RASĀYAN *J. Chem.*
Vol. 17 | No. 2 |696-708| April - June | 2024
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

VALIDATION OF CONTINUOUS FLOW METAL PLATE REACTORS IN THE TERPENE KETONE SYNTHESIS BY ALCOHOL OXIDATION

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ABSTRACT

The present study elucidates the oxidation of alcohols to terpene ketones using dichloro(p-cymene) ruthenium (II) dimer catalyst by continuous flow process using a metal plate reactor. The synthesized products were separated and validated using GC, GCMS, ^{1}H-NMR, and ^{13}C-NMR techniques. The reaction process exhibited product yield in the range of 80-95% on a scale of 1-80 grams. Optimization studies were conducted to calibrate the reaction conditions to improve the product yield. The scope of the reaction was explored using aromatic, cyclic, and aliphatic alcohols under optimized conditions, which resulted in high yields of terpene ketones. A reaction mechanism is proposed for the oxidation of alcohols by a continuous flow process. The significant advantages of the current protocol include synthesis at mild conditions, safer handling of reagents, flexibility to tune reaction conditions, and straightforward scale-up in the range of 1- 80 grams with high efficiency and reproducibility.

Keywords: Continuous Flow Process; Metal Plate Reactor; Oxidation Reaction; Ruthenium Catalyst; Secondary and Tertiary Alcohols.

RASĀYAN *J. Chem.*, Vol. 17, No. 2, 2024

INTRODUCTION

Terpenes are a diverse group of organic compounds found in a variety of plants and essential oils. Terpene carbonyl compounds are typically formed during the drying and curing process of plants.[1] Terpenes and terpene carbonyl compounds demonstrated a diverse array of biological and therapeutic properties, encompassing anti-inflammatory[2-3], analgesic[4], antifungal[5], and antioxidant effects.[6] These molecules are deployed as intermediates in specialty chemicals[7] and pharmaceutical industries[8-9], particularly for formulations of flavors and fragrances.[10-11] Therefore, understanding the synthesis method and properties of terpenes and terpene carbonyl compounds is crucial for industries developing new drugs[12-13], natural remedies[14-15], and innovative products.[16-17] Researchers have extensively studied various conditions for the synthesis and development of terpene carbonyl compounds.[18] Several methods have been developed to achieve this conversion, including oxidation[19-20], dehydration[21-22], and dehydrogenation reactions.[23-24] The transformation of alcohols into carbonyl compounds constitutes a pivotal stage in the synthesis of terpene derivatives. The choice of the method depends on the specific terpene carbonyl compound targeted, as well as the desired yield and purity. The synthesis of terpenes and terpenoids often involves vital oxidation reactions. Several methods can be followed for synthesizing terpene carbonyl compounds using a conventional batch process. Some of the commonly used methods were John's oxidations[25] and Swern oxidations[26], which were performed under cryogenic conditions.[27] Later, the synthesis of carbonyl compounds at room temperature was reported using Dess-Martin reagents.[28] Recently, advanced methods for selective oxidations of carbonyl compounds have been developed using TEMPO-based oxidation conditions[29-30], and copper[31-32], cobalt, manganese, Hypervalent iodine reagents, such as iodobenzene diacetate or iodine monochloride[33] was used to oxidize the alcohol to the corresponding carbonyl compound. Researchers have reported the usage of inorganic catalysts[34], phosphine ligands[35-36], and organometallic catalysts[37-38] in synthesizing carbonyl compounds through environmentally sustainable batch techniques, employing the oxidation of alcohols. However, these methods require sensitive reaction

http://doi.org/10.31788/RJC.2024.1728797

conditions, such as controlled moisture and oxygen content.[39] The usage of harmful catalysts [25] and solvents [26] in conventional batch processes can raise environmental concerns due to their potential toxicity[40] and harmful effects on the environment. In recent decades, the continuous flow process has emerged as a promising technology for resolving many of the challenges associated with traditional processes.[41-42] It has been proven effective in research and implementation and is particularly advantageous in handling sensitive catalysts[43] and hazardous reagents.[44] More recently, oxidation reactions have also been developed using continuous flow processes, including aerobic oxidations[45] and organometallic catalysis for greener processes with safer and more environmentally friendly conditions.[46] Continuous flow techniques present numerous benefits for producing carbonyl compounds via alcohol oxidation, such as heightened safety, increased conversion rates of reactants, and improved scalability.[47-48] Using ruthenium complexes has been well-established in hydrogen transfer hydrogenations.[49] This same catalyst has been attempted for hydrogen transfer oxidation reactions using conventional batch and continuous flow processes.[50-51] These complexes often contain a bipyridine ligand and can function as single and multi-site catalysts. Additionally, ruthenium complexes have been used in the oxidation of amines[52-53], hydrocarbons[54], and sulfides.[55] The high activity and selectivity of ruthenium complexes in oxidation reactions can be attributed to their ability to activate molecular oxygen[56-57] to participate in redox reactions.[58-59] However, the potential benefits of using commercially available Dichloro(p-cymene) ruthenium (II) dimer as a catalyst for oxidation for synthesizing carbonyl compounds via the flow process have not yet been explored in the literature, with continued efforts to optimize the flow reaction condition and understand their mechanism of ruthenium complexes as catalysts could become valuable tools for a wide range of oxidation reactions. The current study focuses on developing an efficient continuous flow process for synthesizing carbonyl compounds using metal plate reactors. We optimized the reaction conditions by varying the parameters such as temperature, molar ratio of triethylamine, pressure, retention time, and effect of solvent and catalyst to achieve a better product yield at a lower cost. The products were separated using GC, and GCMS, and characterized using ^{1}H-NMR, and ^{13}C-NMR methods. A variety of primary and secondary alcohols were employed in the reaction to explore the breadth of its applicability. The reproducibility of the reaction was confirmed on a scale of 1 to 80 grams. Our investigation demonstrates the effectiveness of metal plate reactors in the continuous flow process for the synthesis of terpene carbonyl compounds by oxidation.

