

A study into the use of microwaves and solid acid catalysts for Friedel-Crafts acetylations

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Abstract

A range of solid acids has been used for the acetylation of methyl salicylate by acetyl chloride/acetic anhydride. A comparison between microwave and traditional heating has been also been made. By comparing aluminium chloride, sulfated zirconia, copper triflate on silica, heteropoly tungstic acid on silica and iron(III) chloride on clay (claytec) a wide ranging comparison has been made and it has been discovered that solid acids can offer truly catalytic acetylations of relatively complex substrates albeit in lower yields than their traditional alternatives such as aluminium chloride. Microwave heating enables lower by-product formation and more importantly reaction times in the order of minutes as opposed to hours required by conventional means.

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1. Introduction

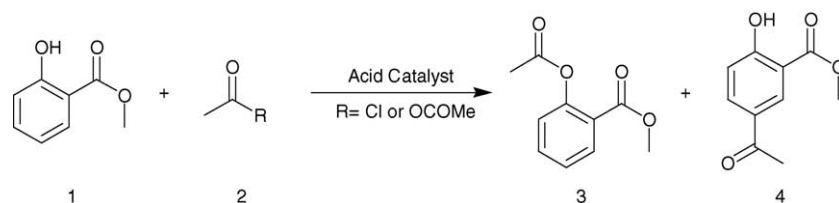
Friedel-Crafts chemistry has been used for acetylating aromatics since the turn of the last century [1]. It is a versatile method capable of acylating a variety of molecules including via intramolecular routes such as the Fries Rearrangement. Typically, a Lewis acid “catalyst” such as aluminium chloride is used (in stoichiometric quantities) but in recent years, following a drive for simplified work-ups, solid acids have become increasingly considered for these reactions though with limited success. One of the first uses of solid acids for these reactions was based on clay supported Lewis acid salts [2]. These solid acids were shown to be capable of facilitating the same reactions as the unsupported reagents, with the advantage of recovery by filtration for subsequent re-use. Applications were however, largely limited to alkylation reactions with acylations requiring at least stoichiometric quantities of the solid acid and/or very long reaction periods.

Microwave-assisted Friedel-Crafts reactions have been reported using graphite as a catalyst [3] and for carrying out thia-Fries rearrangements [4]. Laporte and co-workers studied a range of un-supported Lewis acids for acylation using microwave irradiation [5]. We now report the first use of microwave-assisted solid-acid catalysis for the acetylation of methyl salicylate. Genuinely catalytic reactions in short reaction periods are shown to be possible.

2. Experimental

The reaction under investigation is the acetylation of methyl salicylate (see Scheme 1). The solvent employed is nitrobenzene as it has been proven to be the superior solvent for this reaction [6]. Catalysts were made and activated by standard literature methods [7]. Standard microwave conditions, which were determined following a lengthy optimisation procedure, involved 0.03 g catalyst, 0.25 g methyl salicylate, 0.18 ml (1.1 molar equiv.) acetyl chloride and 4.5 ml nitrobenzene placed with a stirrer bar in the supplied 10 ml tubes for use in the PC controlled Prolabo

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Scheme 1. Acetylation of methyl salicylate.

Synthwave 402 microwave reactor (300 W max) with a nitrogen blanket. The system was then operated using a temperature controlled programme designed to heat the reaction to 120 °C over 2 min, then increase the temperature to 180 °C over the next 2 min and holding for 4 min.

The traditional block heated route was carried out in a 12 position Radleys carousel reactor with nitrogen blanket, water cooling block and stirrer hotplate (for heating and stirring). Into a tube equipped with a stirrer flea were placed 9 ml solvent, 0.48 ml (1.1 molar equiv.) acetic anhydride, 0.51 ml methyl salicylate (1.0 molar equiv.) and 0.06 g solid acid (prepared as necessary). The reactor was set running at 125 °C for 24 h then the temperature was increased to 180 °C. Samples [9] were taken at regular intervals throughout the reaction.

Analysis was carried out using a Hewlett Packard 1100 series HPLC system under PC control. The system uses a Luna 3 μm C18 (2) 50 mm × 2.0 mm i.d. column in a 40 °C oven and mobile phases A 1000 ml water with 0.5 ml trifluoroacetic acid (TFA) and B 1000 ml acetonitrile with 0.5 ml TFA. The flow rate is 1 ml/min with the gradient profile running from 0% B to 95% over 8 min. Ultraviolet (UV) detection is used at 220 nm. Samples [8,10,11] were compared to commercially available standards and LC–MS running a similar system with a positive and negative ion MS analyser.

