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## Chemometric approach to evaluate catalytic activity of [CTAB/ 18-Crown-6]: A binary catalytic system for one pot green synthesis of 4-benzylidene-3-methylisoxazol-5(4H)-one derivatives at room temperature

**Deepali Agarwal, Ankita Verma, Jyotsna Dhanik and Virendra Kumar Kasana**

**Abstract**

A highly efficient binary catalytic system [CTAB/ 18-Crown-6] has been developed for one pot three component green synthesis of 4-benzylidene-3-methylisoxazol-5(4H)-one derivatives by reaction of aromatic aldehydes, ethyl acetoacetate and hydroxylamine hydrochloride. Catalytic productivity of [CTAB/ 18-Crown-6] has been studied using different ratio combination of cetyltrimethylammonium bromide (CTAB) and 18-Crown-6 in varying water: ethanol ratio. Percent yield of isoxazol-5(4H)-ones obtained by different [CTAB/ 18-Crown-6] ratio in variable water: ethanol solution were analyzed by descriptive statistical analysis and variable correlation analysis to evaluate the catalytic efficacy of binary [CTAB/ 18-Crown-6] system.

**Keywords:** binary catalytic system, green synthesis, 4-benzylidene-3-methylisoxazol-5(4H)-ones, [CTAB/18-Crown-6], variable correlation analysis, descriptive statistical analysis

**1. Introduction**

Nitrogen containing heterocycles with an oxygen atom are considered as an important class of compounds in medicinal chemistry because of their diversified biological applications [1]. Isoxazol-5(4H)-ones compounds have served as a versatile building block in organic synthesis and have attracted increasing interest due to their significant pharmaceutical and therapeutic properties, such as hypoglycemic, immunosuppressive, anti-inflammatory, and anti-bacterial activities [2-5]. In recent years, many new methods for the synthesis of isoxazol derivatives have been reported, [6-20] each affording variable yields of condensation compounds in solution or under solvent-free conditions. Using the methods indicated above, there are still some limitations, such as the long reaction time, low yields, and the strict reactive condition. Hence, the introduction of efficient and new methods is still in demand.

Macromolecules like cyclodextrin and crown ethers are well known for its host-guest relationship and phase transfer catalytic properties [21-22]. Ionic liquids have recently identified as “green solvents” as well as “green catalysts” because of their lack of vapour pressure and have been increasingly used in organic synthesis [23]. In continuation of our interest in green catalysis [24-25] we wish to report one-pot synthesis of 4-benzylidene-3-methylisoxazol-5(4H)-one derivatives through a three-component reaction catalyzed by binary system cetyltrimethylammonium bromide (CTAB)/18-Crown-6 in aqueous ethanol. In this study, various ratio of [CTAB/18-Crown-6] in different ratio of aqueous ethanol have been analyzed for its catalytic efficiency for the synthesis of isoxazol-5(4H)-ones in order to achieve advantages such as mild reaction conditions, high yields, short reaction time and operational simplicity. Exploratory data analysis was performed using descriptive statistical functions and correlation coefficient to further explore the catalytic efficiency of [CTAB/18-Crown-6] binary system.

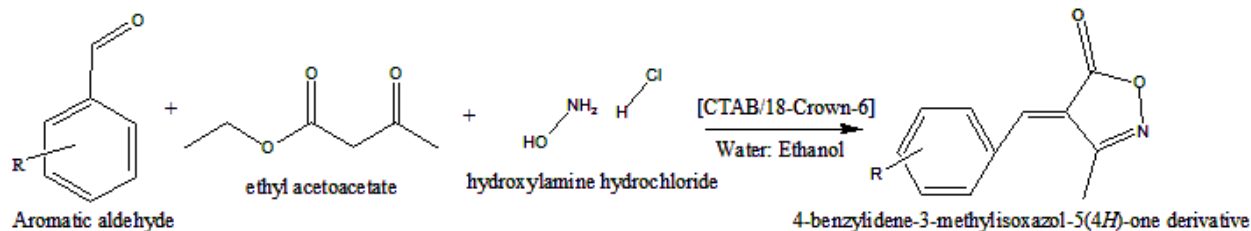
**2. Materials and Methods**

All the reagents and chemicals were obtained from Hi-media and used without further purification. Melting points were measured on a PT-125 melting point apparatus and are

