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High performance method for O-methylation of phenol with dimethyl carbonate

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Abstract

The O-methylation of phenols, including the sterically hindered phenols, with dimethyl carbonate (DMC) under mild conditions of temperature and pressure was described. The reaction was carried out in the presence of tetrabutylammonium bromide (TBAB), in a semi-continuous process. Aryl methyl ethers were rapidly and selectively obtained in good yields.
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Keywords: Dimethyl carbonate; Sterically hindered phenols; O-methylation; Environmental friendly; Tetrabutylammonium bromide

1. Introduction

Aryl methyl ethers useful as intermediates in fine chemicals are conventionally produced by O-methylation of the corresponding phenols with methyl halides or dimethyl sulfate. However, these methods require not only harmful reagents but also a stoichiometic amount of a strong base to neutralise acid by-product. Instead, the O-methylation of phenols can also be conducted with methanol, in the presence of a strong acid catalyst or a zeolite at high temperature. In most of the cases, total conversion of phenols was difficult to attain and the C-methylation always occurred in competition with the O-methylation [1–9].

Given the environmental impact of methyl halides and dimethyl sulfate or the poor performance

of methanol, dimethyl carbonate (DMC)—green reagent—have been looked as a potential substitute for those reagents [10–15].

The continuous-flow process under gas/liquid phase transfer catalysis (GL-PTC) conditions has been widely reported in O-methylation of phenols with DMC by using K_2CO_3 and polyethylene glycol (PEG) as catalysts [16–21]. Although, anisole was selectively obtained in good yield, such procedure poses a serious concern when substrate is a high boiling point compound. The reaction can also be conducted under liquid/solid PTC conditions in the presence of K_2CO_3 and crown ether at 100 °C [22], or K_2CO_3 and tetrabutylammonium bromide (TBAB) at reflux of DMC [23]. However, the molar hourly space velocity of phenolic ether formation per amount of catalysts was relatively slow (e.g. 0.03 and 0.15 h^{-1} for O-methylation of phenol in [22,23], respectively).

Guaiacol and veratrole were synthesised by O-methylation of catechol over a modified alumina

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$$\text{ArOH} + \text{DMC} \xrightarrow{\text{(Bu)}_4\text{NBr}} \text{ArOCH}_3 + \text{MeOH} + \text{CO}_2$$

Scheme 1.

in a continuous process [24]. The alumina loaded with alkali hydroxide provided a good selectivity toward guaiacol [24b], whereas the one loaded with potassium nitrate was efficient for the synthesis of veratrole [24c]. Over catalyst $CrPO_4$ and $CrPO_4$-$AlPO_4$, DMC was more effective than MeOH in O-methylation of phenol [25]. Basic zeolites, alumina or alumina-silica have also been described as catalysts in the continuous-flow process for the preparation of aryl methyl ethers by the reaction of phenols with DMC [26,27]. In these methods, the reactions were carried out at very high temperature (180–300 °C) and they conveyed usually to the mixture of aryl methyl ether and C-methylated products.

In an autoclave, the O-methylation of phenols with DMC has been conducted in the presence of an alkali base [28,29], a tertiary amine and an iodide [30], a nitrogen containing heterocyclic such as [4-dimethlylamino]-pyridine [31], or a pentaalkyl-guanidine [32]. Besides the use of pressure devices, the kinetics of the reactions were slow.

Recently, 1,8-diazabicyclo[5.4.0]undec-7-ene (DB-U) has been reported as an effective catalyst in O-methylation of phenols both at reflux of DMC or under microwave irradiation at 160 °C in 20 bar [33]. However, at reflux of DMC, the kinetic of phenol conversion was very slow. To enable to conduct the reaction in batch, at the temperature in the range of 120–150 °C, under atmospheric pressure, Perosa et al. [34] had used asymmetric carbonates (with a higher boiling than DMC) as methylating agents in the O-methylation of phenols in the presence of K_2CO_3. To improve the selectivity towards methylation, the reaction was conducted in a polar solvent. However, 100% of selectivity of O-methylated product was difficult to obtain.

We report herein an effective process for the O-methylation of phenols as well as the highly hindered phenols with DMC (Scheme 1). The reaction was carried out in the presence of tetrabutylammonium bromide alone, at a temperature higher than the boiling point of DMC but neither pressure devices nor solvent were required.