3. Results and discussion

The reaction profiles for the various catalysts used in the traditional route are shown in Figs. 1–4 (Table 1).

The thermal reactions were carried out at 125 °C for the first 24 h with the intention of fully *O*-acetylating the methyl salicylate before ramping the temperature up to 180 °C to

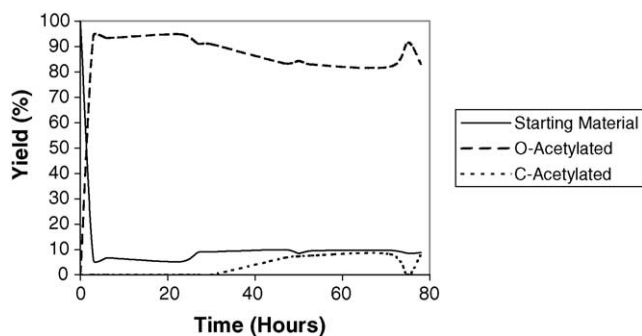


Fig. 1. Sulfated zirconia Friedel-Craft acylation of methyl salicylate.

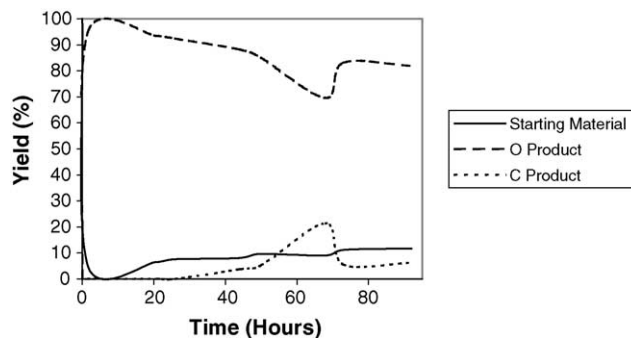


Fig. 2. Claytec Friedel-Craft acylation of methyl salicylate.

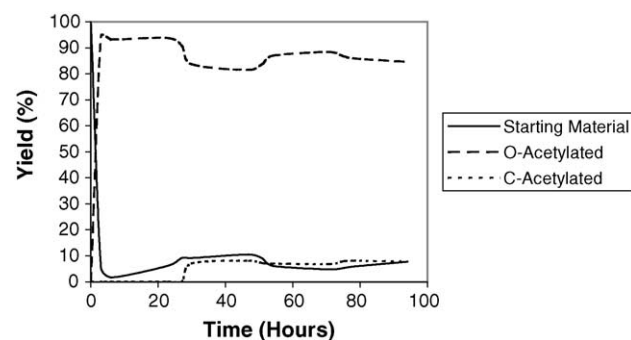


Fig. 3. HPW-Si Friedel-Craft acylation of methyl salicylate.

enable the Fries Rearrangement to the *C*-acetylated product. The choice of acetylating agent has proven to be of significant importance: acetic anhydride was selected for the thermal reaction for its ability to be used at a higher temperature. Both acetic anhydride and acetyl chloride were screened in the microwave reactor and acetyl chloride proved to be far superior for the reaction. Both acetyl sources were screened in thermal

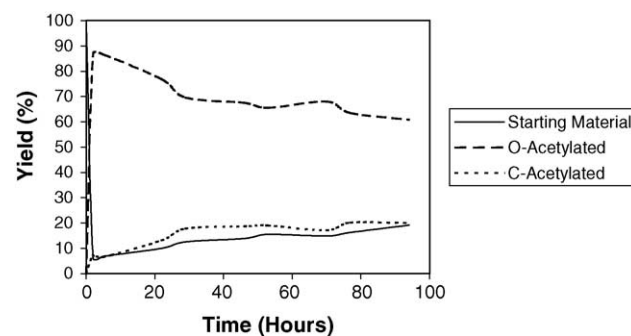
Fig. 4. Cu(OTf)₂-Si Friedel-Craft acylation of methyl salicylate.

Table 1
Results

Entry	Catalyst (loading mmol/g)	Heating method (temperature/°C)	Time (hours)	Yield ^a (%)	TON ^b	TOF ^c
1	AlCl ₃ (–) ^d	Microwave (120–180)	0.13	100	0.22	1.32
2	AlCl ₃ (–) ^d	Traditional (60)	8	100	0.22	0.02
3	Sulfated zirconia (0.5)	Traditional (125–180)	78	8.0	10.40	0.13
4	Claytec (1)	Traditional (125–180)	92	6.3	4.09	0.04
5	HPW-Si (0.09)	Traditional (125–180)	94	7.7	55.61	0.59
6	Cu(OTf) ₂ -Si (0.5)	Traditional (125–180)	94	20	26	0.28
7	Sulfated zirconia (0.5)	Microwave (120–180)	0.13	8.3	10.68	80.12
8	Claytec (1)	Microwave (120–180)	0.13	13.3	8.56	64.19
9	HPW-Si (0.09)	Microwave (120–180)	0.13	0	0	0
10	Cu(OTf) ₂ -Si (0.5)	Microwave (120–180)	0.13	18.5	23.80	178.57

^a HPLC percentage yield of *C*-acetylated product (4) normalised to the products.

