NaBO_4$		KIO_4	
	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)
1a	8.30	72	8.30	70	7.50	72	7.20	70	7.50	72	7.50	70	8.20	70	8.30	70
1b	8.30	72	8.30	70	7.50	72	7.20	70	8.20	70	7.50	70	8.20	70	8.30	70
1c	8.30	72	8.30	70	7.50	72	7.20	70	8.20	70	7.50	70	8.30	69	8.30	70
1d	9.00	70	9.00	68	8.20	70	8.00	68	8.20	70	8.20	68	8.40	69	8.50	68
1e	9.00	68	9.00	68	8.20	68	8.00	65	8.30	65	8.20	65	8.40	68	8.50	68

(b) Under microwave irradiation.

ENTRY	TBHP		H_2O_2		$K_2S_2O_8$		$K_4P_2O_8$		PCC		QCC		$NaBO_4$		KIO_4	
	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)
1a	200	74	200	73	210	75	200	78	210	74	210	74	220	70	210	70
1b	210	72	210	70	210	72	210	75	210	70	210	72	220	70	210	70
1c	210	72	210	70	210	72	210	75	210	70	210	72	220	70	210	70
1d	240	69	250	68	220	70	240	72	240	68	240	70	240	68	230	68
1e	240	68	250	68	220	68	240	70	240	65	240	68	240	65	230	68

Table 3. Oxidation of caffeine and its related compounds in presence of SDS and various oxidizing agents.

(a) Under solution phase conditions.

ENTRY	TBHP		H_2O_2		$K_2S_2O_8$		$K_4P_2O_8$		PCC		QCC		$NaBO_4$		KIO_4	
	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)
1a	9.00	70	9.00	70	8.30	70	8.30	70	8.40	70	8.20	70	8.40	70	9.00	70
1b	9.00	70	9.15	70	8.30	70	8.30	70	8.40	70	8.30	70	8.40	70	9.00	70
1c	9.00	70	9.20	70	8.30	70	8.30	70	8.50	70	8.30	70	8.40	69	9.00	68
1d	9.15	70	9.30	68	8.40	68	8.45	70	9.00	70	8.50	68	9.00	69	9.10	68
1e	9.15	68	9.30	68	8.40	68	8.45	69	9.00	68	8.50	65	9.00	68	9.10	65

(b) Under microwave irradiation.

ENTRY	TBHP		H_2O_2		$K_2S_2O_8$		$K_4P_2O_8$		PCC		QCC		$NaBO_4$		KIO_4	
	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)
1a	240	72	240	70	220	72	220	72	220	72	220	72	240	70	220	70
1b	240	72	240	70	220	72	220	72	220	70	220	70	240	70	220	70
1c	240	72	240	70	220	72	220	72	220	70	220	70	240	70	220	70
1d	270	69	270	69	240	70	260	70	250	68	260	69	260	68	240	68
1e	270	68	270	68	240	65	260	70	250	65	260	68	260	65	240	65

Table 4. Oxidation of Caffeine and its related compounds in presence of CTAB and various oxidizing agents.

(a) Under solution phase conditions.

ENTRY	TBHP		H_2O_2		$K_2S_2O_8$		$K_4P_2O_8$		PCC		QCC		$NaBO_4$		KIO_4	
	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)
1a	9.30	72	9.20	70	9.00	72	9.00	72	9.20	73	9.10	70	9.00	70	9.30	70
1b	9.30	70	9.20	70	9.00	70	9.00	70	9.20	70	9.20	70	9.10	68	9.30	68
1c	9.30	70	9.20	70	9.00	70	9.00	70	9.20	70	9.20	70	9.15	68	9.30	68
1d	9.45	68	9.40	68	9.20	68	9.30	70	9.30	71	9.30	65	9.30	68	9.40	66
1e	9.45	68	9.40	68	9.20	65	9.30	68	9.30	68	9.30	65	9.30	68	9.40	64

(b) Under microwave irradiation.

