Dimethyl carbonate and phenols to alkyl aryl ethers *via* clean synthesis

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The industrially important alkyl aryl ethers (ArOR) were selectively obtained in good yields from the O-alkylation of the corresponding phenols with the environmentally benign reagents, dimethyl carbonate or diethyl carbonate. The reactions were carried out under atmospheric pressure, in a homogenous process, without solvent and in the presence of potassium carbonate as catalyst.

Introduction

The development of sciences and technologies have resulted in a substantial improvement of our lifestyles. These almost unbelievable achievements have, however, led to some impacts on the global environment and public awareness. In particular, chemistry has been contributing to this evolution. Through the combination of knowledge on molecular reactivity, design and other subdisciplines of chemistry and chemical engineering, green chemistry has been looked upon as a sustainable science which accomplishes both economical and environmental goals, simultaneously. With this objective, we developed an alternative process to obtain the industrially important aryl methyl ethers by O-methylation of phenols with dimethyl carbonate (DMC).

Alkyl methyl ethers are useful for the preparation of fragrances, pesticides, cosmetic products, dyes, *etc*.[1] By far the most common method of production is the O-methylation of phenols with dimethyl sulfate[2–5] or methyl halides.[6–11] These reagents are very harmful, and the need for a stoichiometric amount of base to neutralise the acid by-product results in large amounts of inorganic salts to be disposed of. Methanol has also been used as the methylating agent. However, the reaction needs a strong acid catalyst[12–14] or to be carried out at very high temperature (200–400 °C) using zeolite as catalyst.[15–25] Furthermore, the reaction was not selective. Due to these problems, DMC has been emerging as a potential methylating agent.[26–29]

The O-methylation of phenols with DMC can be carried out in an autoclave at a temperature between 120 and 200 °C, in the presence of catalysts such as alkali or organic bases in combination with an iodide,[30] tertiary amines or phosphines,[31] nitrogen-containing heterocyclic compounds (*e.g.* 4-(dimethylamino)pyridine),[32] pentaalkylguanidines[33] or cesium carbonate.[34]

Basic zeolites, aluminas or alumina-silica were described as good catalysts in a continuous-flow process. The reactions were conducted at a temperature range from 180 to 300 °C in the vapour phase. Although high yields of aryl methyl ethers were obtained, by-products of C-methylation were also observed.[35,36] Guaiacol and veratrole were synthesised by O-methylation of catechol over modified aluminas in a continuous-flow process at a temperature between 250 and 300 °C.[37–39] Selectivity towards either guaiacol[38] or veratrole[39] was obtained over alumina loaded with alkali hydroxide or alumina

loaded with potassium nitrate, respectively. Over the catalysts $CrPO_4$ and $CrPO_4$-$AlPO_4$, DMC was demonstrated to be more effective than methanol in the O-methylation of phenol.[40] Calcined Mg-Al hydrotalcite was also an efficient catalyst in the O-methylation of phenols with DMC. A maximum guaiacol yield was obtained at 300 °C under optimised conditions.[41,42] The continuous-flow process under gas/liquid phase transfer catalysis (GL-PTC) conditions, with polyethylene glycol (PEG) as phase transfer catalyst and potassium carbonate as base, has been widely reported.[43–48] The reactions were conducted at a temperature range from 160 to 180 °C. In such conditions, the reaction was O-selective and anisole was obtained in good yield. However, the reaction of high boiling point phenols might be difficult to carry out in a continuous-flow process. Other phase transfer catalysis processes were conducted in a solid/liquid system in the presence of catalysts composed of K_2CO_3 and crown ether at 100 °C[49] or K_2CO_3 and tetrabutylammonium bromide at reflux of DMC.[50] However, in these methods, the rate of ether formation per mole of catalyst was relatively low.

Due to their high boiling point, asymmetric carbonates have been used to accomplish the O-methylation of phenols under atmospheric pressure at a temperature between 120 and 150 °C, in the presence of potassium carbonate and a polar solvent. The selectivity of methylation *vs.* alkylation was better when DMF or triglyme was used as solvent. However, 100% selectivity towards methylation was not obtained.[51]

We report herein the development of an environmentally friendly process for O-methylation of phenol derivatives with DMC (Scheme 1). At 160 °C, under atmospheric pressure, without solvent, in the presence of catalytic amount of potassium carbonate alone, the O-methylation of phenols can be selectively achieved with an excellent conversion velocity, compared to the known processes.

