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Green synthesis of 5-methylpyridinium derivatives by C2-functionalization of pyridine-1-oxide derivatives and their antibacterial activity

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An innovative green economic route has been developed for one pot multicomponent synthesis of 5-methylpyridinium derivatives by the reaction of 3-methylpyridine-1-oxide, aromatic aldehyde and β-ketoester catalysed by different ionic liquids (ILs), [BMIM][OH], [BMIM][Cl], [BMIM][Ac] in good to excellent yields. A relative study reinforced that [BMIM][OH] is the best IL for this C2-functionsalization reaction. The main highlights of this synthetic protocol are simple work-up, cost effectiveness and environmentally benign processing. The synthesized derivatives have been assessed for possible antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* by using the microdilution method. The results of antibacterial activity suggests that compound **4l** shows best antibacterial activity and other compounds show good to moderate activity.

Keywords: Multicomponent reaction, C2-Functionalization, Pyridine-1-oxide, Ionic liquid, Green economic route, Antibacterial activity

Pyridine *N*-oxide derivatives are mesmerizing heterocycles as they have applications in natural product synthesis, catalysis, heterocyclic synthesis[1-3], medicinal chemistry and coordination compounds synthesis[4]. Derivatives of pyridine N-oxide have significant prominence in pharmaceutical chemistry as they show potent biological activity[5] and they also show possibilities in different biochemical reactions[6,7]. 5-Methylpyridinium derivatives display a peculiar class of antibacterial agents that succeed as promising novel drugs for consideration due to the specific structure of pyridine *N*-oxide derivatives. The applicability of IL as catalyst and solvent attracted the researchers to replace harmful volatile organic solvents and imply greener strategy of synthesis. In addition, ILs displays applications in catalysis[8-10], extraction, organic synthesis[11-14], nanomaterials synthesis[15-17], biocatalysis, polymerization reactions and dissolution processes. IL can be recycled and reused in the synthesis several times without losing its catalytic activity which also increases its significance in synthetic organic chemistry[18-24].

In this frame of references, development of a new efficient and green method for the synthesis of pyridine-1-oxide derivatives using IL as catalyst is therefore of great interest. Further, the N-oxide group increases the reactivity in reactions with electrophilic reagents, especially at the C2-position, it allows efficient regioselective C2-functionalization. In the present work, we have done C2-functionalization of pyridine-1-oxide *via* condensation with aldehydes and β–ketoester or 1,3-diketone using IL as catalyst and solvent under mild reaction conditions with excellent yields. A comparative study has been also carried out between ionic liquids [BMIM][OH], [BMIM][Ac] and [BMIM][Cl]. The advantages of this synthetic protocol are environmentally benign, economically profitable, simple work-up, giving pure products in short reaction time, *etc*. Additionally, the synthesized compounds were screened for antibacterial activity toward gram positive and gram negative species, which are *Staphylococcus aureus* and *Escherichia coli* by determining minimum inhibitory concentration (MIC) with standard broth dilution assay (Table 1, Table 2 and Table 3).

Results and Discussion

Chemistry

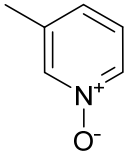
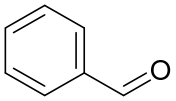
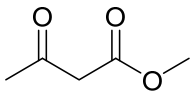
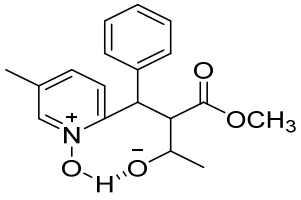
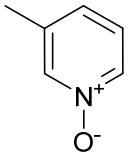
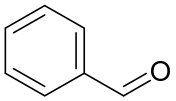
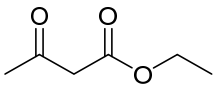
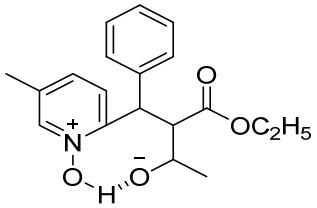
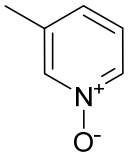
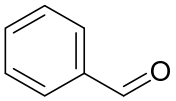
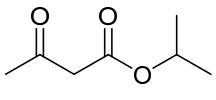
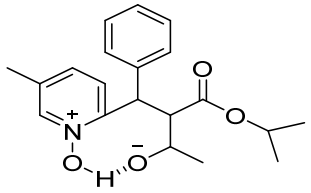
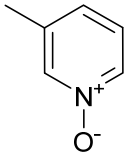
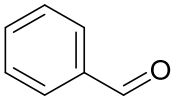
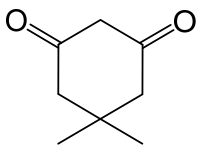
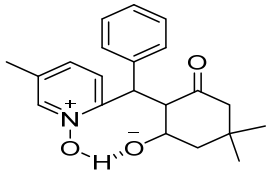
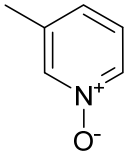
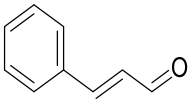
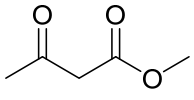
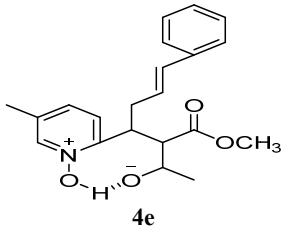
A novel green procedure has been developed for C2 functionalization of 3-methyl pyridine-1-oxide **1** by the reaction of various aromatic aldehydes **2a-d** and β-ketoester or 1,3-diketone **3a-d** with 3-methyl

Table 1 — Optimization of various catalyst for compound **2a**

S. No.	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	Catalyst free	Solvent free	RT	12	0
2	NMe_3	MeCN	70	10	40
3	K_2CO_3	MeCN	70	10	42
4	$NaHCO_3$	MeCN	70	8	37
5	$[BMIM]^+[Ac]^-$	MeCN	60	3.5	75
6	$[BMIM]^+[Cl]^-$	MeCN	60	5	69
7	$[BMIM]^+[OH]^-$	MeCN	60	2	82
8	$[BMIM]^+[OH]^-$	Ethanol	55	4	80
9	$[BMIM]^+[OH]^-$	DMF	55	3.5	86
10	$[BMIM]^+[OH]^-$	Toluene	55	2.5	78
11	$[BMIM]^+[OH]^-$	H_2O	55	2	87
12	$[BMIM]^+[OH]^-$	IL as solvent also	50	1	92