EXPERIMENTAL

Material and Methods

The reagents 1-phenyl ethanol, 1-(2,6,6-trimethyl-cycclohex-2-enyl)-but-2-en-1-ol, 1-(2,6,6-trimethyl-cycclohex-1-enyl)-but-2-en-1-ol, 1-(2,6,6-trimethyl-cycclohexa-1,3-dienyl)-but-2-en-1-ol were acquired from Merck. The solvents cyclohexanol, cyclopentanol, geranyl acetol, 3-methyl pentenol, 4-tertiary butyl benzyl alcohol, benzyl alcohol, crotonol, and 2-methyl pentenol were purchased from Alfa-aiser. All the solvents used were of analytical quality. The dichloro(p-cymene)ruthenium(II) dimer catalyst was obtained from Sigma-Aldrich. The isolated molecules were characterized using Agilent - GCMS and Varian - NMR spectroscopy techniques.

Flow Reactor Description

The experimental set-up for the synthesis of terpene ketones from alcohols via oxidation by continuous flow process consists of a metal plate flow reactor attached with two flom pumps and a thermostat as given in Fig.-1. The reaction was conducted using a metal plate flow reactor constructed using Hastelloy which is highly resistant to a wide range of aggressive chemicals, acids, and environments, including those with oxidizing and reducing conditions. The reactor has a total volume of 10 mL, The reactor is equipped with flom pumps capable of operating within a range of 0.1 to 100 mL/min which helps to tune the flow rates as required by the process. The reactor is connected to an oxygen cylinder equipped with a mass flow controller and needle valves which ensure precise control of flow through a T-joint. The exit of the reactor links to a high-capacity back pressure regulator adept at managing optimal pressure levels of up to 20 bar. The thermostat system ensures a wide temperature range of -10°C to 150°C enabling it to accommodate a variety of chemical processes and reactions. The output from the reactor is consistently collected by downstream processes. The metal flow reactor provides an efficient continuous flow process arrangement for conducting reactions with precise control over volume, pressure, and temperature parameters.

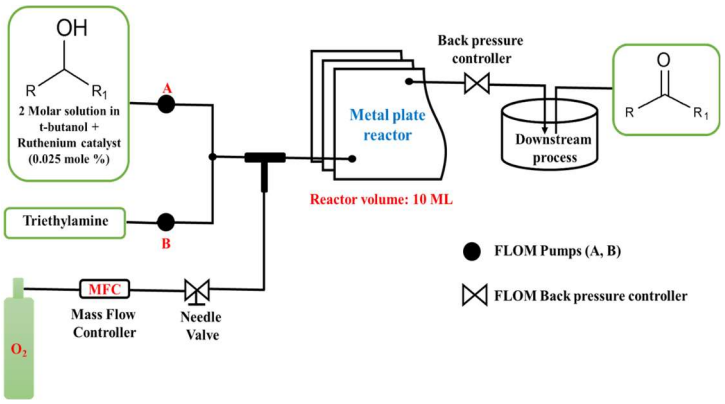
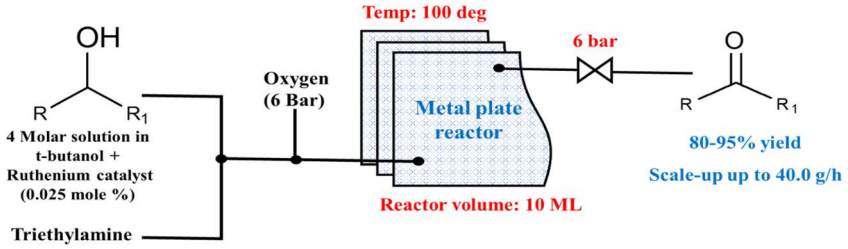


Fig.-1: General Scheme for the Synthesis of Terpene Ketones from Alcohol and Triethylamine as Base in the Presence of Dichloro(p-cymene) Ruthenium (II) Dimer Catalyst Using Metal Plate Flow Reactor

Procedure for the Synthesis of Carbonyl Compounds

The reagents and chemicals of Analytical grade were employed in the current study. A solution of terpene alcohol was made by dissolving 0.2 moles of alcohol in 100 ml of tertiary butanol solvent. This solution was then mixed with 0.025 mol% catalyst and conveyed to the reactor via pump A. The triethylamine base was transferred through pump B. The scheme of the reaction is given as scheme-1.