^b Turnover number: number of moles of product (4) per mole of catalyst.

^c Turnover frequency: turnover number per unit time (h^{–1}).

^d Unsupported reagent: no loading applicable.

conditions and results were similar for both reagents. Acetyl chloride is more corrosive, moisture sensitive and volatile than acetic anhydride. For comparison a “blank” reaction was carried out using the conditions above without the catalyst. This reaction proved the facile nature of the *O*-acetylation step with greater than 90% *O*-product observed after 46 h.

During this study, attempts were made to optimise the amount of catalyst used for the reaction relative to the amount of substrate. We did not observe a simple linear increase in the rate of substrate conversion with increasing quantity of solid acid catalyst due to some of the substrate and/or product being absorbed onto the surface of the catalyst. Simultaneous thermal analysis was employed to determine how much material had been absorbed onto the catalyst (see Fig. 5). As the mass losses appeared to be similar for all catalysts, copper(II) triflate on silica was analysed as an example. Simultaneous Thermal Analysis (STA) indicates two new endothermic events in the DSC trace. These can be equated with the methyl salicylate (1) and *C*-acetylated product (4) evaporating from the silica catalyst support surface. It is unlikely that the major *O*-acetylated product would be observed, as it is thermally unstable and would decompose during the STA.

To determine the organic species present, DRIFTS and DRUV were used to study the dried solids after reaction. These confirmed the presence of aromatic species on the surface of the catalysts, however the excess nitrobenzene present masked the finer detail of the spectra preventing more detailed analysis.

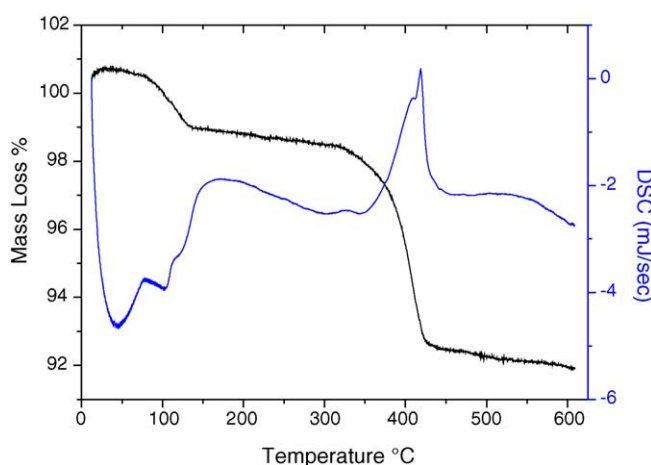
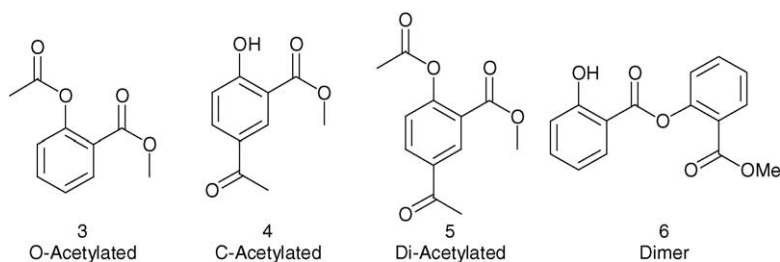


Fig. 5. STA copper(II) triflate on silica filtered from reaction.

During the course of the catalytic reactions a number of products (3–6) were observed and characterised by GC–MS; these are shown in Scheme 2. The di-acetylated product (5) is believed to arise from the trans-acylation [9] between two *O*-acetylated products (3). The final by-product observed is a dimer (6) proposed to be formed via hydrolysis of the methyl ester (1), by trace quantities of water present in the reagents and subsequent reaction between the new acid functionality and phenol functionality of another molecule of starting material (1) thus resulting in a new ester bond between the rings. This could potentially be minimised by careful exclusion of



Scheme 2. Observed reaction products.

moisture from reaction and drying of the reagents. The relative amount of the by-products depends on the catalyst used and the heating method. In general, the microwave produces far less by-products than the thermal method (0% versus up to 7%) the diacetylated product (5) has never been observed. The dimer (6) has never been observed in the microwave system, possibly due to the slow hydrolysis step not having time to occur or the fact that the large dipole of water means it preferentially absorbs microwaves and “boils” from the reaction mixture.