ENTRY	TBHP		H_2O_2		$K_2S_2O_8$		$K_4P_2O_8$		PCC		QCC		$NaBO_4$		KIO_4	
	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)
1a	270	70	270	70	240	72	240	72	260	70	260	70	270	70	240	70
1b	270	70	270	70	240	72	240	72	260	70	260	70	270	70	240	70
1c	270	70	270	70	240	72	240	72	260	70	260	70	270	70	240	70
1d	290	69	300	68	270	70	280	70	280	68	280	69	280	68	260	68
1e	290	68	300	68	270	68	280	68	280	65	280	65	280	65	260	68

Table 5. Oxidation of caffeine and its related compounds in presence of PEG-300 and various oxidizing agents.

(a) Under solution phase conditions.

ENTRY	TBHP		H_2O_2		$K_2S_2O_8$		$K_4P_2O_8$		PCC		QCC		$NaBO_4$		KIO_4	
	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)
1a	8.15	70	8.45	70	7.40	72	7.50	72	7.45	70	7.45	72	8.00	70	8.00	70
1b	8.15	70	8.45	70	7.40	72	7.50	70	8.15	70	7.45	70	8.20	70	8.00	70
1c	8.15	70	8.45	70	7.40	72	7.50	70	8.15	70	7.45	70	8.20	69	8.00	70
1d	9.00	68	9.30	68	8.30	70	8.20	70	8.30	68	8.30	68	8.30	68	8.45	68
1e	9.00	68	9.30	65	8.30	68	8.20	70	8.30	68	8.30	68	8.30	65	8.45	68

(b) Under microwave irradiation.

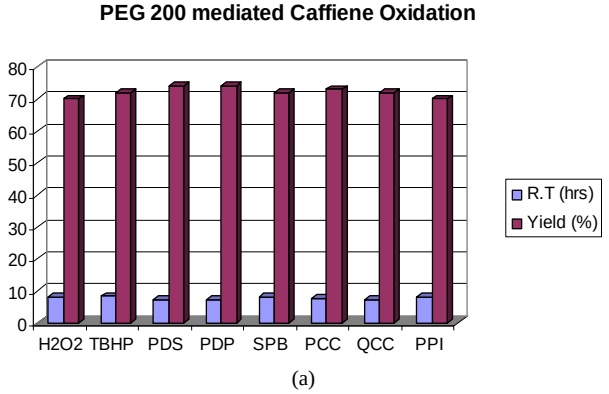
ENTRY	TBHP		H_2O_2		$K_2S_2O_8$		$K_4P_2O_8$		PCC		QCC		$NaBO_4$		KIO_4	
	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)
1a	200	74	210	75	200	78	160	80	200	75	200	75	200	73	200	73
1b	200	70	210	70	200	72	160	76	210	72	200	74	210	72	200	72
1c	200	70	210	70	200	72	160	75	210	70	200	72	200	72	210	72
1d	240	68	250	65	220	68	180	70	240	68	220	70	210	68	220	68
1e	240	68	250	65	220	65	180	68	240	65	220	68	220	65	220	68

2.4. Typical Experimental Procedure for Microwave Irradiated (MWI) Oxidation of Xanthine Alkaloids

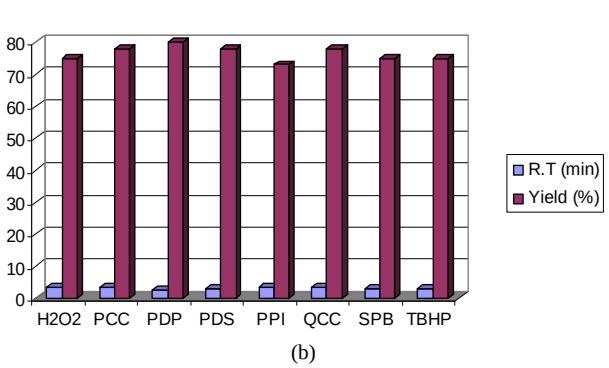
A neat mixture of xanthine alkaloid (1.0 mmol) dissolved in acetonitrile, PEG/micelle forming surfactant and Reagent (1.2 mmol) were placed in a 50 ml R.B. flask. The reaction mixture was inserted in a silica gel bath and placed in a laboratory microwave oven and irradiated (700 W) three times for three 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**). The reactions times decreased from several hours to few minutes under microwave irradiation in presence of PEG/ micelles (**Tables 2-5**).