Scheme-1: Oxidation of Terpene Alcohols for the Synthesis of Terpene Ketones via a Continuous Flow Process

The flow system was primed with tertiary butanol solvent for 10 minutes at 6 bar oxygen pressure. Simultaneously, both pumps were activated under 6 bar oxygen pressure, with Pump-A delivering 1.5 ml/min and Pump-B delivering 0.5 ml/min (equivalent to 1.2 molar equivalents of triethylamine base) into a 10 mL metal plate flow reactor at a temperature of 100 °C, resulting in a residence time of 5 minutes. Stock solutions were prepared and kept under a nitrogen environment to prevent moisture contamination before beginning the flow operation. The resulting products were collected, treated with water to halt the reaction, and subsequently extracted using dichloromethane as the solvent. The organic layer was dried with sodium sulfate, and the solvent was removed under vacuum to obtain crude oils. A mixture of ethyl acetate and hexane in a 1:9 ratio, was employed in Column chromatography to purify the crude oils. The separated products were subsequently characterized using GC, GCMS, using the Agilent 7890 B instrument. The Varian 400 MHz NMR instrument was utilized to record the ^{1}H NMR and ^{13}C NMR spectra of the products. The residue obtained after evaporating the aqueous layer was absorbed using activated carbon to recover and regenerate the ruthenium metal.

RESULTS AND DISCUSSION

The 2.0 M solution of 1-phenyl ethanol in Tert-butanol with 0.5 mol% of Dichloro(p-cymene) ruthenium (II) dimer catalyst and 1.2-mole Eqv of triethylamine was simultaneously pumped into the metal plate flow reactor through different pumps for the synthesis of acetophenone. 1-Phenyl ethanol dissolved in tert-butanol with 0.5 mol% catalyst was pumped via pump A at a flow rate of 1.53 ml/min, while triethylamine was pumped via pump B at a flow rate of 0.479 ml/min. The reaction occurred at a pressure of 6 bar O_2 and a temperature of 100°C, with a retention time of 5 minutes. After the reaction, the stream was quenched in a water solution, and the product was extracted using cyclohexane solvent. The organic phase was then dried over sodium sulfate. The organic phase was monitored using gas chromatography.

Optimization Studies

The desired reaction was optimized by varying the oxygen pressure, temperature, triethylamine base mole ratio, retention time or flow rates, catalyst optimization, and solvent.

Effect of Pressure on the Synthesis of Terpene Ketones by Continuous Flow Process

The impact of pressure variation on the synthesis of carbonyl compounds was explored by adjusting the pressure within the range of 2-10 bars, as illustrated in Fig.-2. The reaction conditions followed are Pump-A for alcohol at 1.53 ml/min, Pump-B for triethylamine at 0.479 ml/min (1.1-mole Eqv of triethylamine), the temperature at 90°C, and a retention duration of 5 minutes. The results revealed a notable increase in the alcohol conversion rate from 2 to 6 bars of pressure. Notably, a significant surge in alcohol conversion rate was evident between 2 to 4 bars pressure, which is attributed to the increase in reagent mixing with the rise in pressure.[60] Nonetheless, within the pressure range of 6-10 bar, there was no significant increase in the conversion rate observed, mainly because the reaction had already reached completion. The attainment of reaction completion at pressures of 6 bar and beyond is credited to the accelerated reaction rate induced by the conversion of reagents into the vapor phase.[61] From a safety perspective, maintaining low pressure is preferable to ensure mild conditions. Consequently, 6 bar pressure is identified as the optimal pressure for further investigation.

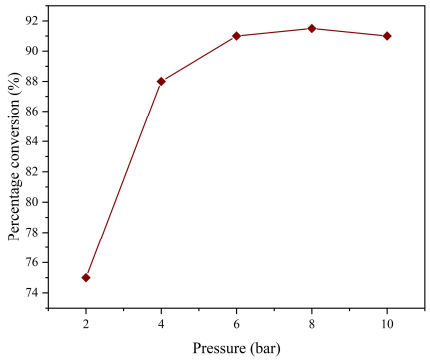


Fig.-2: Effect of Oxygen Pressure for the Synthesis of Ketones by Oxidation

Role of Temperature on the Synthesis of Terpene Ketones by Continuous Flow Process

The influence of temperature on the synthesis of carbonyl compounds by oxidation reaction has been monitored by changing the temperature from 80°C to 120°C at a constant 6 bar oxygen pressure and a 5-minute retention period. The reaction was conducted by maintaining the flow rates of Pump-A and B at 1.53 ml/min and 0.479 ml/min respectively using 1.1 moles equivalent to triethylamine base. An appreciable rise in the conversion rate was noted within the temperature range of 80-90°C, primarily due to the formation of the highest quantity of product. However, within the temperature range of 100-120°C, the conversion percentage remained almost constant, indicative of complete conversion of the reagents, despite minimal visibility of starting materials. The temperature of 100°C is identified as the optimal temperature for further optimization studies.

