Application Note 64:

Direct electrochemical oxidation of 4-tert-butyltoluene

Produced by Vapourtec

Abstract

This application note demonstrates the use of the Vapourtec Ion electrochemical reactor for the direct oxidation of 4-tert-butyltoluene into 4-tert-butyl benzaldehyde dimethyl acetal. After optimization of this key reaction, the desired product was afforded in a yield of 88%.

For more details, please contact:
Dr Manuel Nuño
Manuel.nuno@vapourtec.com
Or Vapourtec Application Support
application.support@vapourtec.com or call:
+44 (0) 1284 728659

Background

Electrochemical reactions offer one of the simplest and environmentally friendly ways of interacting with molecules [1]. Carrying out electrochemical reactions in flow offers clear advantages in terms of easier operation and avoids the issues associated with electrochemical cell limiting throughput in batch.

In this application note we report our successes in the electrochemical oxidation of 4-tert-butyl toluene [2], [3].

We report much improved yields (up to 88%) (with 98% consumption of starting material) to the corresponding and industrially important 4-tert-butyl benzaldehyde dimethyl acetal as well as showing modest control of selectivity towards 4-tert- butylbenzyl methyl ether by simple adjustment of the electrochemical conditions.

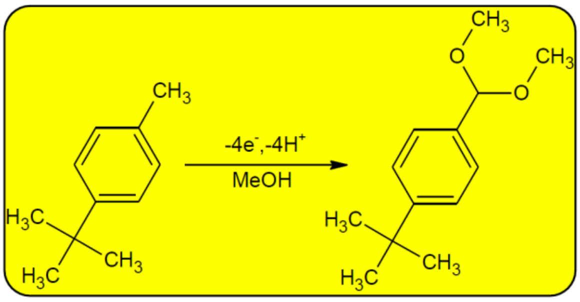


Figure 1 – The oxidative reaction of 4-tertbutyltoluene

Vapourtec has recently developed the Ion electrochemical reactor.

This versatile electrochemical reactor is compatible with both Vapourtec R-Series and E-Series flow chemistry systems. By taking advantage of the extremely large surface-to-volume ratios that a microreactor provides [4], this reactor makes electrochemical reactions more efficient. One of the key features of the Ion electrochemical reactor is its versatility to operate at different conditions:

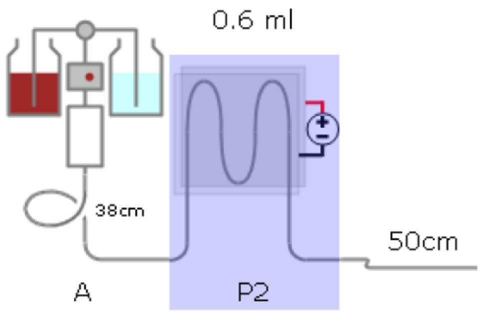
- It can be both heated and cooled (-10 °C to
- 100 °C)
- It can work at pressures of up to 5 bar
- (allowing to work over solvent's boiling
- point and with gas mixtures)
- The reactor's volume can be easily
- changed from 0.15 ml to 1.20 ml
- Any electrode material of dimensions 50
- mm x 50 mm and up to 2.0 mm thick can be
- fitted in the reactor. Vapourtec supplies 20
- different electrodes. Exotic electrodes can
- be sourced elsewhere.

In this application note, we illustrate the oxidative methoxylation of 4-tertbutyltoluene in methanol using this pioneering flow electrochemical reactor.

The reaction proceeded simply and smoothly, producing the corresponding product from the starting material and solvent which are readily commercially available compounds.

Setup

All the experiments were performed using the Vapourtec R-Series equipped with an R2C+ pump module as well as the new Ion electrochemical reactor.