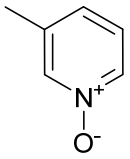
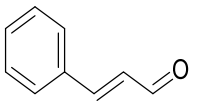
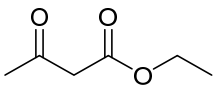
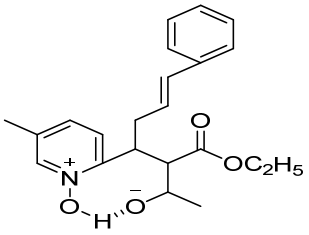
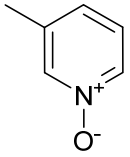
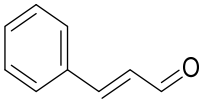
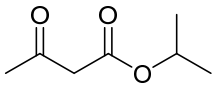
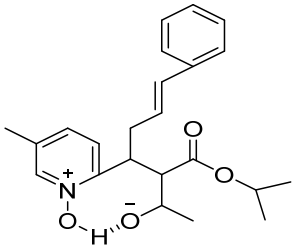
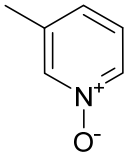
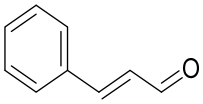
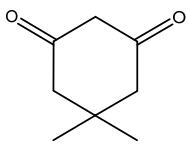
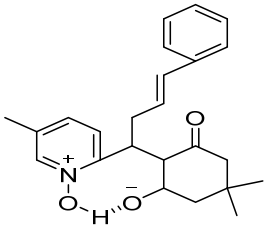
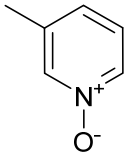
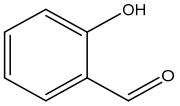
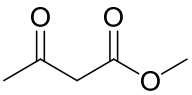
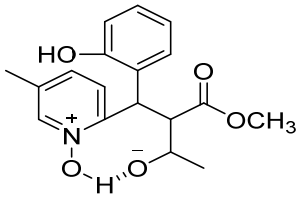
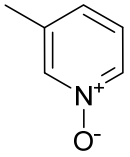
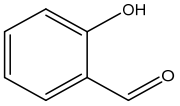
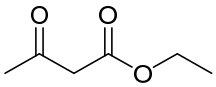
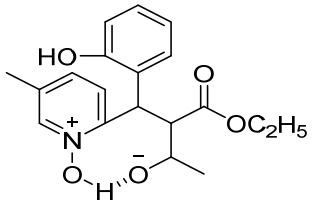
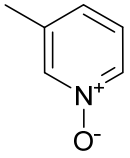
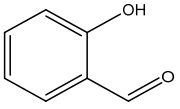
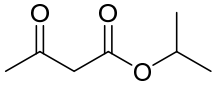
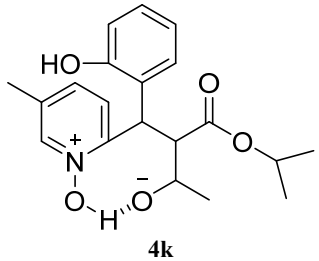
*Aromatic aldehyde (2.0 mmol, **2a-d**) and β-ketoester or dimedone (2.0 mmol, **3a-d**), 3-methyl pyridine-1-oxide (2.0 mmol, 1) and ionic liquid (5 mL) refluxed at 50°C

Table 2 — Percent yields of synthesized 5-methylpyridinium derivatives

S. No.	1	2a-d	3a-d	Products 4a-p	Yield (%)
1				 **4a**	92
2				 **4b**	83
3				 **4c**	88
4				 **4d**	76
5				 **4e**	69

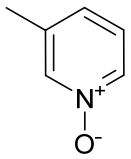
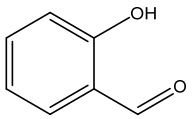
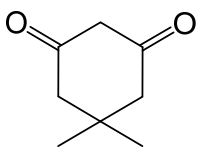
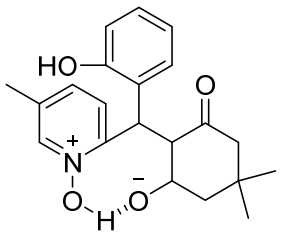
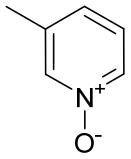
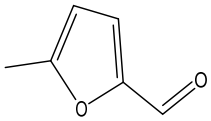
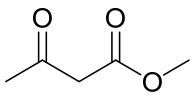
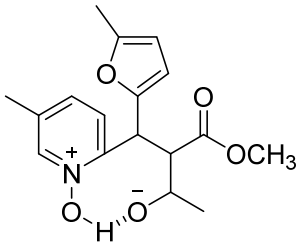
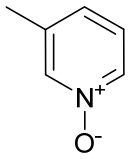
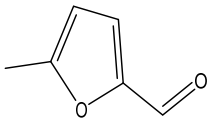
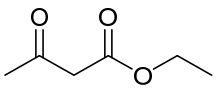
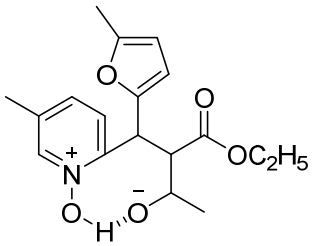
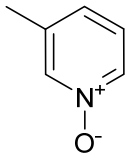
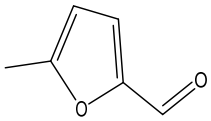
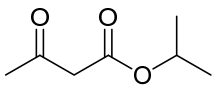
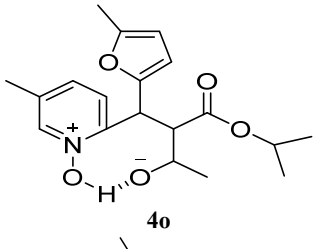
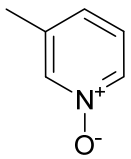
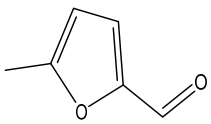
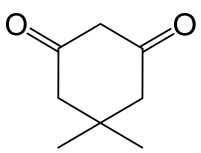
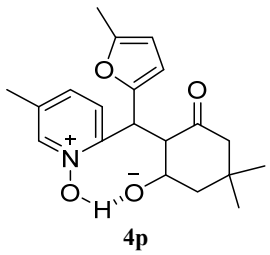
(*Contd.*)

Table 2 — Percent yields of synthesized 5-methylpyridinium derivatives (*Contd.*)

S. No.	1	2a-d	3a-d	Products 4a-p	Yield (%)
6				 **4f**	73
7				 **4g**	77
8				 **4h**	63
9				 **4i**	71
10				 **4j**	75
11				 **4k**	80

(*Contd.*)

Table 2 — Percent yields of synthesized 5-methylpyridinium derivatives (*Contd*.)

S. No.	1	2a-d	3a-d	Products 4a-p	Yield (%)
12				 **4l**	68
13				 **4m**	81
14				 **4n**	86
15				 **4o**	90
16				 **4p**	78

*Aromatic aldehyde **2a-d** (2.0 mmol) and β-ketoester or dimedone **3a-d** (2.0 mmol), 3-methyl pyridine-1-oxide (2.0 mmol, 1) and ionic liquid (5 mL) refluxed at 50°C

pyridine-1-oxide **1**. The synthesis of biologically active 5-methylpyridinium derivatives was carried out in ILs as catalyst and solvent as the application of green chemistry (Scheme 1).