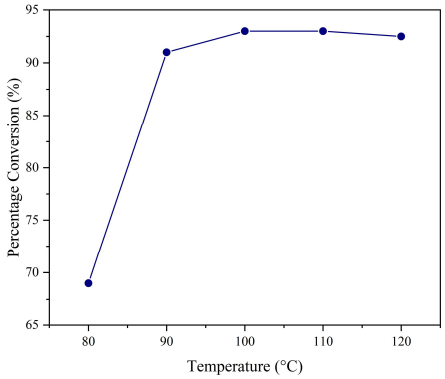


Fig.-3: Effect of Temperature for the Synthesis of Ketones by Oxidation

Effect of Molar Ratio of Triethylamine for the Synthesis of Terpene Ketones

By maintaining optimal conditions, the effect of the amount of triethylamine was studied by varying the molar equivalents of triethylamine (1.1-1.5) with a 5-minute retention duration at a temperature of 100°C and 6 bar O_2 pressure. As indicated in Table-1, the conversion rate was low at 1.0 mole equivalent of triethylamine due to the incompleteness of the reaction, but the reaction was complete at 1.1 mole equivalent of triethylamine. The reactions were found to be completed at 1.2 to 1.5 mole equivalents of triethylamine base. The optimum dose of 1.2 moles equivalent to triethylamine base was preferred in later optimization studies.

Table-1: Effect of Molar Ratio of Triethylamine Base for the Synthesis of Ketones by Oxidation

S. No.	Flow Rate of Pump-A (Substrate 2.0 M solution) ml/min	Flow Rate of Pump-B (Triethylamine) ml/min	The molar equivalent of Triethylamine	GC Conversion (%)
1.	1.55	0.45	1	80
2.	1.53	0.47	1.1	93
3.	1.5	0.5	1.2	95
4.	1.46	0.53	1.3	95
5	1.43	0.56	1.4	95
6.	1.41	0.59	1.5	95

Effect of Flow Rates and Retention Time for the Synthesis of Terpene Ketones

The influence of flow rates and residence times was investigated using 1.2 moles equivalent of triethylamine base at a temperature of 100°C and an oxygen pressure of 6 bar. The reaction performance was assessed by altering the flow rate of pump A, delivering substrate within the range of 0.75-3.0 ml/min, and the flow rate of pump B, delivering triethylamine ranging from 0.25 to 1.0 ml/min. The findings are shown in Table-2. The results revealed that the reaction achieved completion in 2.5 minutes with a conversion rate of 93%. However, at residence times of 5.0, 7.5, and 10.0 minutes the reaction exhibited a higher conversion rate of 95%. The 5.0-minute retention time was preferred as the optimal condition for future optimization experiments.

Table-2: Effect of Retention Time for the Synthesis of Ketones by Oxidation

S. No.	Flow Rate of Pump-A (Substrate 2.0 M solution) ml/min	Flow Rate of Pump-B (Triethylamine) ml/min	Retention time (min)	GC Conversion (%)
1	3.0	1.0	2.5	93
2	1.5	0.5	5.0	95
3	1.0	0.33	7.5	95
4	0.75	0.25	10	95

Effect of Amount of Catalyst on the Synthesis of Terpene Ketones by Continuous Flow Process

To investigate the impact of the amount of catalyst, the reaction was conducted by varying the amount of Dichloro(p-cymene) ruthenium (II) dimer catalyst from 0.05 to 0.5 % mole, while keeping the other parameters at their optimal values. The results are displayed in Fig.-4. The reaction was run under conditions of 2.0 M solution of 1-phenyl ethanol in Tert-butanol, 1.2-mole equivalents of triethylamine as the base at 6 bar oxygen pressure, 100°C temperature, and a 5-minute retention time. At a catalyst amount of 0.01 mole%, the oxidation reaction exhibited incompleteness resulting in a 75% conversion of alcohol. However, nearly complete conversion was achieved at 0.025 mol% of the catalyst surpassing 90% conversion Further increments in the catalyst amount from 0.25 % to 0.5 % mole did not exhibit a significant increase in conversion rate. Further optimization studies, considering economic factors, suggest the utilization of 0.025 % mole of catalyst as the optimum condition for the reaction.

Effect of Solvents on the Synthesis of Terpene Ketones by Continuous Flow Process

The selection of solvent in oxidation reactions can significantly influence reaction rates and selectivity. Optimization studies were carried out employing diverse solvents, the results are shown in Fig.-5. The optimized reaction conditions of 2.0 M solution of 1-phenyl ethanol in various solvents with 0.025 mol%

catalyst and 1.2-mole equivalents of triethylamine as a base under 6 bar oxygen pressure at 100°C with 5 minutes retention time.

