



Lewis acid catalysed microwave-assisted synthesis of diaryl sulfones and comparison of associated carbon dioxide emissions

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ARTICLE INFO

Article history:

Received 8 September 2008

Received in revised form 11 January 2009

Accepted 12 January 2009

Available online 20 January 2009

Keywords:

Microwave

Sulfone

Sulfonation

Carbon dioxide

Catalysis

ABSTRACT

Diaryl sulfones were synthesised using a variety of Lewis acid catalysts under microwave activation. Catalysts were used both homogeneously and heterogeneously (K10 montmorillonite clay). The most effective catalyst in terms of yield was found to be iron(III) chloride with a yield of 89%. Supported iron(III) chloride gave a yield of 77%. The highest selectivity to the 4,4' isomer was obtained using supported bismuth(III) chloride. A series of other diaryl sulfones were synthesised using microwave-assisted Lewis acid catalysis in good yield. The energy used in the reactions was measured and the quantity of carbon dioxide generated per mole of product was compared using microwave and traditional thermal activation (oil bath) methods. Where yields were comparable, microwave-assisted synthesis was shown to produce substantially less carbon dioxide per mole of product.

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1. Introduction

Diaryl sulfones are useful intermediates in organic synthesis [1]. They have been shown to inhibit HIV-1 reverse transcriptase and possibly could address the toxicity and resistance problems of nucleoside inhibitors [2]. They also possess high antifungal and antibacterial activities [3]. Lastly, diaryl sulfones have also been shown to have antitumoral activities [4].

Friedel–Craft sulfonation reactions pose several catalytic issues, as traditional Friedel–Craft Lewis acid catalysts such as aluminium chloride can form stable complexes between sulfone product and Lewis acid catalyst [5]. These complexes must be broken down to obtain the sulfone product, thereby generating substantial quantities of aqueous acidic waste, (which may be toxic) requiring disposal, and for effective catalysis, a greater than stoichiometric quantity of ‘catalyst’ is required [5].

The use of alternative Lewis acid metal salts to aluminium(III) chloride as a catalyst, has been shown to provide higher catalytic activities; in some cases under microwave activation [5].

Microwave-assisted synthesis is a viable alternative to traditional thermal methods of producing sulfones [6]. Microwave-assisted reactions offer potential benefits over traditional thermal activation methods, in terms of improved yield, selectivity and shorter reaction times [6,7]. Microwave-assisted synthesis has been used in a wide range of reactions including base-catalysed hydroly-

sis of esters [8,9], Diels–Alder reactions [10] and dry organic reactions [11]. This shorter reaction time could offer substantial energy savings, especially in a commercial process.

We report our initial observations that alternative Lewis acid metal salts, such as bismuth(III) chloride and zinc(II) chloride display catalytic activity in Friedel–Craft sulfone synthesis under microwave activation, both homogeneously and heterogeneously on a K10 montmorillonite clay.

Currently, when assessing a reaction for ‘greenness’, traditional green chemistry metrics such as E-factor and atom economy are used [12]. However, metrics such as these do not incorporate energy used in a reaction or the environmental impact that the energy generation can have. One of the most significant impacts of energy generation is carbon dioxide produced by burning fossil fuels such as coal, gas and oil to generate electricity.

Methodologies for measuring carbon dioxide emissions from a process are used as part of the UK Emissions Trading Scheme. An estimation of the carbon dioxide footprint from a process can be made using a UK Carbon Trust estimation of 0.1661 kg CO₂/kWh for energy consumption where the precise generation source of the energy used is unknown [13].

Life cycle assessment must take into account the overall environmental impact of a process by considering inputs and outputs of all stages, including energy usage. Using a green chemistry reaction metric which enables the carbon dioxide release (from electricity generation for the energy used in the reaction) associated with each mole of product produced to be estimated, sulfonation reactions using both traditional thermal and microwave activation methods can be compared.

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2. Experimental

2.1. General experimental procedures

All chemicals used in synthesis were purchased from Aldrich UK Ltd. apart from sulfated zirconia from Degussa. GC analysis was performed using a Varian 3800 GC, a DB5 column was used of 30 m length and 0.25 mm thickness. The initial oven temperature was 60 °C, the final temperature being 150 °C. The oven temperature increased to the final value over 15 min. NMR analysis was performed using a JEOL 270 MHz NMR machine.