Optimization of Catalyst

A model reaction was chosen for the selection and optimization of catalyst (Scheme 1). A mixture of benzaldehyde **2a** (2.0 mmol), methylacetoacetate **3a** (2.0 mmol) and 3-methyl pyridine-1-oxide **1** (2.0 mmol) in different catalysts was refluxed for appropriate time given in Table 1.

Subsequently, selected model reaction was performed with different catalysts (NMe_3, K_2CO_3, $NaHCO_3$, [BMIM][Ac], [BMIM][Cl] and [BMIM][OH]) and solvents (MeCN, ethanol, DMF, toluene and H_2O).

Firstly, a comparative study was done to decide the catalyst and it is clear from the Table 1, entry 7 that IL [BMIM][OH] is the best catalyst for this synthetic protocol. Further, different solvent systems were used for the same model reaction with [BMIM][OH]IL but best yield in minimum time was obtained with [BMIM][OH] as solvent and catalyst (Table 1, entry 12).

Similarly, other derivatives were synthesized **4a-p** according to the aforementioned environmentally benign protocol. In all the prepared compounds, the functionalization of the products **4a-p** of the reaction was on position C2. The spectroscopic analysis confirms the structure of the synthesized derivatives.

The yields of the products were found to be practically independent of nature of both the 3-methylpyridine-1-oxide and β-ketoester or dimedone. Most probably, the reaction begins with nucleophilic addition of β-ketoester or dimedone to the aldehyde with the formation of the corresponding enone, followed by the Michael-type addition of 3-methyl pyridine-1-oxide (Scheme 2)[25].

Table 3 — Antibacterial activity of synthesized derivatives 4a-p

Compd	Minimum Inhibitory Concentration (MIC) (μg/mL)	
	S. aureus	*E. coli*
4a	68	64
4b	20	40
4c	128	>1024
4d	104	>1024
4e	64	44
4f	32	60
4o	44	48
4h	28	16
4i	12	72
4j	104	76
4k	32	36
4l	4	16
4m	16	88
4n	8	24
4g	12	>1024
4p	24	112
Ceftazidime	<0.125 (0.06-0.5)*	4 (4-16)*

*Acceptable quality control ranges of MICs (μg/mL) for reference strains[26]

Antibacterial Activity

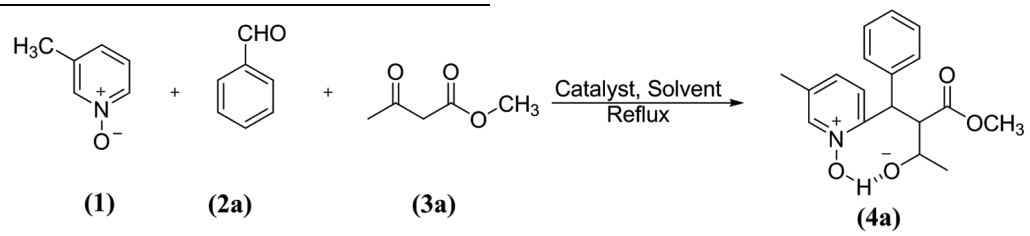
All the synthesized compounds **4a-p** were checked for antibacterial activity against gram positive bacteria *S. aureus* and gram negative bacteria *E. coli*. Ceftazidime was taken as standard reference compound and almost all the compounds showed antibacterial activity against the bacterial strains. Compounds **4l** found to be the most influencing antibacterial agent against both the bacterial organisms as shown by MIC values (4 and 16). **4g** displayed no activity against *E. coli* and **4c** and **4d** displayed negligible activity against *S. aureus* and *E. coli*. All the other compounds showed moderate antibacterial activity. Further, the compounds have more potent activity for gram positive bacteria than gram negative bacteria. The results also suggest that the compounds act on the surface of bacteria causing the inhibition of the bacterial growth (Table 3).

Experimental Details

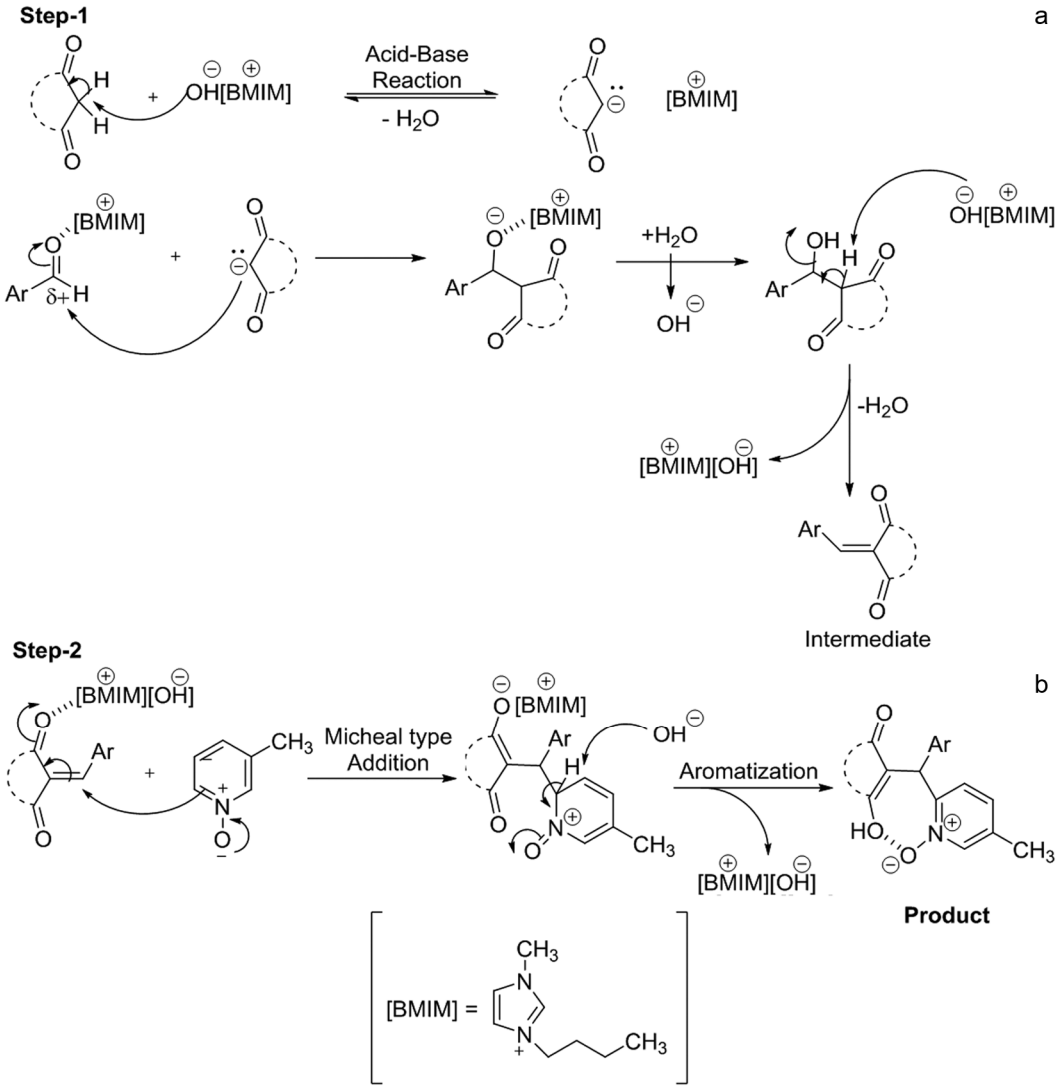
All the chemicals required for synthesis were purchased from Alfa Aesar and Sigma Aldrich and no further purification was done. Melting points were taken in open glass capillary tube using Gallenkamp melting point apparatus. The purity of synthesized compounds were checked by thin layer chromatography (TLC) and visualized by UV light chamber. The IR spectra were recorded in KBr on SHIMADZU 8400S FT-IR spectrophotometer and frequency is given in cm^{-1}. The ^{1}H and ^{13}C NMR were recorded on JEOL AL spectrometer at 400 MHz and 100.5 MHz respectively in $CDCl_3$ using TMS as an internal standard and chemical shift were measured in δ (ppm). FAB (Fast Atom Bombarding) mass spectra were recorded on JEOL SX 102/DA 600 using Argon/Xenon gas. The elemental analysis (C, H and N) was performed using Vario-III analyser.