uncorrected. IR spectra were recorded on a Shimadzu FT-IR 8300 Spectrophotometer using KBr pellets technique.  $^1\text{H}$  NMR spectra were recorded at ambient temperature on a BRUKER AVANCE DRX-400 MHz spectrophotometer using  $\text{CDCl}_3$  as a solvent and TMS as an internal standard. The purity of new synthesized compounds and development of reactions was monitored by thin layer chromatography (TLC) on Merck pre-coated silica gel G and visualized by UV light.

### 2.1 Binary catalytic [CTAB/18-Crown-6] system

Different ratio of cetyltrimethylammonium bromide (CTAB) and 18-Crown-6 (i.e. 0:1, 1:1, 1:2, 2:1 and 1:0) were mixed in variable ratio of aqueous ethanol (i.e. 1:1, 1:2 and 2:1). Each [CTAB/ 18-Crown-6] system was checked as a binary catalyst



**Scheme 1:** Synthesis of 4-benzylidene-3-methylisoxazol-5(4H)-one derivatives

### 2.3 Statistical analysis

Descriptive statistical functions and correlation coefficient were obtained using software The Unscrambler X 10.5 to evaluate the catalytic efficiency of [CTAB/18-Crown-6] in aqueous ethanol for the synthesis of isoxazol-5(4H)-one derivatives.

for the synthesis of 4-benzylidene-3-methylisoxazol-5(4H)-ones with respect to afford high % yield (Scheme 1).

### 2.2 General procedure for the synthesis of 4-benzylidene-3-methylisoxazol-5(4H)-one derivatives

A mixture of [CTAB/18-Crown-6] (0.5 mmol) in aqueous ethanol and hydroxylamine hydrochloride (5.5 mmol) was taken in 100 mL round bottom flask. Then aromatic aldehyde (5 mmol) and ethylacetoacetate (5 mmol) were added to the reaction mixture and stirred at room temperature (Scheme 1). After completion of the reaction as indicated by TLC, the reaction mixture was extracted with ice cold water. Further, purification was done by recrystallization from acetone: hexane (1:1).

## 3. Results and Discussions

### 3.1 Binary [CTAB/18-Crown-6] system and synthesis of 4-benzylidene-3-methylisoxazol-5(4H)-one derivatives

Percent (%) yield of 4-benzylidene-3-methylisoxazol-5(4H)-ones obtained by three component reaction of aromatic aldehyde, ethylacetoacetate and hydroxylamine hydrochloride using different ratio of [CTAB/ 18-Crown-6] in variable water: ethanol ratio are presented in table 1.

**Table 1:** % Yield of 4-benzylidene-3-methylisoxazol-5(4H)-one derivatives using different ratio combinations of [CTAB/ 18-Crown-6] in variable water: ethanol ratio

Entry	[CTAB: 18-Crown-6]														
	[1:0]			[1:1]			[1:2]			[2:1]			[0:1]		
	Water: Ethanol			Water: Ethanol			Water: Ethanol			Water: Ethanol			Water: Ethanol		
	1:2 B1	1:1 B2	2:1 B3	1:2 B4	1:1 B5	2:1 B6	1:2 B7	1:1 B8	2:1 B9	1:2 B10	1:1 B11	2:1 B12	1:2 B13	1:1 B14	2:1 B15
% Yield of 4-benzylidene-3-methylisoxazol-5(4H)-one derivatives															
Is1	55	48	50	62	60	66	68	65	67	80	82	91	59	55	56
Is2	46	50	46	65	66	69	65	68	69	77	79	86	64	58	59
Is3	58	55	42	70	68	72	62	66	71	82	85	93	58	55	54
Is4	64	61	53	69	71	75	61	67	63	75	79	88	62	59	65
Is5	59	62	58	65	72	77	57	59	65	76	81	87	65	61	58
Is6	48	45	39	61	64	70	64	67	70	74	79	85	61	64	59
Is7	61	49	40	61	60	68	66	69	72	84	85	92	58	55	59
Is8	35	44	45	50	48	55	65	67	66	77	76	89	55	53	59
Is9	33	40	38	52	56	57	52	55	58	85	88	94	51	47	45
Is10	41	38	35	53	55	61	45	50	57	81	83	88	51	54	55