2.2. Comparison of alternative catalysts in the synthesis of bis(4-methoxyphenyl) sulfone

2.2.1. Synthesis of bis(4-methoxyphenyl) sulfone (**1**)

0.413 g (2 mmol) 4-methoxybenzenesulfonyl chloride and 0.54 g (5 mmol) of anisole were reacted together in the presence of 0.0325 g (0.2 mmol) of iron(III) chloride catalyst, using a CEM Discover microwave reactor at 300 W for 1 min with stirring.

Aqueous sodium carbonate solution (25 mL) was added. Dichloromethane (25 mL) was then added and the layers separated with the aqueous layer being removed. This was repeated twice.

The organic layer was dried using anhydrous magnesium sulfate for 10 h, the drying agent was removed by filtration. The sample was concentrated through removal of dichloromethane. The light-brown coloured solid obtained was washed three times by heating the product in hexane to 60 °C for 15 min each time. The hexane was removed by filtration to obtain a white-coloured solid, bis(4-methoxyphenyl) sulfone (**1**).

The product (**1**) was analysed using GC and both ^1H and ^{13}C NMR analysis. GC analysis shows peaks indicative of the 2,4'- and 4,4'-substituted isomeric forms at 15.6 and 15.9 min respectively, both of molecular mass 278 as shown by GC-MS. The absence of peaks at 2.4 and 7.8 min show no starting material was present in the final product. For the 4,4' isomer ^1H NMR (270 MHz, DMSO- d_6): δ 7.13 (4H, d), 6.72 (4H, d), 2.49 (6H, s); ^{13}C NMR (270 MHz, DMSO- d_6): δ 164.5, 118.4, 130.5, 137.4. This data for the 4,4' isomer is in agreement with the literature [14]. For the 2,4' isomer ^1H NMR (270 MHz, DMSO- d_6): δ 7.15 (2H, d), 6.77 (2H, d), 2.53 (3H, s), 7.21 (1H, d), 6.91 (1H, t), 6.97 (1H, t), 7.43 (1H, d), 2.72 (3H, s); ^{13}C NMR (270 MHz, DMSO- d_6): δ 164.5, 118.4, 130.5, 137.4, 53.1, 69.2, 142.3, 119.7, 112.4, 116.2, 121.2, 184.3.

2.2.2. Clay-supported catalysts

10 g of K10 montmorillonite clay was placed in a flask. 100 mL of methanol was added and the mixture was stirred. The quantity of desired Lewis acid catalyst to be supported was then added: for a 0.001 mol/g supported catalyst, 0.01 mol of the Lewis acid was required. The mixture was stirred for 2 h without heating. After 2 h, the methanol was decanted and 100 mL of fresh methanol was added. This mixture was then stirred for another 2 h. After this, the catalyst was isolated by filtration and oven-dried at 80 °C for 3 h. Four Lewis acid catalysts were supported: bismuth(III) chloride, iron(III) chloride, copper(II) chloride and zinc(II) chloride.

The filtrate from the process to support iron(III) chloride was analysed using atomic absorption spectroscopy to calculate the actual loading of iron(III) chloride on the support. A calibration chart was obtained using the maximum absorbance values for aqueous standards with 100, 200, 300, 400 and 500 ppm iron concentrations. A catalyst of 1.013 mmol/g loading had been produced. Using the same method, the amount of iron(III) chloride which had leached from the supporting clay during the sulfonation reaction was found to be 12.5% of the total iron(III) chloride originally loaded onto the support.

2.2.3. Comparison of catalysts (both heterogeneous and homogeneous)

Reaction between 0.413 g (2 mmol) 4-methoxybenzenesulfonyl chloride and 0.54 g (5 mmol) of anisole was performed using 10 mol% of the Lewis acid catalyst with respect to the 4-methoxybenzenesulfonyl chloride. In the case of heterogeneous catalysts a 0.001 mol/g loading was assumed to have been achieved. Four previously made heterogeneous (supported) and four homogeneous Lewis acid catalysts were used: bismuth(III) chloride, iron(III) chloride, copper(II) chloride and zinc(II) chloride (not supported). Unsubstituted K10 montmorillonite was also used to test any catalytic ability of the supporting clay. A reaction with no catalyst was also carried out as a further control.

The reaction was performed under microwave activation at 300 W power for 1 min with stirring. Analysis of the reaction yield was performed by GC.

Using a previously prepared sample of bis(4-methoxyphenyl) sulfone (**1**), a solution of known concentration of the sulfone in dichloromethane was made. To this solution was added a known quantity of an internal standard, dodecane. Using the GC peak areas of the bis(4-methoxyphenyl) sulfone (**1**) and dodecane and the known concentrations of these compounds within the solution, a GC response factor was calculated.