Synthesis of [BMIM][OH] [BMIM][Ac] and [BMIM][Cl] ionic liquids

Ionic liquids (1-butyl-3-methylimmidazolium hydroxide [BMIM][OH], 1-butyl-3-methylimmida-



Scheme 1 — Model reaction for optimization of reaction conditions



Scheme 2 — Plausible mechanism for synthesis of 5-methylpyridinium derivatives

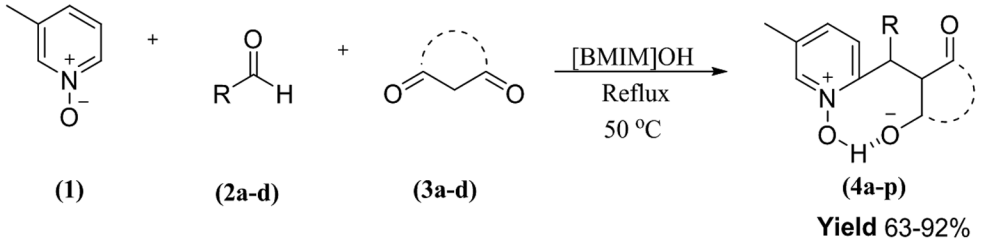
zolium acetate [BMIM][Ac] and 1-butyl-3-methylimmidazolium chloride [BMIM][Cl]) were synthesized according to the reported procedure[27-30].

General method for synthesis of 5-methylpyridinium derivatives, 4a-p

A mixture of aromatic aldehyde **2a-d** (2.0 mmol) and β-ketoester or dimedone **3a-d** (2.0mmol) with [BMIM]OH ionic liquid (5 mL) was refluxed for 15 min at 50°C. Then, 3-methyl pyridine-1-oxide **1** (2.0 mmol), was added in the above mixture and refluxed. The completion of the reaction was checked by TLC (ethyl acetate: hexane 2:8).The catalyst (ILs) was recovered from the reaction mixture for reuse in the same set of reactions. The compound was filtered, washed with water, dried and purified by recrystallization from absolute alcohol (Scheme 3).

Antibacterial activity

The minimum inhibitory concentration (MIC) was concluded by broth microdilution method as maintained by the Clinical and Laboratory Standards Institute (CLSI)[26]. The standard strains, *Staphylococcus aureus* (ATCC 29213) and *Escherichia coli* (ATCC 25922) were used for assessment of antibacterial activity. Mueller-Hinton broth was used for antibacterial assay. The derivatives **4a-p** were weighed (10 mg), dissolved in DMSO (250 µg/mL) and diluted with water (750 µg/mL) to prepare the stock solutions of 10 mg/mL. The serial dilution from 1024 to 1 was made in a 96-well plate. Fifty µL of a bacterial suspension, obtained from a 24 h culture (~10^6 cfu/mL) was added to each well with a final DMSO concentration of 1:16. The plates



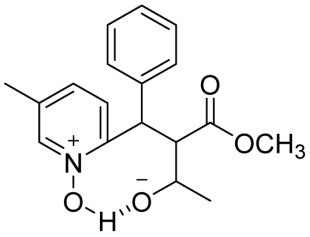
Reaction conditions: Aromatic aldehyde (2.0 mmol) and β-ketoesters or dimedone (2.0 mmol) and 3-methyl pyridine-1-oxide (2.0 mmol), [BMIM][OH]ILs (5 mL) as catalyst, reflux

Scheme 3 — General procedure of synthesis of 5-methylpyridinium derivatives

were incubated at 35°C for 24 h. Ceftazidime was tested as standard antibacterial agent for quality control of the method. Each experiment was carried out in duplicate[31].

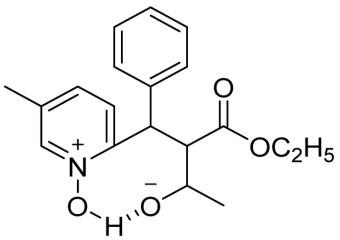
Spectral analysis

1-Hydroxy-2-(2-(methoxycarbonyl)-3-oxo-1-phenylbutyl)-5-methylpyridin-1-ium, 4a



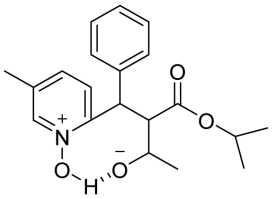
Yield 92%. IR (KBr): 3520 (OH), 1700 (-C=N-), 1750 (C=O), 1600 (C=C Ar) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.47 (s, 1H), 7.34 – 7.25 (m, 2H), 7.25 – 7.18 (m, 3H), 6.89 (s, 1H), 6.55 (s, 1H), 5.96 (s, 1H), 4.59 (s, 1H), 3.75 (s, 3H), 3.21 (s, 1H), 2.44 (s, 3H), 1.10 – 0.95 (d, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 201.33, 170.17, 141.10, 140.45, 139.57, 138.30, 135.15, 131.91, 130.64, 130.24, 129.10, 128.88, 126.80, 56.28, 52.17, 47.95, 30.56, 18.74; HRMS: *m/z* 314.14 (M^+). Anal. Calcd for $C_{18}H_{20}NO_4$: C, 68.77; H, 6.14; N, 4.46. Found: C, 68.75; H, 6.16; N, 4.48%.