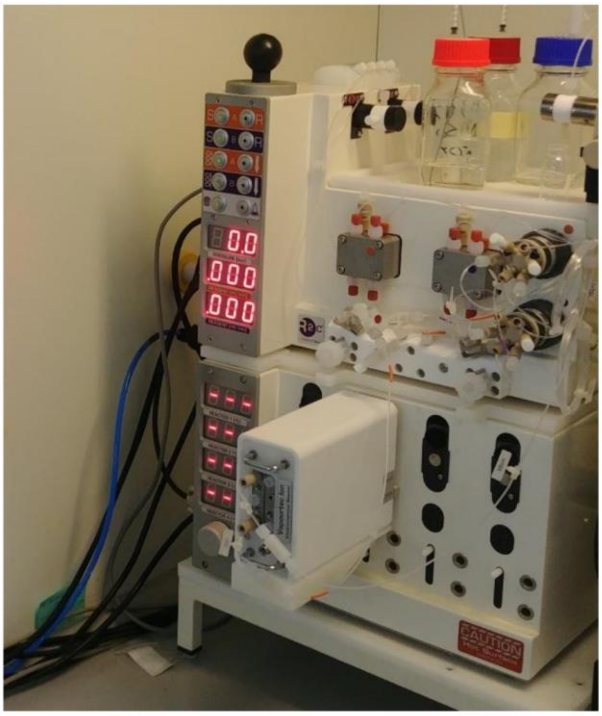


Figure 2 – Schematic diagram of instrumental set up

Reagents

All materials were purchased from Alfa Aesar:

- 4-tert-butyltoluene
- Anhydrous methanol
- Tetraethylammonium tetrafluoroborate (electrolyte)

System Parameters

charged into the vial. After this, the vial was evacuated and backfilled with N_2 three times. 2.0 ml of DMA was added via syringe and it was stirred for 5 min.

Then the aryl iodide (0.2 mmol, 1 eq) and alkyl iodide (0.52 mmol, 2 eq) were added to the mixture.

System Parameters

System solvent – Methanol

Reagent solution – A single solution, containing both electrolyte and 4-tert-butyltoluene was prepared using methanol as solvent. Five different concentrations of 4-tert-butyltoluene were prepared, from 0.1 to 0.5 M, whereas electrolyte concentration was set to 0.01 M and 0.02 M.

Working electrodes

Three different electrode pairs were used:

- Glassy carbon/stainless steel 304 (GC/SS)
- Platinum coated niobium/Stainless steel 304 (Pt/SS)
- Boron Doped diamond/stainless steel 304 (BDD/SS)

Flow rate – from 0.2 to 0.6 ml/min
Reactor volume - 0.6 ml
Reactor temperature: 23 °C
Back pressure regulator: 2 bar

Results and Discussion

The first step for electrochemical reactions is to calculate the required current at a given flow and concentration to ensure the required electrons will flow across the electrodes. This calculation is based on Faraday's first law of electrolysis. A chapter dedicated to explaining these calculations is available in the user manual for the Ion electrochemical reactor. Selecting the correct current will avoid further oxidation leading to undesired products.

1. Effect of electrode pair on conversion

Another critical parameter for electrochemical reactions is to set the right electrode pair. Three different pairs were evaluated for this reaction, CG/SS, Pt/SS and BDD/SS.

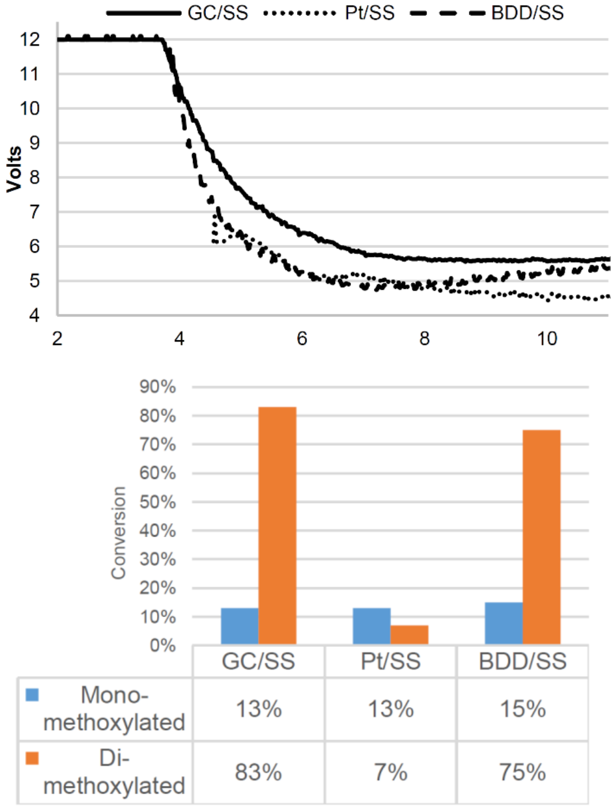
In order to compare results, flow rate, temperature, current and concentrations were fixed; table 1 compiles all the working parameters.