2. Experimental

2.1. General remarks

DMC was furnished by SNPE. Other reagents were commercially available at purity of at least 96% (except di-*tert*-butyl-4-methylanisole[1] and penta-bromoanisole[2]). The products obtained were purified before being identified by ^{1}H and ^{13}C NMR on NMR Brucker[TM] AC 200 (CDCl$_3$ or DMSO, d_6 as solvents, 200 MHz for ^{1}H NMR and 50 MHz for ^{13}C NMR). Thermogravimetry analysis (TGA) measurements was performed in a Setaram 92-16.18 Thermogravimetic Analyser. FT-IR spectra was analysed by Perkin-Elmer[TM] Spectrum BX II FT-IR system.

Yield of each reactions was determined by gas chromatography (GC) on Hewlett-Packard[TM] 5890 using monochlorobenzene 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. The injector and FID-detector temperature were 240 and 260 °C, respectively (300 and 320 °C for the analysis of 2,6-di-*tert*-butyl-4-methylphenol and pentabromophenol). The column head pressure was fixed at 20 psi.

2.2. Reaction procedure

The reaction was conducted in a 250 ml reactor equipped with a mechanical stirrer, a thermometer and a distillation column [2 cm; 25 cm]. Reagents were fed into the reactor by a peristaltic pump. Once the reaction was completed, the reaction medium was allowed to cool down to room temperature. An aqueous solution of hydrochloric acid and MTBE (*tert*-butyl methyl

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[1] 2,6-Di-*tert*-butyl-4-methylanisole—^{1}H NMR (CDCl$_3$) δ (ppm): 1.43 (s, 18H, CH$_3$C), 2.27 (s, 3H, CH$_3$Ar), 3.82 (s, 3H, CH$_3$O), 6.97 (s, 2H, ArH). 13C NMR (CDCl$_3$) δ (ppm): 21.3, 30.5, 34.4, 56.4, 125.4, 126.8, 136.0, 151.6.

[2] Pentabromoanisole—^{1}H NMR (DMSO, d_6) δ (ppm): 3.80 (s, 3H, CH$_3$O). 13C NMR (DMSO, d_6) δ (ppm): 60.3, 114.5, 121.4, 127, 4, 155.2.

ether) were added to the reaction medium. The mixture was allowed to decant in a separatory funnel. After separation, the organic phase was analysed by GC. Whereas TBAB was recovered in the aqueous phase and can be regenerated [35].

2.3. Typical example

Twenty millimoles of Bu_4NBr, 20 mmol of phenol and 40 mmol of DMC were loaded into the above reactor. This mixture was heated to 130 °C, then an other mixture of DMC and phenol (DMC:PhOH molar ratio = 1.6) was fed into the reactor at MHSV[PhOH] = 2 h^{-1} (thus, MHSV[DMC] was 3.2 h^{-1}) during 3.5 h (MHSV is the molar hourly space velocity of reagent fed into the reactor per mole of catalyst). The reaction was kept continuing during 30 min. Thus, total reaction time was 4 h. In the course of the reaction, when the temperature of the medium tended to drop under 130 °C, methanol as well as the excess of DMC were withdrawn from the reaction medium by distillation. After cooling down to room temperature, 50 ml of a solution of hydrochloric acid (2N) and 200 ml of MTBE were added to the reaction medium. After the separation of the organic phase from the aqueous phase, the organic phase was analysed by GC.

3. Results and discussion

We investigated hereafter the influence of different factors on the phenol conversion into anisole. Then, the process was generalised to others phenols and the mechanism of the reaction was proposed.

3.1. Effect of reaction temperature

The reactions were carried out in batch and under atmospheric pressure. The temperature of the reaction higher than the boiling point of DMC can be attained because phenol was used in excess.

The optimum temperature of the reaction is 130 °C because at 120 °C the rate of phenol conversion is too low. Otherwise, at 140 °C, this rate is high at the beginning of the reaction but decreases after 8 h of the reaction (Fig. 1). This evolution of the kinetic at 140 °C can be explained in one hand, by the partial
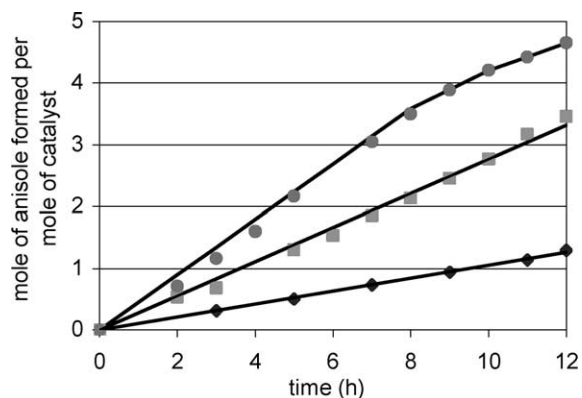