2-(2-(Ethoxycarbonyl)-3-oxo-1-phenylbutyl)-1-hydroxy-5-methylpyridin-1-ium, 4b



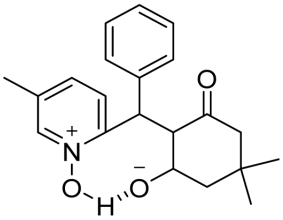
Yield 83%. IR (KBr): 3510 (OH), 1670 (-C=N-), 1735(C=O), 1620 (C=C Ar) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 7.32 – 7.25 (m, 4H), 7.20 (s, 1H), 6.76 (s, 1H), 6.47 (s, 1H), 4.91 (s, 1H), 4.24 – 4.12 (m, 2H), 3.95 (s, 1H), 2.45 (s, 3H), 2.32 (s, 1H), 2.16 – 2.12 (m, 3H), 1.37 – 1.33 (d, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 201.33, 169.37, 141.10, 140.45, 139.57, 138.30, 135.15, 131.91, 130.64, 130.24, 129.10, 128.88, 126.80, 61.80, 56.31, 47.95, 30.56, 18.74, 14.70; HRMS: *m/z* 328.15 (M^+). Anal. Calcd for $C_{19}H_{22}NO_4$: C, 69.49; H, 6.75; N, 4.27. Found: C, 69.51; H, 6.77; N, 4.25%.

1-Hydroxy-2-(2-(isopropoxycarbonyl)-3-oxo-1-phenylbutyl)-5-methylpyridin-1-ium, 4c



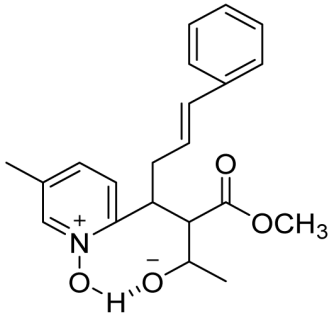
Yield 88%. IR (KBr): 3490 (OH), 1640 (-C=N-), 1745 (C=O), 1640 (C=C Ar) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 4H), 7.20 (d, 2H), 6.67 (d, 2H), 4.91 (s, 1H), 4.87 (s, 1H), 3.95 (s, 1H), 2.41 (s, 3H), 2.13 – 2.09 (d, 3H), 1.46 – 1.34 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 201.33, 170.36, 141.10, 140.45, 139.57, 138.30, 135.15, 131.91, 130.64, 130.24, 129.10, 128.88, 126.80, 71.24, 56.32, 47.95, 30.56, 22.65, 22.44, 18.74; HRMS: *m/z* 342.17 (M^+). Anal. Calcd for $C_{20}H_{24}NO_4$: C, 70.15; H, 7.07; N, 4.09. Found: C, 70.17; H, 7.10; N, 4.11%.

2-((4,4-Dimethyl-2,6-dioxocyclohexyl)(phenyl)methyl)-1-hydroxy-5-methylpyridin-1-ium, 4d



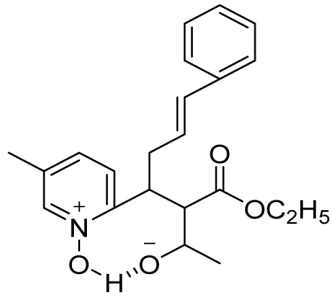
Yield 76%. IR (KBr): 3450 (OH), 1672 (-C=N-), 1740 (C=O), 1630 (C=C Ar) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.32 – 7.24 (m, 2H), 7.24 – 7.06 (m, 3H), 6.82 (s, 1H), 6.28 (s, 1H), 4.83 (s, 1H), 3.98 (s, 1H), 2.77 (s, 1H), 2.46 (s, 3H), 2.29 – 2.22 (m, 4H), 1.19 – 1.15 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 200.11, 199.89, 141.10, 140.45, 139.57, 138.30, 135.15, 131.91, 130.64, 130.24, 129.10, 128.88, 126.80, 59.37, 52.06, 51.67, 45.61, 32.50, 28.92, 28.61, 18.74; HRMS: *m/z* 339.18 (M^+). Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.33; H, 7.40; N, 4.11%.

(E)-1-Hydroxy-2-(5-(methoxycarbonyl)-6-oxo-1-phenylhept-1-en-4-yl)-5-methylpyridin-1-ium, 4e



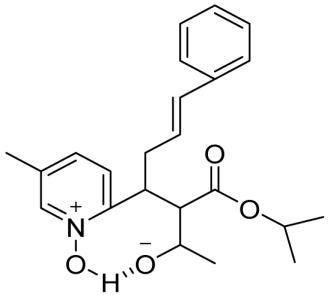
Yield 69%. IR (KBr): 3480 (OH), 1680 (-C=N-), 1750 (C=O), 1610 (C=C Ar) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.33 – 7.21 (m, 4H), 7.18 (s, 1H), 7.11 (s, 1H), 6.58 (d, 2H), 6.28 (s, 1H), 6.11 (d, 2H), 3.79 (s, 3H), 3.14 (d, 2H), 2.74 (s, 1H), 2.43 (s, 3H), 2.25 (s, 1H), 1.09 – 0.94 (d, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 201.97, 171.71, 140.46, 139.05, 138.05, 137.67, 135.56, 131.78, 129.30, 129.08, 128.08, 127.85, 127.18, 126.97, 125.38, 52.85, 52.17, 40.33, 32.29, 30.56, 18.74; HRMS: *m/z* 354.17 (M^+). Anal. Calcd for $C_{21}H_{24}NO_4$: C, 71.17; H, 6.83; N, 3.95. Found: C, 71.19; H, 6.85; N, 3.93%.

(E)-2-(5-(Ethoxycarbonyl)-6-oxo-1-phenylhept-1-en-4-yl)-1-hydroxy-5-methylpyridin-1-ium, 4f



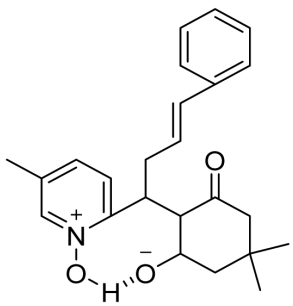
Yield 73%. IR (KBr): 3500 (OH), 1690 (-C=N-), 1730 (C=O), 1610 (C=C Ar) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.20 (m, 4H), 7.16 (s, 1H), 6.94 (s, 1H), 6.57 (s, 1H), 6.35 (s, 1H), 6.26 (s, 1H), 6.20 (s, 1H), 4.26 – 4.14 (m, 2H), 3.66 (s, 1H), 3.47 (s, 1H), 2.69 (s, 1H), 2.44 (s, 3H), 2.20 – 2.15 (m, 4H), 1.40 – 1.36 (d, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 201.97, 170.62, 140.46, 139.05, 138.05, 137.67, 135.56, 131.78, 129.30, 129.08, 128.08, 127.85, 127.18, 126.97, 125.38, 61.80, 52.66, 40.33, 32.29, 30.56, 18.74, 14.70; HRMS: *m/z* 368.19 (M^+). Anal. Calcd for $C_{22}H_{26}NO_4$: C, 71.72; H, 7.11; N, 3.80. Found: C, 71.74; H, 7.14; N, 3.83%.