Green Context

The replacement of salt-forming reagents with more efficient systems is exemplified by the use of dimethyl carbonate (DMC) in place of *e.g.* methyl chloride. Here, DMC is successfully used to methylate phenols in good yield and with only (recyclable) methanol and CO_2 as co-products. Separation is relatively simple. *DJM*
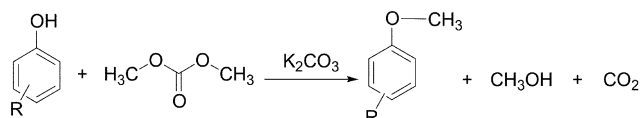
Scheme 1

Results and discussion

In this investigation, *p*-cresol (pC) was used to optimise the reaction conditions. Following the optimum conditions for the O-methylation of *p*-cresol, other phenols have also been tested.

We have reported that the reaction of phenols with DMC can easily be achieved in the presence of tetrabutylammonium bromide at 130 °C under atmospheric pressure. The performance of this reaction at a temperature higher than the boiling point of DMC can be achieved by progressive introduction of DMC into the reactor. Although excellent yields and rates of conversion were simultaneously obtained, the thermal stability of tetrabutylammonium bromide is a limitation.[51,52] To overcome this problem, we replaced the organic base by a mineral base, an alkaline carbonate, which is thermally more stable.

The reaction was carried out at 160 °C, in a semi-continuous process in which DMC was progressively fed into the preheated reactor already containing *p*-cresol and K_2CO_3. The pC/K_2CO_3 molar ratio was 120. To maintain the reaction medium at 160 °C under atmospheric pressure, the low boiling point by-product (methanol) and the excess of DMC were progressively distilled from the reaction medium. After 30 h of the reaction, pC was totally converted into 4-methylanisole (Fig. 1). The molar hourly space velocity of 4-methylanisole (4MA) formation per mole of catalyst (herein, MHSV[4MA]) varied form 3.25 h^{-1} at the beginning of the reaction to 4.1 h^{-1} during the steady state (Fig. 2).
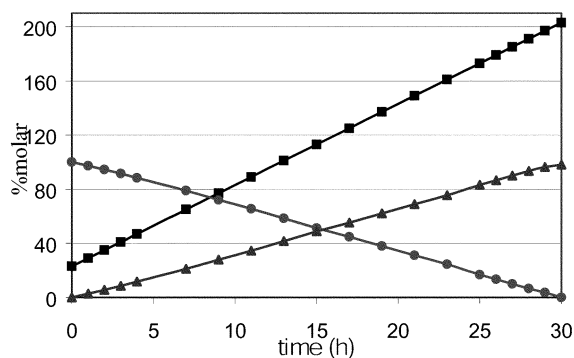

Fig. 1 Progression of O-methylation of *p*-cresol with DMC. (■) Amout of DMC fed into the reactor; (●) amount of *p*-cresol, (▲) yield of 4-methylanisole.
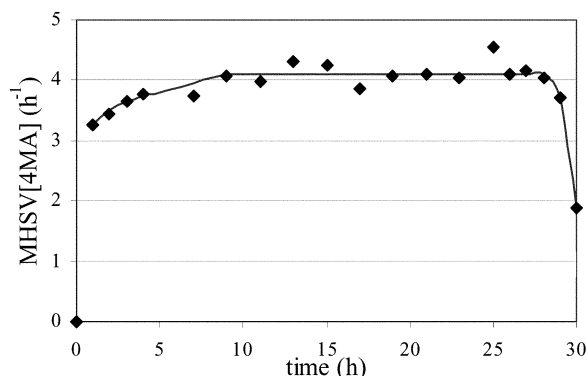

Fig. 2 Evolution of molar hourly space velocity of 4MA formation per mole of catalyst, MHSV[4MA].

Influence of substrate concentration

The reaction medium was homogeneous since during the pre-heating period, K_2CO_3 was progressively dissolved in *p*-cresol. While nearly total conversion of pC was attained, the base reappeared in the solid state. This phenomena can be explained by the formation of $CH_3(C_6H_4)OK$ which is miscible with *p*-cresol. The formation of this potassium salt was confirmed by FTIR spectra (Fig. 3). The spectrum of the mixture of *p*-cresol and K_2CO_3, after heating to 160 °C, shows a decrease of intensity of a broad band characteristic of OH of *p*-cresol at 3338 cm^{-1}. The degree of solubility depends on temperature as shown in Fig. 4. Therefore at 160 °C, the pC/K_2CO_3 molar ratio should be > 23 (or K_2CO_3/pC molar ratio < 0.043) to ensure that the medium is homogeneous.