Following each of the screening reactions, the entire crude product was dissolved to 10 mL in dichloromethane with the addition of a known quantity of the external standard dodecane. GC analysis was performed on these solutions. From the areas of the combined GC product peaks (both isomeric forms) and the known concentration internal standard peak, the concentration of the product in the solution could be calculated using the response factor previously calculated. From the concentration of the product within this solution, the total number of moles of the product formed in the reaction could be calculated. Using the number of moles of 4-methoxybenzenesulfonylchloride used in the synthesis (the limiting reagent in the reaction), the yield of bis(4-methoxyphenyl) sulfone (**1**) could be calculated. The yields obtained are for both isomeric forms combined.

GC analysis also provided the ratio between the two isomeric forms of the product which were measured by comparison of the respective peak areas of the individual isomers.

The supported catalysts were examined for possible reusability with a negligible loss in catalytic activity or change in isomeric selectivity after 6 usages. In these experiments, the used catalysts were filtered from the final reaction mixture, washed with dichloromethane and dried at 60 °C for 2 h.

2.3. Carbon dioxide emission generated by synthesis of a variety of sulfones thermally and using microwave irradiation

2.3.1. Synthesis of 4-(4-methoxybenzene-sulfonyl)phenol (**1a**)

3.1 g (11 mmol) of bis(4-methoxyphenyl) sulfone (**1**) previously prepared was added to 25 mL glacial acetic acid and 2.2 g of 57% hydriodic acid. The mixture was refluxed for 16 h and made slightly alkaline with 20 mL dilute sodium hydroxide before filtration. The filtrate was extracted with diethyl ether (25 mL). The aqueous solution was made acidic with hydrochloric acid and the resulting precipitate collected. After crystallisation from water and thorough drying, crystallisation from benzene gave, 0.8 g of 4-(4-methoxybenzene-sulfonyl)phenol (**1a**) (yield 27%). GC and GC-MS analysis gave two product peaks indicative of the two isomeric forms at 12.9 and 13.3 min of 264 mass. ^1H NMR (270 MHz, DMSO- d_6): δ 10.54 (1H, s), δ 7.66 (2H, d), δ 7.16 (2H, d), δ 6.89 (2H, d), 6.75 (2H, d), 2.48 (3H, s); ^{13}C NMR (270 MHz, DMSO- d_6): δ 164.8, 163.9, 137.0, 131.6, 130.8, 128.4, 115.8, 118.4.

Table 1
Comparison of catalysts in the microwave-activated reaction of 4-methoxybenzenesulfonyl chloride and anisole.

Catalyst	Selectivity to 4-4' isomer (%)	Yield (both isomers) (%)	Catalyst	Selectivity to 4-4' (%)	Yield (both isomers) (%)
BiCl ₃	73	26	BiCl ₃ supported on K10	93	64
CuCl ₂	83	12	CuCl ₂ supported on K10	91	49
FeCl ₃	78	89	FeCl ₃ supported on K10	90	77
ZnCl ₂	76	82	ZnCl ₂ supported on K10	82	61
No catalyst	79	0.5	K10 alone	80	47
ZSM-5 zeolite	75	15	Zinc(II) triflate	71	17
Sulfated zirconia	74	46	Copper(II) triflate	69	14

2.3.2. Carbon dioxide emission per mole of product

The amount of energy required for the reaction was measured using a standard six-dial domestic energy meter. This value in kWh was converted to a quantity of carbon dioxide using the expression given in Section 3. The energy used for work-up of reaction mixture, computer control programmes and to provide cooling (water for reflux and air for the microwave) is not included.

3. Results and discussion

Table 1 shows the performance of a variety of catalysts in the microwave-activated reaction between anisole and 4-methoxybenzenesulfonyl chloride to form bis(4-methoxyphenyl) sulfone Fig. 1. Iron(III) chloride was found to be the best catalyst in terms of yield both homogeneously and heterogeneously with yields of 89% and 77% respectively. The homogeneous (unsupported) value is comparable with the literature [5]. The next most effective catalyst after iron(III) chloride in terms of yield is zinc(II) chloride, with yields of 82% and 61% for homogeneous and heterogeneous catalysts, respectively. Supporting the catalyst in both these cases appears to show a minimal decrease in catalytic activity with the added advantages associated with a heterogeneous catalyst.