Is1- 4-(4-methoxybenzylidene)-3-methylisoxazol-5(4H)-ones

Is2- 4-(4-hydroxybenzylidene)-3-methylisoxazol-5(4H)-ones

Is3- 4-(2-hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4H)-ones

Is4- 4-(3,4-dimethoxybenzylidene)-3-methylisoxazol-5(4H)-ones

Is5- 4-(4-dimethylaminobenzylidene)-3-methylisoxazol-5(4H)-ones

Is6- 4-(4-hydroxy-3,5-dimethoxybenzylidene)-3-methylisoxazol-5(4H)-ones

Is7- 4-(4-methylbenzylidene)-3-methylisoxazol-5(4H)-ones

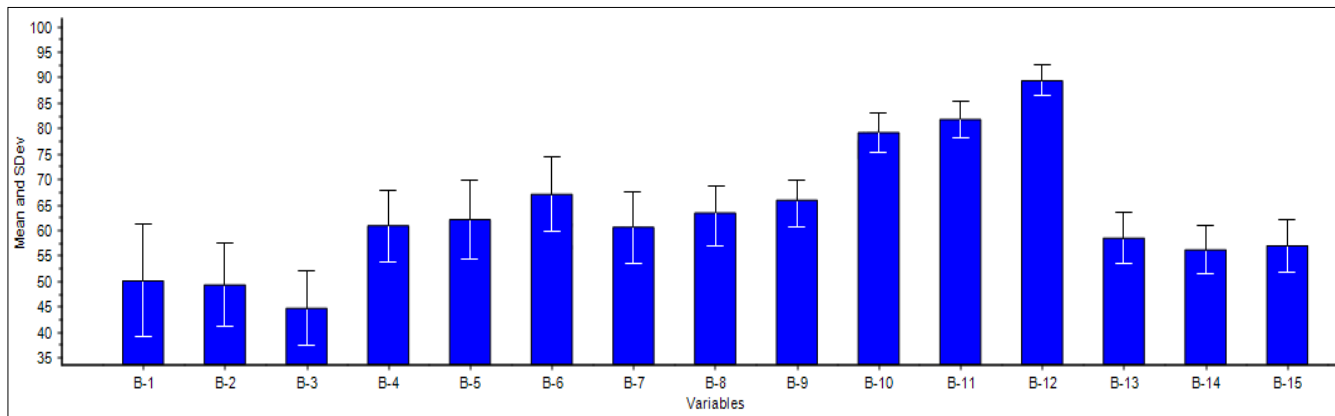
Is8- 4-(4-nitrobenzylidene)-3-methylisoxazol-5(4H)-ones