To reduce the reaction time, the pC/K_2CO_3 molar ratio was decreased from 120 to 25. In the investigation of the effect of solvent, we found that the solvent does not influence the MHSV[4MA] (Table 1 entries 5–10). Meanwhile, the pC/K_2CO_3 molar ratio has a slight influence on MHSV[4MA], because when the reaction medium is too concentrated in *p*-cresol (entries 1 and 4), MHSV[4MA] is slightly decreased. Hydrogen-bonding among molecules of *p*-cresol might disturb phenolate anion formation, and consequently the reaction kinetics are slowed down.
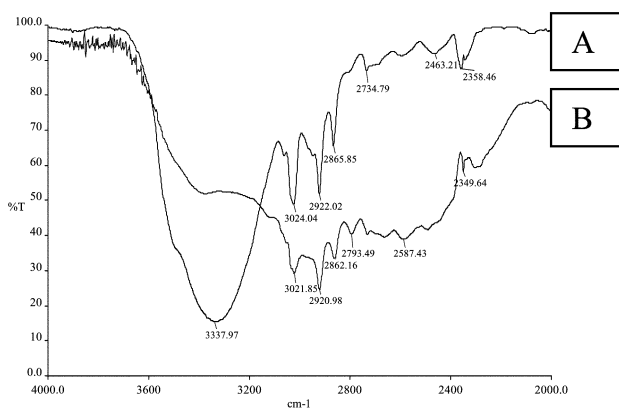

Fig. 3 Comparison of FTIR spectra of pure *p*-cresol (A) and a mixture of *p*-cresol/K_2CO_3 after being heated to 160 °C (B).
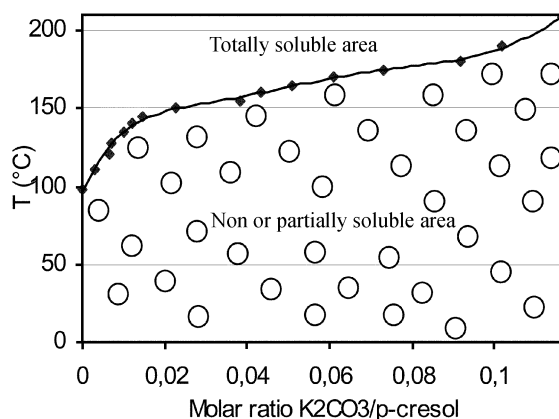

Fig. 4 Relation between temperature and solubility of K_2CO_3 in *p*-cresol.
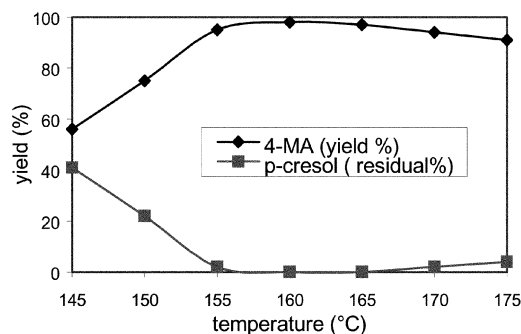
Influence of temperature of the reaction medium

The temperature of the reaction is one of the most influential factors on the reaction kinetics. At 100 °C, the catalyst is totally

Table 1 Effect of *p*-cresol concentration on yield and on MHSV[4MA] of the reaction

	Reaction conditions												Average
Entry	pC/mol	K$_2$CO$_3$/mol	DMC (t_0)/mol	Solvent Identity	Wt/g	T/°C	Time/h	DMC flow/mol h^{-1}	pC flow/mol h^{-1}	Total DMC/mol	Total pC/mol	Yield (%)	MSHV[4MA]/h^{-1}
1	1.2	0.01	0.277	None	0	160	30	0.072	0	2.437	1.2	98	3.92
2	0	0.01	0	4MA	50	160	26	0.096	0.08[a]	2.496	1.2	99	4.57
3	0.3	0.01	0.1	4MA	50	160	24	0.072	0.06[a]	1.728	1.2	99	4.97
4	1.2	0.01	0.277	4MA	50	160	26	0.072	0	2.149	1.2	99	4.55
5	0.5	0.02	0.133	4MA	50	160	5	0.120	0	0.733	0.5	97	4.85
6	0.5	0.02	0.133	4MA	25	160	5	0.120	0	0.733	0.5	96	4.8
7	0.5	0.02	0.133	4MA	12	160	5	0.120	0	0.733	0.5	98	4.9
8	0.5	0.02	0.133	4MA	6	160	5	0.120	0	0.733	0.5	97	4.85
9	0.5	0.02	0.133	4MA	3	160	5	0.120	0	0.733	0.5	98	4.9
10	0.5	0.02	0.133	None	0	160	5	0.120	0	0.733	0.5	97	4.85