Fig. 1. Effect of reaction temperature on the conversion of phenol into anisole. In each experiment, the amount of Bu_4NBr loaded in the reactor was 20 mmol and the molar ratio PhOH:DMC:TBAB was 20:10:1. (●) $T = 140$ °C; (■) $T = 130$ °C; (◆) $T = 120$ °C.

degradation of the catalyst. The thermogravimetry analysis has confirmed this hypothesis: Bu_4NBr is readily to decompose at 133 °C. On the other hand, we have noticed that if the reaction was conducted at high temperature under atmospheric pressure, the concentration of DMC in liquid phase is automatically reduced following vapour/liquid equilibrium. To overcome this problem a semi-continuous system was adopted.

3.2. Effect of phenol concentration

We define herein a semi-continuous process as a process in which reagents are continuously fed into the reactor and if necessary, by-products and excess of DMC are progressively extracted from the reaction medium by distillation.

The reactor was loaded (at t_0) with some amount of TBAB, phenol and DMC. This mixture was heated to 130 °C. Fig. 2 compares the yields of anisole in the conditions in which total amount of phenol was loaded into the reactor at the beginning of the reaction (●) (only DMC was progressively fed into the reactor) and in which phenol and DMC were progressively fed into the reactor (■). These results show the influence of phenol concentration on the kinetic of the reaction. Contrary to the classical kinetic of a nucleophilic substitution, while the concentration of phenol increases, the velocity of phenolic ether formation
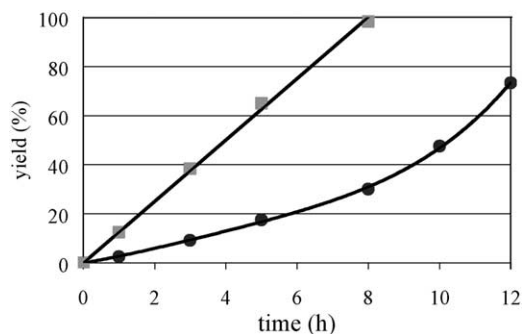
Fig. 2. Influence of phenol concentration on the yield of anisole.

decreases. This phenomena is probably due to the hydrogen-bonding formation among the molecules of phenol, inhibiting the phenolate formation by the action of catalyst (Fig. 3).

3.3. Effect of reagents flow rate

Fig. 4 shows that the optimum MHSV[PhOH] is $2 \, h^{-1}$. When the MHSV[PhOH] is larger than $2 \, h^{-1}$, the consumed phenol is less than the fed phenol, resulting in the accumulation of phenol in the reaction medium. The kinetic of phenol conversion is, therefore, slowed down.

When the optimum MHSV[PhOH] is $2 \, h^{-1}$, that of DMC (MHSV[DMC]) is $3.2 \, h^{-1}$. Thus, the optimum

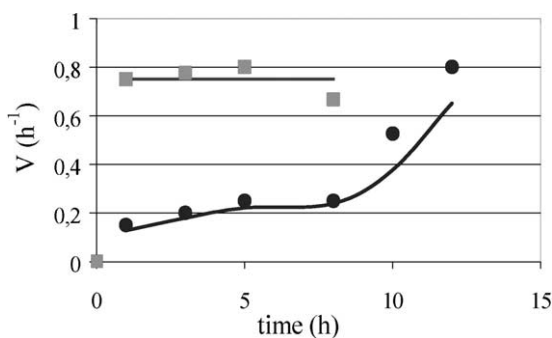Fig. 3. Effect of phenol concentration on the molar hourly space velocity of anisole formation per mole of catalyst, $V \, (h^{-1})$. (■) At t_0, the reactor was loaded by 20 mmol of catalyst, 20 mmol of phenol and 40 mmol of DMC; $T = 130 \, °C$; MHSV[PhOH] = $0.75 \, h^{-1}$; MHSV[DMC] = $1.2 \, h^{-1}$ (thus, total amount of phenol fed into the reactor was 140 mmol). (●) At t_0, the reactor was loaded by 20 mmol of catalyst, 140 mmol of phenol and 40 mmol of DMC; $T = 130 \, °C$; MHSV[PhOH] = 0; MHSV[DMC] = $1.2 \, h^{-1}$.
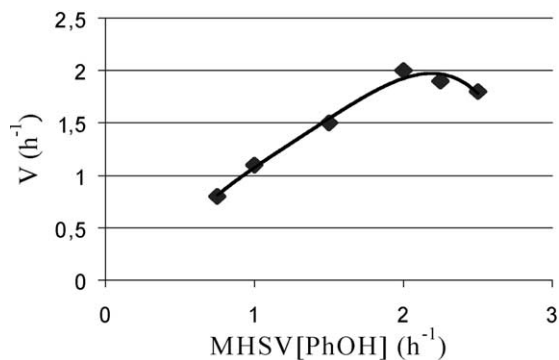