(E)-1-Hydroxy-2-(5-(isopropoxycarbonyl)-6-oxo-1-phenyl-hept-1-en-4-yl)-5-methylpyridin-1-ium, 4g



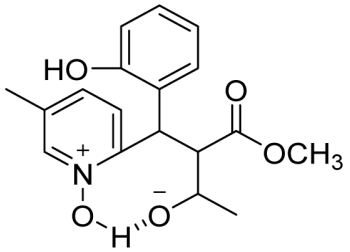
Yield 77%. IR (KBr): 3520 (OH), 1650 (-C=N-), 1735 (C=O), 1600 (C=C Ar) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 4H), 7.19 (s, 1H), 6.43 (d, 2H), 6.36 (s, 1H), 6.30 (s, 1H), 6.10 (s, 1H), 4.88 (s, 1H), 3.66 (s, 1H), 3.47 (s, 1H), 2.60 (s, 1H), 2.40 (s, 3H), 2.34 (s, 1H), 2.20 – 2.16 (d, 3H), 1.47 – 1.35 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 201.97, 171.89, 140.46, 139.05, 138.05, 137.67, 135.56, 131.78, 129.30, 129.08, 128.08, 127.85, 127.18, 126.97, 125.38, 71.24, 52.60, 40.33, 32.29, 30.56, 22.65, 22.44, 18.74; HRMS: *m/z* 382.20 (M^+). Anal. Calcd for $C_{23}H_{28}NO_4$: C, 72.23; H, 7.38; N, 3.66. Found: C, 72.25; H, 7.40; N, 3.68%.

(E)-2-(1-(4,4-Dimethyl-2,6-dioxocyclohexyl)-4-phenylbut-3-en-1-yl)-1-hydroxy-5-methylpyridin-1-ium, 4h



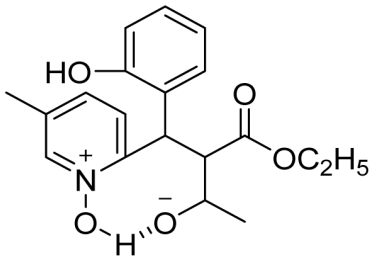
Yield 63%. IR (KBr): 3460 (OH), 1700 (-C=N-), 1750 (C=O), 1620 (C=C Ar) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 2H), 7.26 – 7.23 (m, 2H), 7.18-7.08 (m, 3H), 6.92 (s, 1H), 6.41 (s, 1H), 3.55 (s, 1H), 3.25 (s, 1H), 2.51 – 2.42 (m, 8H), 2.23 (s, 3H), 2.02 (s, 1H) 1.21 – 1.17 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 200.98 – 200.58, 140.46, 139.05, 138.05, 137.67, 135.56, 131.78, 129.30, 129.08, 128.08, 127.85, 127.18, 126.97, 125.38, 60.82, 52.06, 51.67, 36.30, 32.50, 32.29, 28.92, 28.61, 18.74; HRMS: *m/z* 379.21 (M^+). Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69. Found: C, 75.98; H, 7.72; N, 3.67%.

1-Hydroxy-2-(1-(2-hydroxyphenyl)-2-(methoxycarbonyl)-3-oxobutyl)-5-methylpyridin-1-ium, 4i



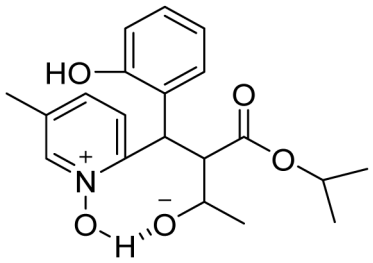
Yield 71%. IR (KBr): 3530 (OH), 1660 (-C=N-), 1745(C=O), 1625 (C=C Ar) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 7.14 (s, 1H), 7.07 (d, 2H), 6.86 (s, 1H), 6.73 (s, 1H), 6.66 (d, 2H), 4.91 (s, 1H), 3.95 (s, 1H), 3.80 (s, 3H), 3.63 (s, 1H), 2.46 (s, 3H), 2.13 – 2.09 (d, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 201.33, 170.17, 156.88, 140.05, 139.70, 137.87, 135.44, 131.74, 130.70, 128.08, 127.97, 127.89, 119.89, 119.17, 55.79, 52.17, 39.91, 30.56, 18.74; HRMS: *m/z* 330.14 (M^+). Anal. Calcd for $C_{18}H_{20}NO_5$: C, 65.44; H, 6.10; N, 4.24. Found: C, 65.46; H, 6.12; N, 4.26%.

2-(2-(Ethoxycarbonyl)-1-(2-hydroxyphenyl)-3-oxobutyl)-1-hydroxy-5-methylpyridin-1-ium, 4j



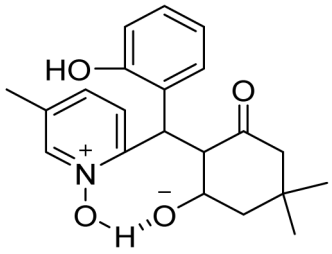
Yield 75%. IR (KBr): 3470 (OH), 1675 (-C=N-), 1740 (C=O), 1650 (C=C Ar) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.21 (d, 2H), 7.02 (s, 1H), 6.85 (s, 1H), 6.75 – 6.66 (m, 3H), 4.91 (s, 1H), 4.22 – 4.09 (m, 2H), 3.95 (s, 1H), 3.57 (s, 1H), 2.44 (s, 3H), 2.22 – 2.18 (m, 3H), 1.32 – 1.28 (d, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 201.33, 169.37, 156.88, 140.05, 139.70, 137.87, 135.44, 131.74, 130.70, 128.08, 127.97, 127.89, 119.89, 119.17, 61.80, 55.89, 39.91, 30.56, 18.74, 14.70; HRMS: *m/z* 344.15 (M^+). Anal. Calcd for $C_{19}H_{22}NO_5$: C, 66.27; H, 6.44; N, 4.07. Found: C, 66.25; H, 6.42; N, 4.09%.