Meanwhile, bismuth(III) chloride homogeneously achieves a yield of just 26%, but a yield of 64% when used heterogeneously. Thus, supporting the Lewis acid in this case offers a significantly higher sulfone yield. The same applies to copper(II) chloride with a yield of 12% homogeneously compared with 49% heterogeneously. The improved yields of the Lewis acid catalysts when using the K10 montmorillonite clay support can at least partly be attributed to the effect of the acid support itself which achieves a 47% yield of product under the same conditions as the other catalysts.

There are two isomeric forms of the product. In terms of isomer selectivity, when using the metal chlorides, there is a greater selectivity to the 4,4' isomer when using a heterogeneous catalyst in all cases. This is most significant when using bismuth(III) chloride which shows a fourfold increase in selectivity compared to the homogeneous reaction. Arguably, the much improved selectivity achieved when using BiCl₃ outweighs the disadvantage of relatively lower activity when compared to more active catalysts such as FeCl₃ and makes BiCl₃ on K10 one of the most useful catalysts for the synthesis of bis(4-methoxyphenyl) sulfone with a yield of 59% of the

4,4' isomer alone. However, ultimately homogeneous FeCl₃ has the highest yield of the 4,4' isomer alone at 70% making it the most effective catalyst for the synthesis of the 4,4' isomer.

Experiments were also carried out to test the reusability of the supported Lewis acids. These showed a negligible loss in catalytic activity or selectivity after 6 reuses. This demonstrates a further advantage of the heterogeneous catalysts over their unsupported equivalents in that they offer potential reuse and significantly higher turnover numbers.

Tests were also performed on an alternative clay to K10. K11 clay gave a yield of 21% compared to 47% using K10 with no supported metal salt. However, the reaction requires a catalyst of some sort to achieve a reasonable yield, as just 0.5% is achieved with no catalyst at all.

As well as the metal chlorides, other catalysts were screened for activity. ZSM-5 zeolite was used giving a yield of 15% much lower than the metal chlorides. Copper and zinc triflates were also tested for activity as alternatives to metal chlorides giving yields of 14% and 17% respectively. The highest yield achieved by alternative catalysts to the metal chlorides was sulfated zirconia which gave a yield of 46%. However, in no cases did these catalysts match the supported metal salts in terms of selectivity to the 4,4' isomer.

These reactions were all performed using microwave activation methods which have been shown to provide high yields over very short periods of time. 300 W energy was found to be necessary to reach the required sealed reaction vessel temperatures (approximately 180 °C) for the reaction to achieve the highest sulfone yields achieved. However, no increase in yield or change in product selectivity was to be found through reactions lasting longer than 1 min.

To show the true extent of the reduced energy (and time) this microwave activation approach requires, comparison was made between traditional thermal methods (i.e. an oil bath) and microwave activation in a variety of sulfonation type reactions.

From the UK Carbon Trust website [13], an expression can be used to estimate the carbon dioxide emission associated with a process. This expression has been adapted to calculate the quantity of carbon dioxide emitted from the associated heating activation required per mole of product and is given below:

$$\text{CO}_2 \text{ emission (kg/mol)} = \frac{\text{energy consumption (kWh)} \times 0.1661}{\text{number of moles of product}}$$

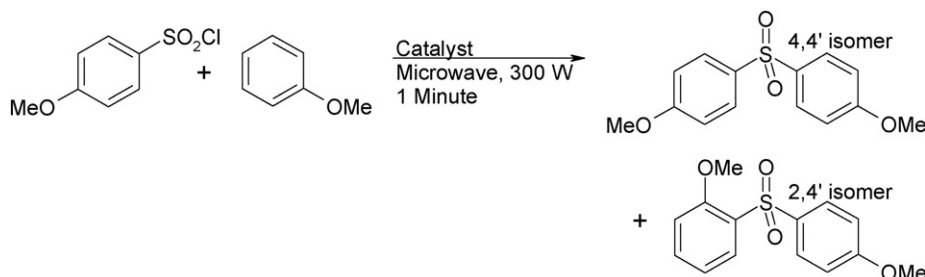
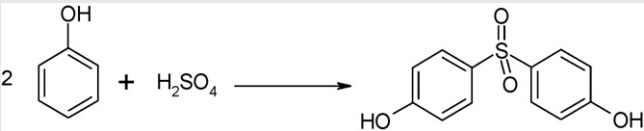
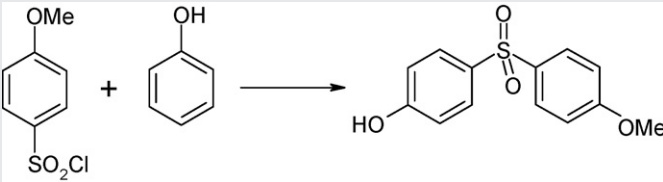
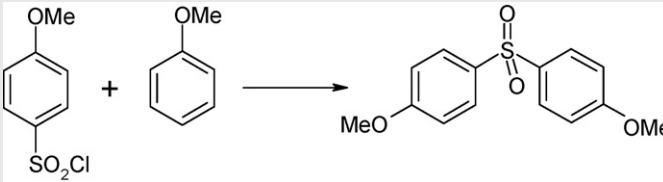