The turnover numbers for the reaction provide interesting observations. Firstly, they can be used to quantify the fact that aluminium chloride is in fact a reagent rather than a catalyst. An excess of aluminium chloride is typically used in Friedel-Crafts type chemistry and the catalyst cannot be recycled which increases the environmental burden of the reaction. Using a catalytic amount of aluminium chloride, no yield was observed in the microwave reaction. The relative amount of aluminium chloride was increased and no yield was observed until 1 equivalent was used. This study was also linked in with the substrate/catalyst ratio optimisation described before: when 3 equivalents of solid acid was used to give a direct comparison between the catalysts it resulted in absorption on to the large quantity catalyst support and an undeterminable conversion.

The thermal reactions using sulfated zirconia, HPW-Si and clayfec showed long induction periods of ca. 30–40 h. Whereas with aluminium chloride and $\text{Cu}(\text{OTf})_2\text{-Si}$ reactions started immediately. Once started, reactions followed the order AlCl_3 (0.49 mmol/h)¹⁰ > HPW-Si (0.093 mmol/h)¹¹ > $\text{Cu}(\text{OTf})_2\text{-Si}$ (0.083 mmol/h)¹⁰ > clayfec (0.016 mmol/h)¹¹ > sulfated zirconia (0.015 mmol/h)¹¹. Microwave reactions were only sampled once and we were unable to calculate meaningful rate data.

With aluminium chloride the microwave reaction offered significant improvements on the catalyst TOF as the reaction was complete within the 8 min microwave experiment while the TON remained the same. The TON was very similar for the microwave irradiated and thermally heated solid acid catalysed reactions, yields of up to 20% *C*-acetylation being achieved. For sulfated zirconia the yields were very similar for the two different heating methods. Clayfec offered around twice the yield in the microwave compared with the traditional heating. HPW-Si gave the highest TON thermally but failed to give any conversion in the microwave. Supported copper(II) triflate gave the best yield of all of the solid catalysts: around 20% both thermally and in the microwave. The extremely high TON for heteropolytungstic acid was due to it having around one tenth the loading of active material compared to clayfec, the loading used was that recommended by Kozhevnikova and co-workers [8], this relatively low loading is required as the catalyst is a large molecule with a tendency to cluster. However, the supported heteropoly acid gave zero conversion in the microwave, probably due to the HPW polyhedra being unsuitable for interacting with microwave energy. It is unlikely to be a problem with the

support material as copper triflate is supported onto the same K100 chromatographic amorphous silica gel. Clayfec gave an improved yield in the microwave compared to in the thermal heating, it has been suggested that transition metal elements can have a novel reaction under microwave irradiation. To date no explanation has been suggested for this but to further support this we also found copper triflate to be particularly effective under microwave conditions.

From a “green” perspective aluminium chloride is an undesirable catalyst. It requires use in greater than stoichiometric quantities, it is moisture sensitive, corrosive and produces a great deal of hazardous waste on work up, although it is highly active in many reactions. Alternative solid acids can achieve reasonable conversions, they can be reused and their handling is relatively simple. Importantly, aluminium chloride, when used in low amounts is a poorer catalyst than many of the solid acids studied in this work. The low conversions when working at low catalyst: substrate ratios may not be such a significant issue as the crude reaction mixture has few by-products and thereby has the potential to be recycled. Microwaves offer considerable time advantages over thermal heating methods for this reaction. However, microwaves do have a limited penetration (around 1 cm) meaning the vessels used must be small. Microwave flow system technology is currently developing rapidly and this reaction would be suitable for use in such a system. The use of a flowed system or microreactor would be of interest to the chemical industry as it decreases the inventory of chemicals held on a manufacturing site. Moreover it reduces the quantity of material at high temperature or pressure which thereby increases safety, which is a clean chemical technology goal.

4. Conclusions

Solid acids show genuine catalytic activity in the Friedel-Crafts acetylation of methyl salicylate, albeit in lower yields than the traditional alternatives such as aluminium chloride. When combined with microwave activation, it is possible to achieve catalytic reactions in short reaction periods. Flow microwave reactors would enable the large scale acetylation of methyl salicylate without the co-production of large quantities of hazardous waste material.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [10.1016/j.molcata.2004.12.030](https://doi.org/10.1016/j.molcata.2004.12.030).

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