1-Hydroxy-2-(1-(2-hydroxyphenyl)-2-(isopropoxycarbonyl)-3-oxobutyl)-5-methylpyridin-1-ium, 4k



Yield 80%. IR (KBr): 3450 (OH), 1690 (-C=N-), 1740 (C=O), 1650 (C=C Ar) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.04 (s, 1H), 6.99 (s, 1H), 6.86 – 6.72 (m, 3H), 6.46 (s, 1H), 6.34 (s, 1H), 4.90 (d, 2H), 3.95 (s, 1H), 2.83 (s, 1H), 2.39 (s, 3H), 2.22 – 2.18 (d, 3H), 1.43 – 1.30 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 201.33, 170.36, 156.88, 140.05, 139.70, 137.87, 135.44, 131.74, 130.70, 128.08, 127.97, 127.89, 119.89, 119.17, 71.24, 56.02, 39.91, 30.56, 22.65, 22.44, 18.74; HRMS: *m/z* 358.40 (M^+). Anal. Calcd for $C_{20}H_{24}NO_5$: C, 67.02; H, 6.75; N, 3.91. Found: C, 67.05; H, 6.72; N, 3.93%.

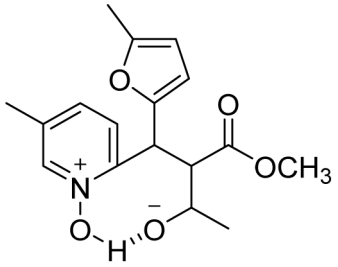
2-((4,4-Dimethyl-2,6-dioxocyclohexyl)(2-hydroxyphenyl)-methyl)-1-hydroxy-5-methylpyridin-1-ium, 4l



Yield 68%. IR (KBr): 3520 (OH), 1650 (-C=N-), 1735 (C=O), 1600 (C=C Ar) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.06 (d, 2H), 6.86 (s, 1H), 6.78 (d, 2H), 6.29 (s, 1H), 4.76 (s, 1H), 3.98 (s, 1H), 2.98 (s, 1H), 2.76 (s, 1H), 2.46 (s, 3H), 2.30 – 2.24 (m, 4H), 1.15 – 1.11 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 200.11, 199.89, 156.88, 140.05,

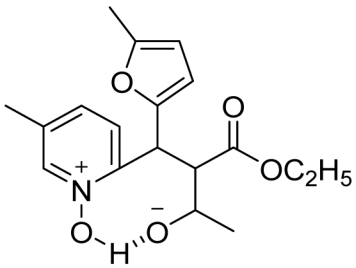
139.70, 137.87, 135.44, 131.74, 130.70, 128.08, 127.97, 127.89, 119.89, 119.17, 59.35, 52.06, 51.67, 38.93, 32.50, 28.92, 28.61, 18.74; HRMS: *m/z* 355.18 (M^+). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.93; H, 7.07; N, 3.91%.

1-Hydroxy-2-(2-(methoxycarbonyl)-1-(5-methylfuran-2-yl)-3-oxobutyl)-5-methylpyridin-1-ium, 4m



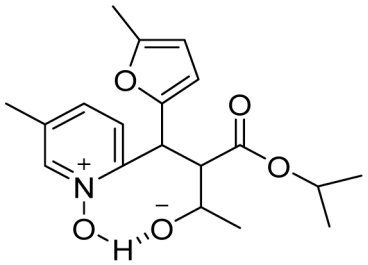
Yield 81%. IR (KBr): 3480 (OH), 1690 (-C=N-), 1740 (C=O), 1650 (C=C Ar) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.14 (s, 1H), 7.29 (s, 1H), 7.13 (s, 1H), 6.34 (s, 1H), 6.05 (s, 1H), 5.95 (s, 1H), 4.07 (s, 1H), 3.81 (s, 3H), 2.94 (s, 1H), 2.52 (s, 3H), 2.17 (s, 3H), 1.38 – 1.19 (s, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 202.73, 171.09, 151.76, 148.24, 139.86, 138.45, 133.84, 133.52, 131.08, 116.38, 106.78, 57.15, 52.17, 51.56, 30.56, 18.74, 14.50; HRMS: *m/z* 318.13 (M^+). Anal. Calcd for $C_{17}H_{20}NO_5$: C, 64.14; H, 6.33; N, 4.40. Found: C, 64.17; H, 6.35; N, 4.43%.

2-(2-(Ethoxycarbonyl)-1-(5-methylfuran-2-yl)-3-oxobutyl)-1-hydroxy-5-methylpyridin-1-ium, 4n



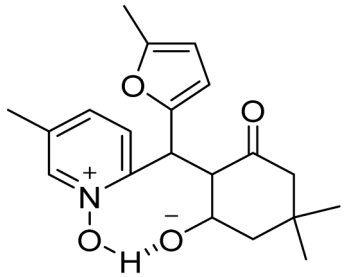
Yield 86%. IR (KBr): 3520 (OH), 1705 (-C=N-), 1735 (C=O), 1620 (C=C Ar) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.68 (s, 1H), 6.61 (s, 1H), 6.39 (s, 1H), 6.15 (s, 1H), 5.98 (s, 1H), 5.37 (s, 1H), 4.26 – 4.14 (m, 2H), 3.95 (s, 1H), 2.43 (s, 3H), 2.16 – 2.10 (m, 6H), 1.42 – 1.37 (d, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 202.73, 170.23, 151.76, 148.24, 139.86, 138.45, 133.84, 133.52, 131.08, 116.38, 106.78, 61.80, 57.67, 51.56, 30.56, 18.74, 14.70, 14.50; HRMS: *m/z* 332.15 (M^+). Anal. Calcd for $C_{18}H_{22}NO_5$: C, 65.05; H, 6.67; N, 4.21. Found: C, 65.07; H, 6.65; N, 4.23%.

1-Hydroxy-2-(2-(isopropoxycarbonyl)-1-(5-methylfuran-2-yl)-3-oxobutyl)-5-methylpyridin-1-ium, 4o



Yield 90%. IR (KBr): 3500 (OH), 1680 (-C=N-), 1740 (C=O), 1670 (C=C Ar) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.37 (s, 1H), 7.27 (s, 1H), 7.13 (s, 1H), 6.39 (s, 1H), 6.03 (s, 1H), 5.69 (s, 1H), 4.92 (s, 1H), 4.11 (s, 1H), 2.89 (s, 1H), 2.51 (s, 3H), 2.18 (s, 3H), 1.47 – 1.35 (m, 6H), 1.32 – 1.24 (d, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 202.73, 170.35, 151.76, 148.24, 139.86, 138.45, 133.84, 133.52, 131.08, 116.38, 106.78, 71.24, 57.98, 51.56, 30.56, 22.65, 22.44, 18.74, 14.50; HRMS: *m/z* 346.16 (M^+). Anal. Calcd for $C_{19}H_{24}NO_5$: C, 65.88; H, 6.98; N, 4.04. Found: C, 65.86; H, 6.95; N, 4.02%.