3. Results & Discussion

Oxidation reactions with xanthine alkaloids were too sluggish in acetonitrile media even under reflux conditions with longer reaction times. However, micelle mediated and PEG mediated reactions are underwent with moderate progress, which could be seen from the data presented in **Table 2-5** and **Figures 1-4**. These data also depict that nature of Oxidizing agent had significant effect on the rate of oxidation. Peroxide reagents are found superior over other reagents while structural variation of PEG had only a little influence on the rate of oxidation. But when the reactions are conducted in micellar media noticeable rate enhancements were noticed with TX-100 on par with PEG. However, anionic (SDS) and ca-



(a)



(b)

Figure 1. PEG mediated caffeine oxidation with various reagents. (a) Under solution phase; (b) Under Microwave Irradiation.

tionic (CTAB) micelle mediated reactions are relatively less effect over TX-100 (**Tables 2-4**; **Figures 3(a)**, **3(b) 4(a)** and **4(b)**). It is interesting to note that PEG (**Table 5**; **Figures 1**, **2(a)** and **2(b)**), and TX-100 probably behave in the same way because both of them have polyoxy ethylene moieties.

The efficient catalytic activity of micelles could be attributed to the fact micelles act as "micro reactors" to facilitate the reactions through electrostatic/hydrophobic interactions operating between reactive species [37-41]. The catalytic activity of PEGs could be explained in similar lines to those of non-ionic micelles due to their structural resemblance. Reaction times are reduced from several hours (6 to 9 hr) to few minutes (6 to 9 minutes) between reactions performed under standard oil-bath conditions (heating under reflux) and microwave irradiations. The observed dramatic rate enhancements under microwave irradiations in the present study could be well explained due to the formation of "molecular radiators" by direct coupling of microwave energy to specific reagents in homogeneous solution (microscopic hotspots) [45-47] and by the elimination of wall effects caused by inverted temperature gradients.

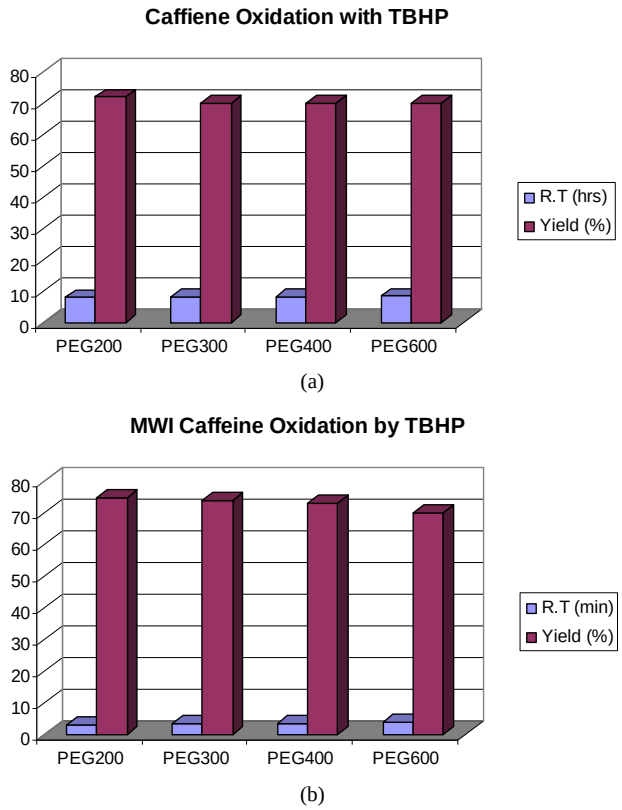


Figure 2. Effect of structure of PEG on TBHP oxidation of caffeine (a) Under solution phase; (b) Under microwave Irradiation.