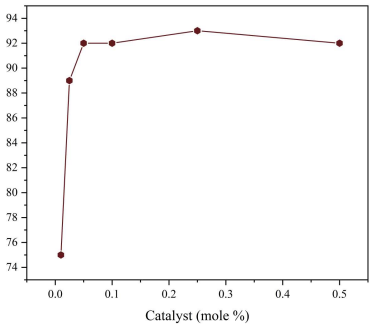


Fig.-4: Optimization of Catalyst for the Synthesis of Ketones by Oxidation

The lowest alcohol conversion was found when nonpolar solvents like Isopropyl alcohol and acetone were used. However, the reaction was found to be completed when tert-butanol, dimethylformamide, and dimethyl acetamide were facilitated as solvents. The completion of the reaction is attributed to the better stabilization of the intermediates, allowing the reaction to proceed till completion. Subsequent optimization experiments were conducted using tertiary butanol as a solvent to enhance the reaction conditions.

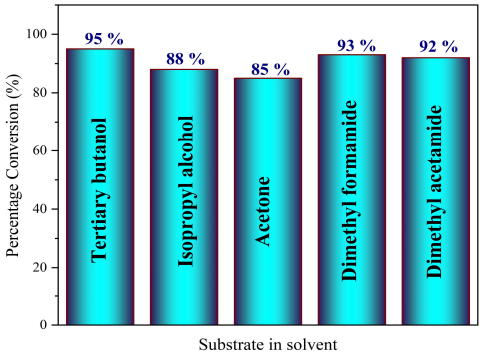


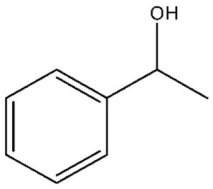
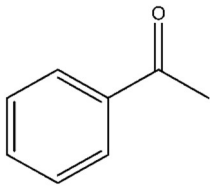
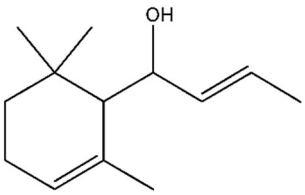
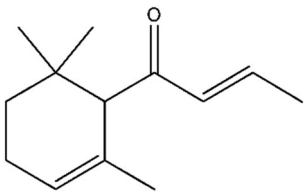
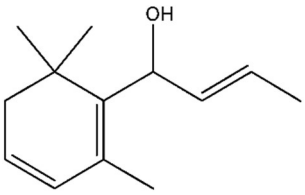
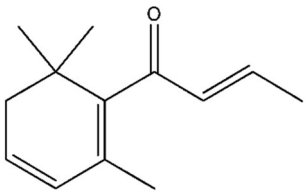
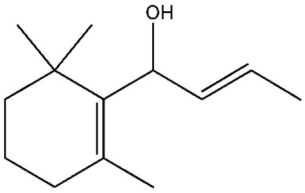
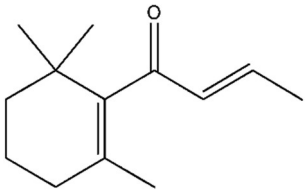
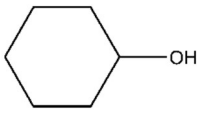
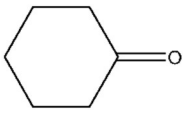
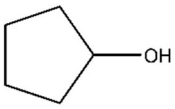
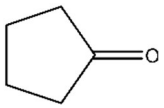
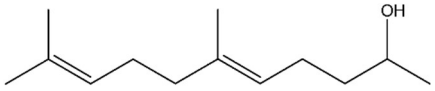
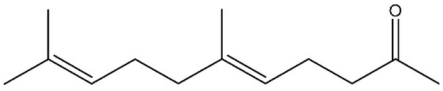
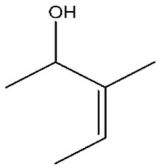
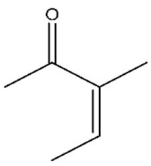
Fig.-5: Solvent Optimization for the Synthesis of Ketones by Oxidation

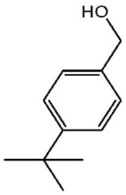
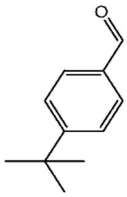
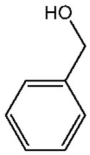
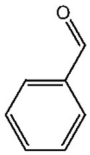
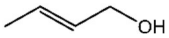
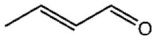
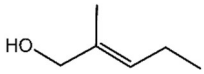
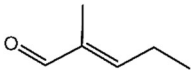
Drawing from the findings of optimization studies, the optimal conditions for ensuring the efficient and safe operation of the flow process include the usage of tertiary butanol as the solvent for substrates, 0.025 mol% catalyst, 1.2 molar equivalents of triethylamine as the base, 6 bar oxygen pressure at 100°C with 5 minutes retention time.