Is9- 4-(4-chlorobenzylidene)-3-methylisoxazol-5(4H)-ones

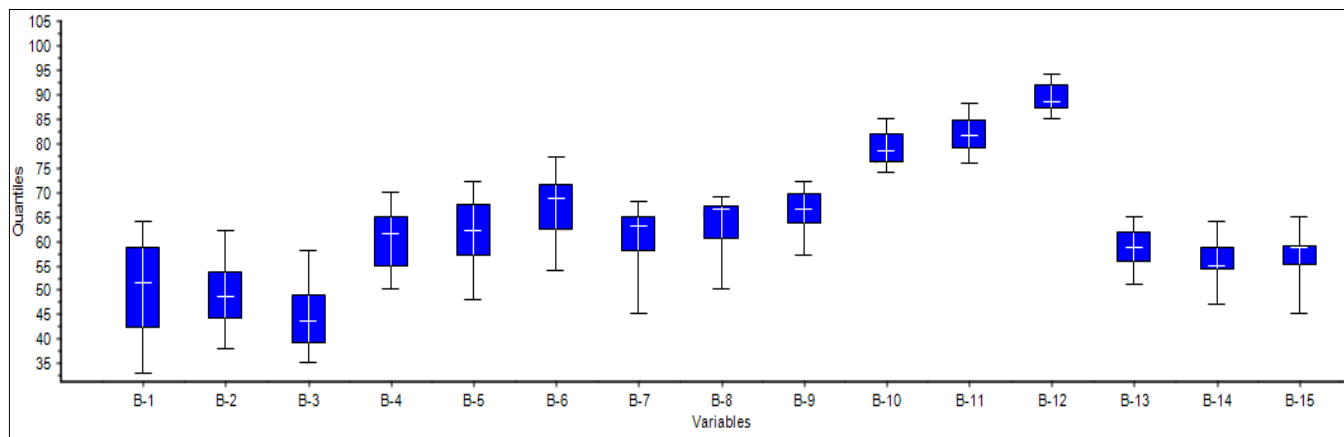
Is10- 4-(4-fluorobenzylidene)-3-methylisoxazol-5(4H)-ones

Applying descriptive statistics function on the entire data of table 1, it is observed that the mean-standard deviation (figure1) and quantile (figure 2) values are higher for B1

binary system, explaining higher catalytic activity of 2:1 [CTAB/ 18-Crown-6] in 2:1 aqueous ethanol binary system.



**Fig 1:** Mean-standard deviation of % yield of isoxazol-5(4H)-ones obtained via descriptive statistical function analysis



**Fig 2:** Quantiles of % yield of isoxazol-5(4H)-ones obtained via descriptive statistical function analysis

Further, correlation coefficient matrix (Table 2) achieved shows correlation in four groups of different ratio combinations of binary [CTAB/ 18-Crown-6] systems. Table 2 reveals that group III has high negative correlation with group IV and low negative correlation with group I and II. It was observed that 2:1 [CTAB/18-Crown-6] binary system tremendously increase its catalytic activity than that of 1:2

[CTAB/18-Crown-6] binary system. Groups obtained by correlation coefficient matrix are specified as below:

Group I: B1, B2, B3, B4, B5, B6, B13

Group II: B7, B8, B9

Group III: B10, B11, B12

Group IV: B5, B6, B13, B14, B15

**Table 2:** Correlation matrix for different binary [CTAB/ 18-Crown-6] catalytic system in aqueous ethanol

	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B12	B13	B14	B15
B1	1.00													
B2	0.81	1.00												
B3	0.54	0.83	1.00											
B4	0.86	0.84	0.52	1.00										
B5	0.77	0.85	0.58	0.92	1.00									
B6	0.87	0.86	0.59	0.92	0.96	1.00								
B7	0.39	0.34	0.34	0.40	0.15	0.25	1.00							
B8	0.45	0.42	0.28	0.49	0.25	0.34	0.94	1.00						
B9	0.50	0.37	0.14	0.53	0.31	0.43	0.85	0.86	1.00					
B10	-0.19	-0.42	-0.53	-0.30	-0.38	-0.43	-0.28	-0.34	-0.17	1.00				
B11	0.01	-0.21	-0.42	-0.04	-0.01	-0.10	-0.40	-0.44	-0.21	0.88	1.00			
B12	-0.04	-0.17	-0.27	-0.14	-0.28	-0.34	-0.05	-0.12	-0.07	0.88	0.77	1.00		
B13	0.66	0.80	0.74	0.77	0.79	0.83	0.56	0.59	0.58	-0.67	-0.47	-0.56	1.00	
B14	0.54	0.53	0.42	0.58	0.65	0.76	0.33	0.40	0.47	-0.81	-0.57	-0.80	0.81	1.00
B15	0.57	0.55	0.49	0.46	0.37	0.53	0.47	0.60	0.41	-0.72	-0.75	-0.63	0.65	0.72

Correlation analysis was done using coefficient values higher than 0.6. B1-B15 are different binary [CTAB/ 18-Crown-6] catalytic system in aqueous ethanol as mentioned in table 1.