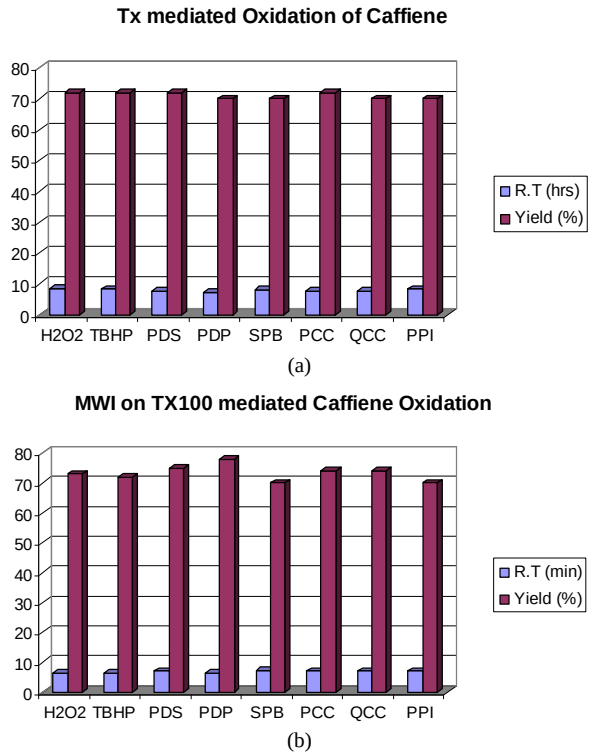


Figure 3. TX-100 mediated caffeine oxidation with various reagents. (a) Under solution phase; (b) Under microwave irradiation.

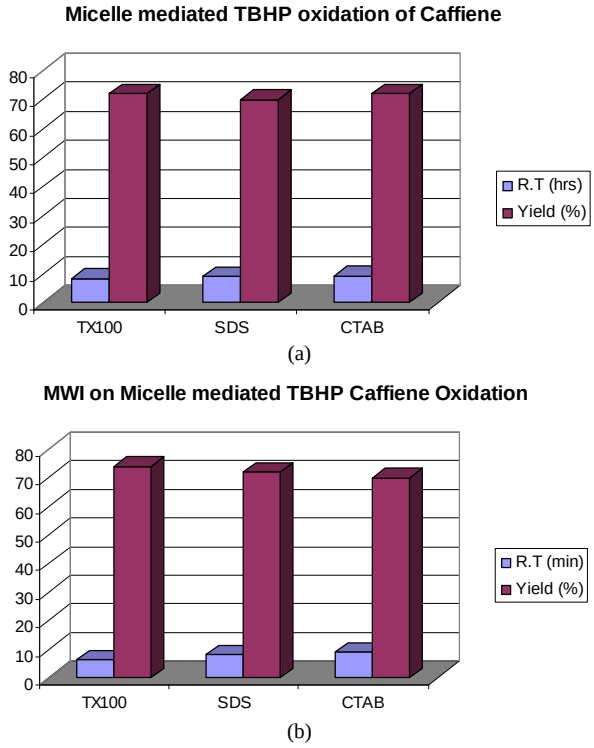


Figure 4. TBHP oxidation of caffeine under micellar conditions. (a) Under micellar conditions in solution phase; (b) Micellar effects under microwave irradiation.

4. Conclusions

In summary, we have developed a simple and efficient method for oxidation of xanthine alkaloids using PEGs and micelle forming surfactants. Xanthine alkaloid oxidation is too sluggish in solution phase but moderately progressed in presence of PEGs and micelles. 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.

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Electronic Supplementary Material

Elaborated data presented separately in **Tables S1-S3** as supplementary data depict the oxidation of various xanthine related compounds with different oxidizing ag- ents in other PEG media.

Table S1. Oxidation of caffeine and its related compounds in presence of PEG-200 and various oxidizing agents.

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

(a) Under solution phase conditions.

ENTRY	TBHP		H_2O_2		$K_2S_2O_8$		$K_4P_2O_8$		PCC		QCC		$NaBO_4$		KIO_4	
	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)
1a	8.00	72	8.30	70	7.30	74	7.30	74	7.45	73	7.30	72	8.00	72	8.00	70
1b	8.00	72	8.30	70	7.30	73	7.30	72	8.00	70	7.45	70	8.00	70	8.00	70
1c	8.00	72	8.30	70	7.30	72	7.30	72	8.00	70	7.45	70	8.00	69	8.00	70
1d	9.00	70	9.30	68	8.00	70	8.00	68	8.20	68	8.00	68	8.30	68	8.45	68
1e	9.00	68	9.30	68	8.00	68	8.00	65	8.30	68	8.00	68	8.30	68	8.45	68

(b) Under microwave irradiation.