Scope of Oxidation Reaction by Continuous Flow Process for Synthesis of Terpene Ketones

The scope of the continuous flow processes for synthesizing terpene ketones was evaluated by deploying aromatic, cyclic, and aliphatic terpene alcohols on a gram scale under optimized conditions. An efficient synthesis of carbonyl compounds from a variety of alcohols (entries 1-12) was achieved using triethylamine and tertiary butanol as the solvent for substrate dilutions along with a 0.025 mole% of Dichloro(p-cymene) ruthenium (II) dimer catalyst. The resulting isolated yields of the synthesized terpene ketones are detailed in Table-3. The results of GCMS ^{1}H-NMR and ^{13}C NMR spectra of the isolated yields are given below. Aromatic ketones (entries 1-4) exhibited a high yield of 92-95% compared to cyclic and aliphatic ketones. The enhanced yield of aromatic ketones is attributed to the high stability due to resonance stabilization and delocalization of pi electrons across the ring. As the aromatic rings are more stable in aromatic terpene alcohol the oxidation reactions are more directed towards functional groups outside the aromatic ring. Cyclic terpene alcohols such as cyclopentanol (Entry 5) and cyclohexanol (Entry 6) exhibited a lower yield of 90% due to the lower boiling point and absence of aromatic structure. In contrast, aliphatic ketones (entries 7,8, 11 & 12) exhibited the lowest yield of 80-85% compared to aromatic and cyclic ketones, attributed to the lower stability of aliphatic ketones in comparison with cyclic and aromatic ketones. The results confirm the efficiency and cost-effectiveness of the continuous flow method and adopted optimized experimental conditions.

Table-3: Scope of Oxidation of Terpene Alcohols by Continuous Flow Process

Entry	Alcohols	Carbonyl compound	Yield (%)
1			94 %
2			95 %
3			94 %
4			94 %
5			90 %
6			90 %
7			85 %
8			80 %

9			94 %
10			92 %
11			82 %
12			85 %

GCMS, ^{1}H-NMR, and ^{13}C-NMR data of the isolated ketones synthesized by a continuous flow process

Phenylethan-1-one (Entry-01)
Yield: 94%; Pale yellowish colour liquid; m/z value: 120; ^{1}H-NMR ($CdCl_3$): δ 2.612 (3H, s), 7.263-7.487 (2H, dd, J = 89.6 Hz), 7.551-7.569 (1H, tt, J = 7.2 Hz), 7.588-7.974 (2H, dd, J = 154.4 Hz). ^{13}C-NMR ($CdCl_3$): δ 26.54 (1C, s), 128.234 (1C, s), 128.54 (2C, s), 133.039 (2C, s), 137.04 (1C, s), 198.097 (1C, s).

1-(2,6,6-Trimethyl-cyclohex-2-enyl)-but-2-en-1-one (Entry-02)
Yield: 95%; Yellowish colour liquid; m/z value: 192; ^{1}H-NMR ($CdCl_3$): δ 0.86-0.951 (6H, s), 1.145-1.198 (2H, dd, J = 21.2 Hz), 1.566 (3H, s), 1.906-1.908 (3H, d, J = 0.8 Hz), 2.033-2.073 (2H, dd, J = 16 Hz), 2.85 (1H, s), 5.61 (1H, dd, J = 7.1 Hz), 6.29-6.33 (1H, d, J = 16 Hz), 6.83-6.93 (1H, m, J = 40 Hz). ^{13}C-NMR ($CdCl_3$): δ 18.228 (1C, s), 22.669 (1C, s), 23.314 (1C, s), 27.823-28.073 (2C, 27.0 (s), 28.073 (s)), 31.308 (1C, s), 32.401 (1C, s), 61.278 (1C, s), 123.54 (1C, s), 130.557 (1C, s), 132.174 (1C, s), 142.248 (1C, s), 202.288 (1C, s).

1-(2,6,6-Trimethyl-cyclohexa-1,3-dienyl)-but-2-en-1-one (Entry-03)
Yield: 94%; Yellowish colour liquid; m/z value: 190; ^{1}H-NMR ($CdCl_3$): δ 0.886-1.094 (6H, s), 1.598-1.734 (3H, s), 1.928-1.945 (3H, d, J = 6.8 Hz), 2.111-2.16 (2H, dd, J = 19.6 Hz), 5.796-5.874 (2H, d, J = 31.2 Hz), 6.17-6.273 (1H, dd, J = 41.2 Hz), 6.797-6.871 (1H, m, J = 29.6 Hz). ^{13}C-NMR ($CdCl_3$): δ 18.334 (1C, s), 19.42 (1C, s), 26.13-26.221 (2C, s), 33.767 (1C, s), 39.347 (1C, s), 127.24 (1C, s), 127.953 (1C, s), 128.021 (1C, s), 134.52 (1C, s), 139.249 (1C, s), 146.127 (1C, s), 200.929 (1C, s).