[a] Over 15 h

insoluble in the reaction medium and the yield of 4MA is almost zero. The rate of conversion increases with increasing temperature and reaches a maximum at 160 °C (Fig. 5). At a temperature higher than 160 °C, the reaction medium becomes low in DMC under atmospheric pressure and the reaction is therefore slowed down.

Fig. 5 Effect of temperature on reaction yield. Conditions: pC = 0.5 mol, K$_2$CO$_3$ = 0.02 mol, DMC (t_0) = 0.13 mol, flow rate of DMC = 0.12 mol h^{-1}, time = 5 h.

Influence of the catalyst nature

Among various catalysts tested, bases containing the potassium cation are more effective, in particular, potassium carbonate (Table 2).

**Table 2** Effect of the catalyst on yield of the reaction

Catalyst	Yield of 4MA (%)
KOH	47
KHCO$_3$	69
KNO$_3$	0
K$_2$CO$_3$	90
Na$_2$CO$_3$	21
Cs$_2$CO$_3$	63
CaCO$_3$	0
No catalyst	0

Reaction conditions: *p*-cresol = 0.5 mol, K$_2$CO$_3$ = 0.02 mol, DMC (t_0) = 0.13 mol; DMC continuous flow rate = 0.15 mol h^{-1}; temperature = 160 °C time = 4 h.

Catalyst and DMC recycling

To meet economical interest and the principles of clean synthesis the recycling of the catalyst was studied. After total conversion of *p*-cresol (in conditions of entry 10), the reaction medium was treated by distillation to obtain the pure 4-methylanisole. The catalyst was re-used consecutively five times without any decline in its reactiviy though the reactivity of the recycled catalyst was slightly lower than the fresh catalyst (Fig. 6). DMC can be separated from methanol by extractive distillation[53] or on an ion exchanger.[54]
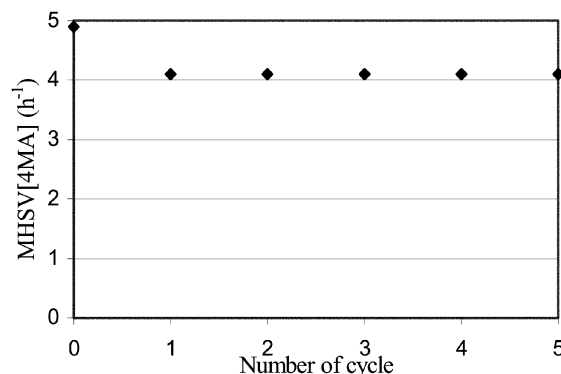
Fig. 6 Reactivity of K$_2$CO$_3$ according to the number of cycles.

Process generalisation

Table 3 shows the results of O-alkylation of various phenols with dialkyl carbonate by using the same procedure as for O-methylation of *p*-cresol with DMC. Therefore, the generalisation can easily be adopted to other phenols (entries 11–19) as well as to other alkyl carbonates (entries 20 and 21). Total conversion would be obtained if the reaction time is adequately extended. The reaction is totally O-selective except in the case of catechol in which various by-products were detected by gas chromatography analysis (entries 19).

Conclusion

The combination of the use of dimethyl carbonate as reagent and potassium carbonate as recyclable catalyst avoids the use of conventional methylating agents. DMC is obviously more atom economic than MeI, MeBr or dimethyl sulfate (DMS). Furthermore, when DMC is used as the methylating agent, it only leads to methanol and carbon dioxide. These by-products can easily be separated from the alkyl aryl ethers and methanol can be re-used according to the principle of life cycle assessment. Compared with methanol, DMC is a better methylating agent