ENTRY	TBHP		H_2O_2		$K_2S_2O_8$		$K_4P_2O_8$		PCC		QCC		$NaBO_4$		KIO_4	
	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)
1a	180	75	200	75	180	78	150	80	180	75	180	75	200	73	200	73
1b	200	70	210	70	180	72	150	78	210	72	200	74	210	72	200	72
1c	200	70	210	70	180	72	150	78	180	70	180	72	200	72	210	72
1d	240	68	250	65	200	68	180	72	240	68	220	70	210	68	220	68
1e	240	65	250	65	200	65	180	70	240	65	220	68	220	65	220	68

Table S2. Oxidation of caffeine and its related compounds in presence of PEG-400 and various oxidizing agents.

(a) Under solution phase conditions.

ENTRY	TBHP		H_2O_2		$K_2S_7O_8$		$K_4P_2O_8$		PCC		QCC		$NaBO_4$		KIO_4	
	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)
1a	8.30	70	8.45	70	8.00	72	8.00	72	8.15	70	8.00	72	8.20	70	8.15	70
1b	8.30	68	9.00	70	8.15	70	8.00	70	8.30	70	8.00	70	8.30	69	8.20	68
1c	8.30	68	9.00	70	8.15	70	8.00	70	8.30	70	8.00	70	8.30	69	8.20	68
1d	9.30	68	9.30	68	8.30	70	8.30	69	8.30	68	8.00	68	8.30	68	8.45	68
1e	9.30	68	9.30	65	8.30	68	8.30	68	8.30	68	8.30	68	8.30	65	8.45	68

(b) Under microwave irradiation.

ENTRY	TBHP		H_2O_2		$K_2S_2O_8$		$K_4P_2O_8$		PCC		QCC		$NaBO_4$		KIO_4	
	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)
1a	210	73	220	75	210	78	180	78	210	74	210	73	210	70	210	72
1b	210	70	220	70	210	72	180	75	210	72	200	72	210	68	220	70
1c	210	70	220	70	210	72	180	74	210	70	200	70	210	68	210	70
1d	260	68	250	65	240	65	200	68	240	65	220	70	220	68	220	68
1e	260	68	250	65	240	65	200	65	240	65	220	68	220	65	220	65

Table S3. Oxidation of caffeine and its related compounds in presence of PEG-600 and various oxidizing agents.

(a) Under solution phase conditions.

ENTRY	TBHP		H_2O_2		$K_2S_2O_8$		$K_4P_2O_8$		PCC		QCC		$NaBO_4$		KIO_4	
	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)	RT (hrs)	Yield (%)
1a	8.45	70	9.00	70	8.20	72	8.20	72	8.30	70	8.20	72	8.30	70	8.30	70
1b	8.45	68	9.20	70	8.30	70	8.20	70	8.45	70	8.20	70	8.30	69	8.30	68
1c	8.45	68	9.20	70	8.30	70	8.20	70	8.45	70	8.20	70	8.30	69	8.30	68
1d	9.45	68	9.40	68	8.45	70	8.40	69	8.45	68	8.40	68	8.40	68	8.45	68
1e	9.45	68	9.40	65	8.45	68	8.40	68	8.45	68	8.40	68	8.40	65	8.45	68

(b) Under microwave irradiation.

ENTRY	TBHP		H_2O_2		$K_2S_2O_8$		$K_4P_2O_8$		PCC		QCC		$NaBO_4$		KIO_4	
	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)	RT (sec)	Yield (%)
1a	240	70	240	72	220	75	200	74	220	74	220	72	220	70	210	70
1b	240	70	250	68	220	70	200	72	220	70	220	70	220	68	220	70
1c	240	70	250	68	220	70	200	72	220	70	220	70	220	68	220	70
1d	280	68	280	65	260	65	220	68	250	65	220	68	240	68	220	68
1e	280	68	280	65	260	65	220	65	250	65	220	68	240	65	220	68