2-((4,4-Dimethyl-2,6-dioxocyclohexyl)(5-methylfuran-2-yl)methyl)-1-hydroxy-5-methylpyridin-1-ium, 4p



Yield 78%. IR (KBr): 3450 (OH), 1682 (-C=N-), 1735 (C=O),1650 (C=C Ar) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.22 (s, 1H), 6.75 (s, 1H), 6.66 (s, 1H), 6.00 (d, *J* = 28.9 Hz, 2H), 4.73 (s, 1H), 3.98 (s, 1H), 2.56 – 2.50 (m, 4H), 2.47 (s, 3H), 2.18 – 2.14 (d, 3H), 1.27 – 1.23 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 201.86, 201.47, 151.76, 148.24, 139.86, 138.45, 133.84 – 133.62, 131.08, 116.38, 106.78, 58.51, 52.06, 51.67, 49.20, 32.50, 28.92, 28.61, 18.74, 14.50; HRMS: *m/z* 343.18 (M^+). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.92; H, 7.36; N, 4.05%.

Conclusion

As a result of the C2-functionalization of 3-methyl pyridine-1-oxides with aldehyde, 1,3-diketone or β-ketoester in the presence of an ionic liquid as a

catalyst under solvent-free conditions, we have reported the synthesis of 5-methylpyridinium derivatives. This synthetic pathway offers a straight forward, inexpensive, effective, ecologically safe, and gentle technique, making it a practical synthetic method for C2-functionalization of pyridine *N*-oxides. Further research into this particular synthesis procedure revealed that the catalytic action of ionic liquids differed depending on the anionic counter part of the ionic liquid rather than the cationic component. Additionally, it was determined that the anionic portion of the ionic liquids' Brϕnsted basicity favourably influences the percentage yield of the products. Comparing the catalytic effects of ionic liquids [BMIM][OH], [BMIM][Ac], and [BMIM][Cl], we also found that [BMIM][OH]IL produced outstanding product yields while [BMIM][Ac] and [BMIM][Cl] ionic liquid produced fair to moderate yields. When compared to the microorganisms employed, the majority of the synthesised compounds were shown to have a variety of antibacterial properties with low minimum inhibitory concentrations. However, none of the examined compounds demonstrated more activity than the control substance. The substances **4l** and **4n** were discovered to exhibit outstanding activity against *S. aureus* and *E. coli*. Additional clinical studies are required. Thus our finding opens a new therapeutic window for the synthesis of innovative scaffolds with a green approach to treat bacterial infections, which are actually a significant danger in today's society.

Acknowledgment

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References

1 Joule J A & Mills K, *Heterocyclic Chemistry*, 5th Edn (Wiley, Chichester, UK) (2010).
2 Jasselin-Hinschberger A, Comoy C, Chartoire A & Fort Y, *Eur J Org Chem*, 2015 (2015) 2321.
3 Fumagalli F & Emery F S, *J Org Chem*, 81 (2016) 10339.
4 Beyeh N K & Puttreddy R, *Dalton Trans*, (2015). DOI: 10.1039/C5DT01143D.
5 Badgujar D M, Talawar M B, Asthana S N & Mahulikar P P, *Indian J Chem*, 49B (2010) 1675.
6 Vamos M & Cosford N D P, *J Org Chem*, 79 (2014) 2274.
7 Younis Y, Douelle F, Feng T S, Cabrera D G, Manach C L, Nchinda A T, Duffy S, White K L, Shackleford D M, Morizzi J, Mannila J, Katneni K, Bhamidipati R, Zabiulla K M, Joseph J T, Bashyam S, Waterson D, Witty M J, Hardick D, Wittlin S, Avery V, Charman S A & Chibale K, *J Med Chem*, 55 (2012) 3479.
8 Zhu A, Feng W, Li L, Li Q & Wang J, *Catal Lett*, 147 (2017) 261.
9 Mahato S, Santra S, Chatterjee R, Zyryanov G V, Hajra A & Majee A, *Green Chem*, 19 (2017) 3282.
10 Yang Y, Fan H, Meng Q, Zhang Z, Yang G & Han B, *Chem Commun*, 53 (2017) 8850.
11 Xie L-Y, Qu J, Peng S, Liu K-J, Wang Z, Ding M-H, Wang Y, Cao Z & He W-M, *Green Chem*, 20 (2018) 760.
12 Kai-Jian L, Si J, Ling-Hui L, Ling-Li T, Shan-Shan T, Hai-Shan T, Zilong T, Wei-Min H & Xinhua X, *Green Chem*, (2018). DOI: 10.1039/ C8GC00223A
13 Wu C, Wang Z, Hu Z, Zeng F, Zhang X-Y, Cao Z, Tang Z, He W-M & Xu X-H, *Org Biomol Chem*, 16 (2018) 3177.
14 Liu K-J, Fu Y-L, Xie L-Y, Wu C, He W-B, Peng S, Wang Z, Bao W-H, Cao Z, Xu X & He W-M, *ACS Sustainable Chem Eng*, 6 (2018) 4916.
15 Zhang S, Miran M S, Ikoma A, Dokko K & Watanabe M, *J Am Chem Soc*, 136 (2014) 1690.
16 Zhang S, Dokko K & Watanabe M, *Chem Mater*, 26 (2014) 2915.
17 Duan X C, Ma J M, Lian J B & Zheng W J, *Cryst Eng Comm*, 16 (2014) 2550.
18 Kaur N, *Catal Rev*, 57 (2015) 1.
19 Kaur N & Kishore D, *Synth Commun*, 44 (2014) 3082.
20 Kaur N & Kishore D, *Synth Commun*, 44 (2014) 3047.
21 Kaur N, Dwivedi J & Kishore D, *Synth Commun*, 44 (2014) 1671.
22 Sescousse R, Gavillon R & Budtova T, *Carbohydr Polym*, 83 (2011) 1766.
23 Stark A, *Energy Environ Sci*, 4 (2011) 19.
24 Gericke M, Fardim P & Heinze T, *Molecules*, 17 (2012) 7458.
25 Youseftabar-Miri L & Hosseinjani H, *Asian J Green Chem*, 2 (2017) 56.
26 Clinical and Laboratory Standards Institute (CLSI): Performance standards for antimicrobial susceptibility testing; eighteen informational supplement M100–S18. CLSI, Wayne, PA, USA (2008).
27 Padvi S A, Tayade Y A, Wagh Y B & Dalal D S, *Chinese Chem Lett*, (2016). DOI:10.1016/j.cclet.2016.01.016
28 Trimurti L & Deo S, *J Chin Adv Mater Soc*, (2017). DOI: 10.1080/22243682.2017.1288584.
29 Liu F, Li L, Yu S, Lv Z & Ge X, *J Hazard Mater*, 189 (2011) 249.
30 Liu F, Li Z, Yu S & Ge X, *J Hazard Mater*, 174 (2010) 872.
31 Alptüzün V, Parlar S, Taşlı H & Erciyas E, *Molecules*, 14 (2009) 5203.