1-(2,6,6-Trimethyl-cyclohex-1-enyl)-but-2-en-1-one (Entry-04)
Yield: 94%; Yellowish colour liquid; m/z value: 192; ^{1}H-NMR ($CdCl_3$): δ 0.97-1.195 (6H, s), 1.432-1.48 (2H, dd, J = 19.2 Hz), 1.571 (3H, s), 1.604-1.706 (2H, m, J = 40.8 Hz), 1.853-2.002 (5H, dd, J = 59.6 Hz), 6.125-6.167 (1H, d, J = 16.8 Hz), 6.683-6.774 (1H, m, J = 36.4 Hz). ^{13}C-NMR ($CdCl_3$): δ 18.324 (1C, s), 18.916 (1C, s), 21.268 (1C, s), 28.834 (2C, s), 31.134 (1C, s), 33.365 (1C, s), 38.814 (1C, s), 130.402 (1C, s), 134.606 (1C, s), 140.214 (1C, s), 145.746 (1C, s), 202.184 (1C, s).

Cyclohexanone (Entry-05)
Yield: 90%; Colourless liquid; m/z value: 98; ^{1}H-NMR ($CdCl_3$): δ 1.695-1.738 (2H, t, J = 17.2 Hz), 1.822-1.883 (4H, dd, J = 24.4 Hz), 2.31-2.342 (4H, dd, J = 12.8 Hz). ^{13}C-NMR ($CdCl_3$): δ 24.901 (1C, s), 26.935 (2C, s), 41.89 (2C, s), 212.111 (1C, s).

Cyclopentanone (Entry-06)
Yield: 90%; Colourless liquid; m/z value: 84; ^{1}H-NMR ($CdCl_3$): δ 1.939-1.993 (4H, dd, J = 21.6 Hz), 2.147-2.185 (4H, dd, J = 15.2 Hz). ^{13}C-NMR ($CdCl_3$): δ 23.128 (1C, s), 26.505 (2C, s), 38.26 (2C, s), 220.738 (1C, s).

6,10-Dimethyl-undeca-5,9-dien-2-one (Entry-07)
Yield: 92%; Colourless liquid; m/z value: 194; ^{1}H-NMR ($CdCl_3$): δ 1.566-1.679 (9H, s), 2.041-2.137 (9H, t, J = 38.4 Hz), 2.256-2.292 (2H, t, J = 14.4 Hz), 5.059-5.094 (2H, t, J = 14 Hz).
^{13}C-NMR ($CdCl_3$): δ 15.888 (1C, s), 17.558-17.595 (1C, s), 25.609-25.632 (1C, s), 26.429-26.543 (2C, 26.429 (s), 26.543 (s)), 29.851 (1C, s), 39.572 (1C, s), 43.685-3.928 (1C, s), 122.472 (1C, s), 124.118 (1C, s), 131.313-131.578 (1C, s), 136.397 (1C, s), 208.664 (1C, s).

3-Methyl-pent-3-en-2-one (Entry-08)
Yield: 80%; Pale yellowish colour liquid; m/z value: 98; ^{1}H-NMR ($CdCl_3$): δ 1.771-1.875 (6H, 1.771 (s), 1.858 (d, J = 6.8 Hz)), 2.3 (3H, s), 6.726-6.777 (1H, q, J = 20.4 Hz). ^{13}C-NMR ($CdCl_3$): δ 10.652 (1C, s), 14.705 (1C, s), 25.257 (1C, s), 138.293 (1C, s), 138.642 (1C, s), 199.6 (1C, s).

4-tert-Butyl-benzaldehyde (Entry-09)
Yield: 94%; Colourless viscous liquid; m/z value: 162; ^{1}H-NMR ($CdCl_3$): δ 1.358 (9H, s), 7.544-7.565 (2H, dd, J = 8.4 Hz), 7.812-7.832 (2H, dd, J = 8.0 Hz), 9.984 (1H, s). ^{13}C-NMR ($CdCl_3$): δ 31.012 (3C, s), 35.293 (1C, s), 125.396 (2C, s), 129.646 (2C, s), 134.026 (1C, s), 158.387 (1C, s), 192.001 (1C, s).

Benzaldehyde (Entry-10)
Yield: 92%; Colourless liquid; m/z value: 106; ^{1}H-NMR ($CdCl_3$): δ 7.501-7.561 (2H, dd, J = 24 Hz), 7.624-7.661 (1H, t, J = 14.8 Hz), 7.883-7.901 (2H, dd, J = 7.2 Hz), 10.031 (1H, s).
^{13}C-NMR ($CdCl_3$): δ 128.383 (1C, s), 128.922 (2C, s), 129.666 (2C, s), 133.574 (1C, s), 192.349 (1C, s).

Crotonaldehyde (Entry-11)
Yield: 82%; Pale yellowish color liquid; m/z value: 70; ^{1}H-NMR ($CdCl_3$): δ 2.027-2.047 (3H, d, J = 8.0 Hz), 6.122-6.182 (1H, dd, J = 24 Hz), 6.834-6.924 (1H, m, J = 36 Hz), 9.491-9.511 (1H, d, J = 8 Hz). ^{13}C-NMR ($CdCl_3$): δ 18.476 (1C, s), 134.409 (1C, s), 154.079 (1C, s), 193.897 (1C, s).