Fig. 1. Reaction between 4-methoxybenzenesulfonyl chloride and anisole to give bis(4-methoxyphenyl) sulfone and 2-methoxyphenyl 4-methoxyphenyl sulfone.

Table 2
Carbon dioxide emissions generated by the synthesis of a variety of sulfones using both traditional and microwave activation.

Reaction	MW Yield (%)	CO ₂ emission (kg/mol)	Oil bath yield (%)	CO ₂ emission (kg/mol)
Phenol and sulfuric acid ^a 	16	35	55	313
4-Methoxybenzenesulfonyl chloride and phenol ^b 	19	47	42	42
4-Methoxybenzenesulfonyl chloride and anisole ^b 	86	8	82	80

^a Using an oil bath this reaction was performed under vacuum distillation (to remove water from the reaction mixture) at 35 mbar. The energy used for the vacuum distillation was not taken into account for the calculations. In the microwave reaction, 3 Å molecular sieves were used to aid water removal.

^b Both of these processes employed iron(III) chloride as a catalyst using both thermal activation methods.

For several diaryl sulfone syntheses, the energy used to provide the thermal activation for the reaction was measured using an electricity meter. From this value, a quantity of carbon dioxide emitted to produce the energy required for the reaction to occur can be estimated. Thus, a quantity of carbon dioxide produced to make a mole of each sulfone product can be calculated.

Table 2 shows estimated carbon dioxide emissions per mole of product formed for a variety of sulfonation reactions. The lowest carbon dioxide emission is just 8 kg CO₂/mol in the case of the microwave-activated reaction between 4-methoxybenzenesulfonyl chloride and anisole. This compares to 80 kg of carbon dioxide per mole when using an oil bath to provide activation for the same reaction to occur. Therefore, in this case, the considerably faster microwave reaction is far more time- and energy-efficient than using a traditional thermal activation approach.

This greater energy efficiency converts to a much reduced carbon dioxide emission and therefore carbon footprint from the reaction using microwave activation. It is found that in two of the three cases above there is an order of magnitude (or greater) decrease in CO₂ emissions.

This trend of lower carbon dioxide emissions per mole of product when using microwave activation is consistently observed in all reactions, except where there are substantially lower yields in the microwave reactions compared to the oil bath. If a reaction has a comparable yield when using microwave activation compared to traditional thermal activation method, the microwave reaction is significantly more energy-efficient and gives a lower carbon dioxide emission.

There are, however, a number of limitations to these carbon emission estimations. In estimating the entire energy consumption of a process, and therefore associated carbon dioxide emissions, additional energy demands of the processes must be considered.

These estimations do not take into account the energy used for cooling (providing water or air to perform the reactions at reflux), the energy used for product work-up and vacuum distillation to extract water (in the case of 4,4'-dihydroxydiphenyl sulfone synthesis) among other possible sources of energy consumption.

Also, it must be considered that the microwave reactions are also performed on a much smaller scale, and the effects of 'scaling-up' the microwave reactions is unknown, although this is unlikely to result in a significant reduction in energy efficiency.

4. Conclusions

Diaryl sulfones have been synthesised in reasonable yields using a variety of Lewis acid catalysts, both homogeneously and heterogeneously, under microwave activation. The highest yield obtained for the synthesis of bis(4-methoxyphenyl) sulfone was using iron(III) chloride with respective yields of 89% and 77% for homogeneous and heterogeneous catalysis.

In all cases, supporting a catalyst on K10 montmorillonite clay also provided a greater selectivity to the 4,4'-substituted isomer over the 2,4'-substituted one. Bismuth(III) chloride offered the greatest selectivity to the 4,4' isomer, 93% of the product was 4,4'-substituted compared to 7% of the 2,4'.

These reactions not only offer good yields and isomer selectivity but also have very short reaction times of 1 min under microwave activation. Such short reaction times offer significant potential energy savings and a reduced environmental impact as a result.

Acknowledgement

The authors would like to acknowledge the assistance and financial support of Clariant UK Ltd.

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