Detailed observations of the synthesized 4-benzylidene-3-methylisoxazol-5(4H)-ones with respect to reaction time, % yield using 2:1 binary catalytic system [CTAB/ 18-Crown-6]

in 2:1 aqueous ethanol at room temperature are demonstrated in table 3.

**Table 3:** Synthesis of 4-benzylidene-3-methylisoxazol-5(4*H*)-one derivatives using 2:1 [CTAB/ 18-Crown-6] in 2:1 aqueous ethanol binary system

Entry	Compounds	Yield (%)	Time (min)	Melting Point
Is1	1. 4-(4-methoxybenzylidene)-3-methylisoxazol-5(4 <i>H</i> )-ones	91	45	164°C
Is2	2. 4-(4-hydroxybenzylidene)-3-methylisoxazol-5(4 <i>H</i> )-ones	86	30	190°C
Is3	3. 4-(2-hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4 <i>H</i> )-ones	93	60	108°C
Is4	4. 4-(3,4-dimethoxybenzylidene)-3-methylisoxazol-5(4 <i>H</i> )-ones	88	30	92°C
Is5	5. 4-(4-dimethylaminobenzylidene)-3-methylisoxazol-5(4 <i>H</i> )-ones	87	20	184°C
Is6	6. 4-(4-hydroxy-3,5-dimethoxybenzylidene)-3-methylisoxazol-5(4 <i>H</i> )-ones	85	15	100°C
Is7	7. 4-(4-methylbenzylidene)-3-methylisoxazol-5(4 <i>H</i> )-ones	92	35	201°C
Is8	8. 4-(4-nitrobenzylidene)-3-methylisoxazol-5(4 <i>H</i> )-ones	89	25	144°C
Is9	9. 4-(4-chlorobenzylidene)-3-methylisoxazol-5(4 <i>H</i> )-ones	94	20	181°C
Is10	10. 4-(4-fluorobenzylidene)-3-methylisoxazol-5(4 <i>H</i> )-ones	88	40	139°C

### 3.2 Spectral Characterization

#### 3.2.1 FT-IR Spectral Analysis

The FT-IR spectra of isoxazol-5(4*H*)-ones showed absorption band at 1720 cm<sup>-1</sup> due to aromatic C=O group, at 1515 cm<sup>-1</sup> due to C=N group, at 1112 cm<sup>-1</sup> due to C-O-N group, at 1015 cm<sup>-1</sup> due to the P-O-C group and at 812 cm<sup>-1</sup> appeared due to the P-CH group.

#### 3.2.2 <sup>1</sup>H NMR Spectral Analysis

##### 3.2.2.1 4-(4-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-ones

<sup>1</sup>H NMR (CDCl<sub>3</sub>, TMS): 2.95 (s, 3H, -CH<sub>3</sub>), 3.32 (s, 3H, -OCH<sub>3</sub>), 6.83 (s, 1H, =CH), 7.35 (d, 2H, -ArH), 8.23(d, 2H, -ArH).

##### 3.2.2.2 4-(4-hydroxybenzylidene)-3-methylisoxazol-5(4*H*)-ones

<sup>1</sup>H NMR (CDCl<sub>3</sub>, TMS): 3.01 (s, 3H, -CH<sub>3</sub>), 7.24 (s, 1H, =CH), 7.65 (d, 2H, -ArH), 8.44(d, 2H, -ArH), 10.62 (s, 1H, -OH).

##### 3.2.2.3 4-(2-hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-ones

<sup>1</sup>H NMR (CDCl<sub>3</sub>, TMS): 2.86 (s, 3H, -CH<sub>3</sub>), 3.35 (s, 3H, -OCH<sub>3</sub>), 7.05 (d, 1H, -ArH), 7.43 (d, 1H, -ArH), 8.25 (s, 1H, =CH), 8.54 (d, 1H, -ArH), 10.62 (s, 1H, -OH).