2-Methyl-pent-2-enal (Entry-12)
Yield: 85%; Pale yellowish color liquid; m/z value: 98; ^{1}H-NMR ($CdCl_3$): δ 1.103-1.141 (3H, t, J = 15.2 Hz), 1.746 (3H, s), 2.336-2.411 (2H, m, J = 30 Hz), 6.466-6.502 (1H, t, J = 14.4 Hz), 9.399 (1H, s). ^{13}C-NMR ($CdCl_3$): δ 8.967 (1C, s), 12.761 (1C, s), 22.263 (1C, s), 138.765 (1C, s), 156.219 (1C, s), 195.384 (1C, s).

Scalability of Continuous Flow Process for the Synthesis of Terpene Ketones at Higher Concentration
To validate the scalability of the protocol, the reaction was conducted using a large concentration of beta damascone (Entry-04) at an optimized scale. The substrate was continuously pumped for 2 hours, and 42 g of pale yellowish-coloured liquid product was isolated after purification with a molar yield of 94%. Furthermore, the scalability of the reaction was validated by conducting the reaction at a higher substrate concentration (4 molar solution) in tertiary butanol solvent, using 0.025 mol% of catalyst under optimized conditions for 120 minutes. The reaction was complete, and 80 g of pale yellowish-coloured liquid product was isolated after purification with a molar yield of 93.5% (entry-04). The results confirmed the efficiency of the reaction on a larger scale demonstrating its economic viability and suitability for the commercial production of carbonyl compounds from alcohols.

Proposed Mechanism for Terpene Ketone Synthesis via Continuous Flow Process
The depicted Fig.-6 illustrates the proposed reaction mechanism for this process. The ruthenium dichloride complex undergoes a transformative reaction upon interaction with a base, forming a coordination bond with alcohols. The following stages encompass hydride transfer and reductive elimination, resulting in the generation of carbonyl compounds and the formation of a ruthenium chloride intermediate. Upon further reaction with oxygen, a consequential by-product, hydrogen peroxide, emerges, concurrently regenerating the ruthenium chloride complex.

CONCLUSION

In the present study, we successfully synthesized terpene ketones by oxidation of alcohols using metal plate reactors by a continuous flow process. The products were isolated and confirmed using GC, GCMS, ^{1}H-NMR, and ^{13}C-NMR methods. The reaction conditions were optimized and a maximum product yield of (80-95) percent was obtained at 100°C, with 6 bar oxygen pressure and 0.025 mol% of Dichloro(p-cymene)

ruthenium (II) dimer as the catalyst. The reaction was found to be completed when tert-butanol, dimethylformamide, and dimethylacetamide were facilitated as solvents due to the better stabilization of the intermediates, which allowed the reaction to proceed till completion.

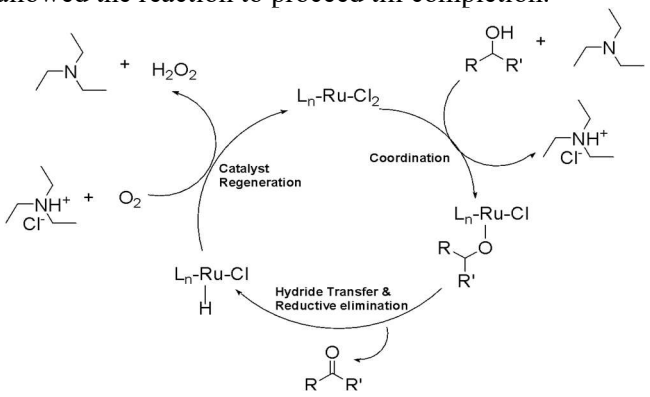


Fig.-6: Proposed Reaction Mechanism for the Synthesis of Terpene Ketones by Oxidation of Alcohols using Metal Plate Reactors by Continuous Flow Process

The scope of the reaction was confirmed with diverse alcohols and the product yield was reproducible on a scale of 1-80 grams under optimal conditions. Aromatic ketones exhibited a high yield of 92-95%, cyclic terpene ketones exhibited a yield of 90% and aliphatic ketones exhibited the lowest yield of 80-85%. The enhanced yield of aromatic ketones is attributed to the high stability due to resonance stabilization and delocalization of pi electrons across the ring. The lower boiling point and stability of aliphatic ketones are attributed to the lower yield of aliphatic ketones. The current study contributes to developing a sustainable and cost-effective flow process for the industrial production of terpene carbonyl compounds by oxidation.

ACKNOWLEDGMENTS

The authors thank Amol Raykar, Abhijeet Kulkarni of FlowRHEX®, Proburgeon Pvt Ltd, Pune -411041, India for providing the flow reactor facilities and Dr. C. U Aniz, Center for Refining and Petrochemicals, King Fahd University of Petroleum and Minerals, Dhahran, Kingdom of Saudi Arabia for the characterization facilities.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID IDs, given below:

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[RJC- 8797/2024]