Table 1 – Reaction conditions for experiments in Section 1

Flow rate	0.2 ml/min
Temperature	RT
Current *(Relative current)*	0.28 A *(2.2 F)*
Concentrations	4-Tert-butyltoluene 0.1M Electrolyte 0.01M

By using Vapourtec's unique power source, both current density and voltage data were accurately recorded over time. Figure 3 shows the conversion yields and voltage evolution per electrode pair.

From this data, a correlation between the ohmic drop of each electrode pair and yield can be noted. The lower the drop, the better ionic flow across electrodes and, therefore, the better yield.



	GC/SS	Pt/SS	BDD/SS
🟦 Mono-methoxylated	13%	13%	15%
🟧 Di-methoxylated	83%	7%	75%

Figure 3 – i) Voltage drop over time for each electrode pair ii) Conversion for each electro pair

The mono- methoxylated product was present in all the cases at a low percentage, circa 13%. This indicates the first step of this reaction path is the mono-methoxylation of 4-tertbutyl-toluene, as previous publications reported [2]. The results of using the electrode pair Pt/SS revealed that sufficient current density throughout the reaction was not provided, hence less than 10% of starting material was converted to the desired di-methoxylated product. The authors postulate a lack of surface equilibrium between the electrode and electrolyte was the reason of such a dramatic difference in yields.

The electrode pair CG/SS was chosen to study the effect of starting material's concentration, as well as the effect of flow in conversion.

2. Effect of flow rate on conversion

To evaluate the optimum flow rate to maximize reaction yield for the electrochemical methoxylation of 4-tertbutyl-toluene, three flow rates were evaluated. Current was adjusted accordingly to flow rate. Table 2 compiles reaction conditions and figure 4 shows the afforded mono and di-methoxylated products.

Table 2 – Reaction conditions for experiments in Section 2

Starting material concentration	Electrolyte concentration	Flow rate	Temperature	Current *(Relative current)*
0.1 M	0.01 M	0.2 ml/min	RT	0.28 A *(2.2 F)*
0.1 M	0.01 M	0.4 ml/min	RT	0.56 A *(2.2 F)*
0.1 M	0.01 M	0.6 ml/min	RT	0.84 A *(2.2 F)*

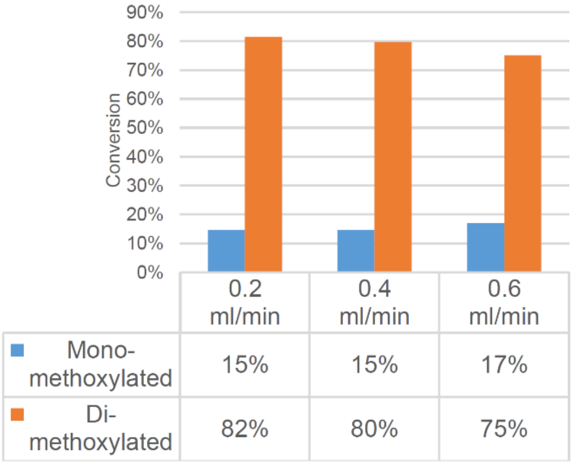


Figure 4 – Conversion rate at different flow rates

Although there was a measurable difference in conversion rates, the difference at working at high flow rates was less than 7%. Thanks to the Ion power controller, current was adjusted to flow rate accurately, therefore the electron flow was not affected of high flow rates.

3. Effect of concentration on conversion

Five different concentrations of 4-tert-butyltoluene were evaluated in this study, from 0.1 to 0.5 M in 0.1 M increments. In order to consistently provide the four electrons that the di-methoxylation reaction requires; current was adjusted accordingly to concentration.

Table 3 and Figure 5 compiles reaction conditions and conversion rates.

Table 3 – Reaction conditions for experiments in Section 3

Starting material concentration	Electrolyte concentration	Flow rate	Temperature	Current *(Relative current)*
0.1 M	0.01 M	0.2 ml/min	RT	0.28 A *(2.2 F)*
0.2 M	0.01 M	0.2 ml/min	RT	0.56 A *(2.2 F)*
0.3 M	0.01 M	0.2 ml/min	RT	0.84 A *(2.2 F)*
0.4 M	0.02 M	0.2 ml/min	RT	1.12 A *(2.2 F)*
0.5 M	0.02 M	0.2 ml/min	RT	1.40 A *(2.2 F)*