##### 3.2.2.4 4-(3,4-dimethoxybenzylidene)-3-methylisoxazol-5(4*H*)-ones

<sup>1</sup>H NMR (CDCl<sub>3</sub>, TMS): 2.81 (s, 3H, -CH<sub>3</sub>), 3.62 (s, 6H, 2-OCH<sub>3</sub>), 7.32 (d, 1H, -ArH), 7.93 (s, 1H, -ArH), 8.21 (s, 1H, =CH), 8.44 (d, 1H, -ArH).

##### 3.2.2.5 4-(4-dimethylaminobenzylidene)-3-methylisoxazol-5(4*H*)-ones

<sup>1</sup>H NMR (CDCl<sub>3</sub>, TMS): 2.84 (s, 3H, -CH<sub>3</sub>), 3.32 (s, 6H, 2-CH<sub>3</sub>), 7.10 (d, 2H, -ArH), 7.52 (s, 1H, =CH), 8.60 (d, 2H, -ArH).

##### 3.2.2.6 4-(4-hydroxy-3,5-dimethoxybenzylidene)-3-methylisoxazol-5(4*H*)-ones

<sup>1</sup>H NMR (CDCl<sub>3</sub>, TMS): 3.10 (s, 3H, -CH<sub>3</sub>), 3.55 (s, 6H, 2-OCH<sub>3</sub>), 7.01 (s, 1H, -ArH), 7.64 (s, 1H, -ArH), 8.32 (s, 1H, =CH), 10.9 (s, 1H, -OH).

##### 3.2.2.7 4-(4-methylbenzylidene)-3-methylisoxazol-5(4*H*)-ones

<sup>1</sup>H NMR (CDCl<sub>3</sub>, TMS): 2.75 (s, 3H, -CH<sub>3</sub>), 2.82 (s, 3H, -CH<sub>3</sub>), 7.10 (d, 2H, -ArH), 7.61 (s, 1H, =CH), 8.42(d, 2H, -ArH).

##### 3.2.2.8 4-(4-nitrobenzylidene)-3-methylisoxazol-5(4*H*)-ones

<sup>1</sup>H NMR (CDCl<sub>3</sub>, TMS): 2.83 (s, 3H, -CH<sub>3</sub>), 7.65 (d, 2H, -ArH), 8.10 (s, 1H, =CH), 8.46 (d, 2H, -ArH).

##### 3.2.2.9 4-(4-chlorobenzylidene)-3-methylisoxazol-5(4*H*)-ones

<sup>1</sup>H NMR (CDCl<sub>3</sub>, TMS): 2.96 (s, 3H, -CH<sub>3</sub>), 7.82 (d, 2H, -ArH), 8.13 (s, 1H, =CH), 8.63 (d, 2H, -ArH).

##### 3.2.2.10 4-(4-fluorobenzylidene)-3-methylisoxazol-5(4*H*)-ones

<sup>1</sup>H NMR (CDCl<sub>3</sub>, TMS): 3.05 (s, 3H, -CH<sub>3</sub>), 7.68 (d, 2H, -ArH), 8.22 (s, 1H, =CH), 8.41 (d, 2H, -ArH).

### 4. Conclusion

The efficient binary catalytic [CTAB/ 18-Crown-6] system has been developed in aqueous ethanol for green synthesis of isoxazol-5(4*H*)-ones *via* a one-pot, three-component condensation of ethyl acetoacetate, aryl aldehydes, and hydroxylamine hydrochloride at room temperature. The 2:1 [CTAB/ 18-Crown-6] in 2:1 aqueous ethanol exhibited advantages such as mild conditions, easy work-up and shorter reaction time affording high yield of isoxazol-5(4*H*)-ones. In addition, descriptive statistical analysis and variable correlation analysis provide a significant exploratory statistical tool to study the catalytic efficiency of binary catalyst [CTAB/ 18-Crown-6].

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