Table 3 Results of the O-methylation of various phenols with DMC

Entry	Substrate Identity	Mol	Reaction conditions K$_2$CO$_3$/ mol	DMC (t_0)/ mol	T/°C	Time/h	DMC flow/ mol h^{-1}	DMC total/mol	Yield (%)	Residual substrate (%)	Average MSHV/ h^{-1}
11	Phenol	0.5	0.02	0.1	150	5	0.13	0.75	70	26	3.5
12	4-Chlorophenol	0.5	0.02	0.135	160	4.5	0.15	0.81	99	0	5.5
13	4-Hydroxybenzophenone	0.5	0.02	0.175	160	5	0.13	0.82	52	44	2.6
14	4'-Acetophenone	0.5	0.04	0.145	160	9	0.88	0.94	86	14	1.2
15	2-Naphthol	0.5	0.04	0.2	160	6	0.1	0.80	96	3	2.0
16	4-Hydroxyphenylacetic acid	0.5	0.04	0.15	160	11	0.1	1.25	29	65	0.33
17	Eugenol	0.5	0.04	0.145	170	6	0.12	0.86	93	5	1.9
18	2,4-Dihydroxybenzophenone	0.5	0.02	0.15	160	10	0.1	1.15	80[a]	15	2.0
19	Catechol	0.5	0.04	0.15	160	3	0.2	0.75	48[b]	31	2.0
20	p-Cresol[c]	0.5	0.02	0.17	160	12	0.08	1.13	94[d]	0	1.9
21	Phenol[c]	0.5	0.02	0.1	155	8	0.08	0.74	90[e]	8	2.8

[a] Yield of 2-hydroxy-4-methoxybenzophenone. [b] Yield of guaiacol. [c] O-Ethylation with diethyl carbonate (DEC). [d] Yield of 4-ethoxytoluene. [e] Yield of phenetole.

due to its high reactivity and high selectivity. Therefore, waste of substrate can be avoided by using DMC. This process approaches to the twelve principles of green chemistry proposed by Anastas and Warner.[55]

Experimental

The reaction was conducted in a 250 ml reactor equipped with a mechanical stirrer, a thermocouple linked to heater by an automatic regulator and a distillation column. The top of distillation column was equipped with a reflux system, enabling adjustment of the outlet flow rate of by-product. The reagents were fed into the reactor by a peristaltic pump (Scheme 2). At the end of the reaction, residual DMC can be separated from the product by distillation.

Dimethyl carbonate and diethyl carbonate were obtained from SNPE. Other reagents were commercially available in a purity of at least 97%.

The yield of each reaction was determined by gas chromatography on a Hewlett Packard™ 5890 with monochlorobenzene used as internal standard. The capillary column (BP1, 50 m × 0.25 mm × 0.25 μm) was temperature-programmed from 50 to 220 °C with a heating rate of 20 °C min^{-1}. The injector and detector temperature were 240 and 260 °C, respectively. The column head pressure was 20 psi.

The products obtained were purified before being identified by ^{13}C and ^{1}H NMR on NMR Brucker™ AC 200 equipment (CDCl$_3$ as solvent, 200 MHz for ^{1}H NMR and 50 MHz for ^{13}C NMR).
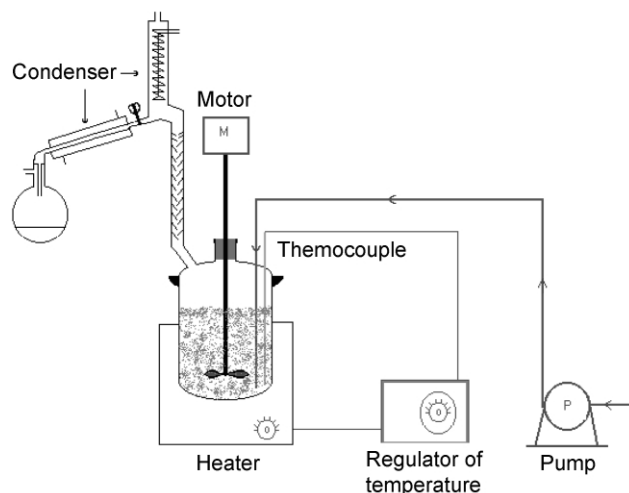
FT-IR spectra analysis: the mixture of p-cresol and K$_2$CO$_3$ (4% molar of K$_2$CO$_3$) was heated to 160 °C with stirring and the mixture became homogeneous. After cooling down to room temperature, a brown solid was obtained which was analysed using a PERKIN ELMER™ Spectrum BX II FT-IR system.

Scheme 2 Schematic plot of the reactor used in O-alkylation of phenols with DMC.

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