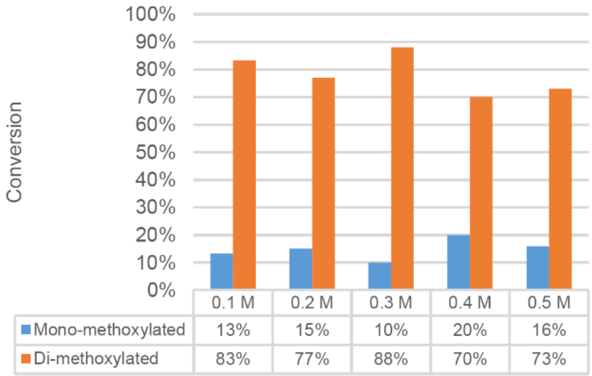


Figure 5 – Conversion rate at different concentrations

In all the reactions a conversion greater than 70 % was achieved for the di-methoxylated product. When using a starting material's concentration of 0.3 M, maximum 88% conversion was achieved. When the starting material's concentration was increased over 0.3 M, electrolyte's concentration was also increased to 0.02 M, ensuring the solution will conduct the electrons. Despite of those efforts, the di-methoxylated product's conversion dropped to the region of 70 %.

Conclusion

By using the newly developed Ion electrochemical reactor, we have successfully achieved a direct oxidation of 4-tert-butyltoluene. By selecting the right electrode pair, current, starting material's concentration and flow rate, yield was improved to 88%. This novel electrochemical approach to oxidations will be a useful technique for any synthetic chemist who wish to perform clean oxidations without the need of hazardous chemical reagents.

Supporting information

Table 4 – Reaction conditions for all the experimental work

Appearing in Sections	Entry reference	SM Concentration	Electrolyte Concentration	Electrode pair	Flow rate	Temperature	Current limit / Relative current	Conversion of SM (%)	Mono-methoxylated (%)	Di-methoxylated (%)
1,2 and 3	CG-020	0.1 M	0.01 M	CG/SS	0.2 ml/min	23 °C	0.28 A / 2.2 F	96.7	13.3	83.3
1	CG-025	0.1 M	0.01 M	Pt/SS	0.2 ml/min	23 °C	0.28 A / 2.2 F	19.5	12.7	6.8
1	CG-028	0.1 M	0.01 M	BDD/SS	0.2 ml/min	23 °C	0.28 A / 2.2 F	90.0	15.0	75.0
2	CG-003	0.1 M	0.01 M	CG/SS	0.4 ml/min	23 °C	0.56 A / 2.2 F	94.4	14.7	79.7
2	CG-004	0.1 M	0.01 M	CG/SS	0.6 ml/min	23 °C	0.84 A / 2.2 F	92.2	171	75.1
3	CG-022	0.2 M	0.01 M	CG/SS	0.2 ml/min	23 °C	0.56 A / 2.2 F	91.8	14.8	77.0
3	CG-024H	0.3 M	0.01 M	CG/SS	0.2 ml/min	23 °C	0.84 A / 2.2 F	98.4	10.0	88.4
3	CG-029	0.4 M	0.02 M	CG/SS	0.2 ml/min	23 °C	1.12 A / 2.2 F	89.7	19.6	70.2
3	CG-030	0.5 M	0.02 M	CG/SS	0.2 ml/min	23 °C	1.40 A / 2.2 F	89.2	16.2	73.0

The sample was dried in vacuo, dissolved in acetonitrile and analyzed by analytical HPLC.

System: Agilent 1200 equipped with an Eclipse XDB-C18 5 µm column (4.6 mm x 150 mm). The column was eluted at a flow rate of 1.0 ml/min, using a linear gradient from 65-95 % solvent B over 5.5 min.

Solvent Solvent A: Water; **Solvent B:** Acetonitrile

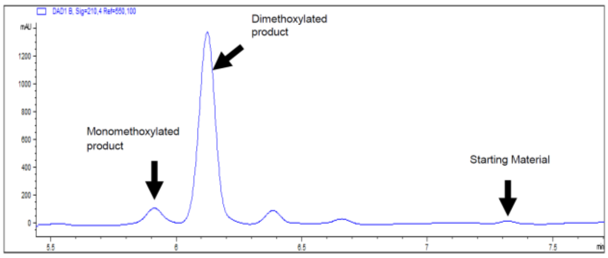


Figure 6 – HPLC of entry CG-024H

References

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