Fig. 4. Effect of MHSV[PhOH] on conversion of phenol. At t_0, the reactor was loaded by 20 mmol of catalyst, 20 mmol of phenol and 40 mmol of DMC; $T = 130 \, °C$; DMC:PhOH molar ratio was 1.6.

DMC:PhOH molar ratio is 1.6. As the temperature of the reaction is maintained at $130 \, °C$, under atmospheric pressure, a DMC:PhOH molar ratio larger than 1.6 is not recommended. Because that excess of DMC will be distilled from the reaction medium along with methanol. When DMC:PhOH molar ratio decreases from 1.6 to 1.2, the molar hourly space velocity of anisole formation per mole of catalyst (V) diminishes slightly from 2 to $1.7 \, h^{-1}$ (Fig. 5).

3.4. Effect of catalyst nature

Instead of TBAB, we have tested others catalysts, including those already reported in previous papers literature such as [4-dimethylamino]-pyridine or
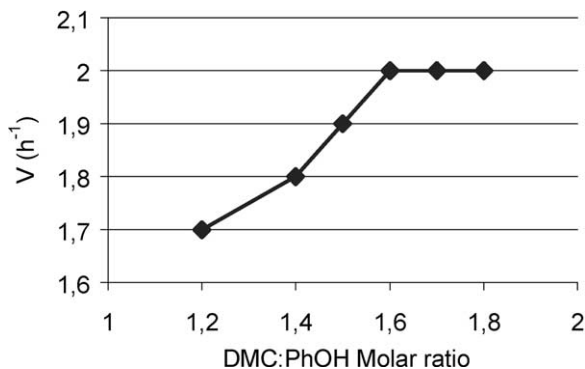

Fig. 5. Effect of DMC:PhOH molar ratio on conversion of phenol. At t_0, the reactor was loaded by 20 mmol of catalyst, 20 mmol of phenol and 40 mmol of DMC; $T = 130 \, °C$; MHSV[PhOH] was kept at $2 \, h^{-1}$.

Table 1
Effect of catalyst nature on the yield and on the molar space velocity of anisole formation per mole of catalyst (V)

Catalysts	Yield (%)	V (h^{-1})
Tetrabutylammonium bromide	100	2.00
Tetrabutylphosphonium bromide	68.5	1.37
[4-Dimethylamino]-pyridine	67	1.34
Hydrochloride of hexamethylguanidinium chloride	8	0.16
Hydrochloride of hexabutylguanidinium chloride	13.5	0.27
Diethylene triamine	0	0

At t_0, the reactor was loaded by 20 mmol of catalyst, 20 mmol of phenol and 40 mmol of DMC; $T = 130\,°C$; MHSV[PhOH] = $2\,h^{-1}$; MHSV[DMC] = $3.2\,h^{-1}$; the mixture of phenol and DMC was fed into the reactor during 3.5 h, the reaction was kept continuing during 30 min. Thus, total reaction time was 4 h.

pentaalkylguanidines. we found that TBAB is still the most efficient (Table 1).

3.5. Generalisation

Table 2 shows the results of the O-methylation of various phenols with DMC by using the above

procedure. Surprisingly, the sterically hindered phenols such as 2,6-di-*tert*-butyl-4-methylphenol or pentabromophenol can be successfully O-methylated in such conditions. Generally, the O-methylation of sterically hindered phenols is difficult to achieved. For example, when we used the conditions described in the references [22,23] for the O-methylation of 2,6-di-*tert*-butyl-4-methylphenol, we did not obtain the corresponding ether at all. Therefore, this process provides an alternative way to obtain the sterically hindered anisoles under mild conditions by using the environmentally benign reagent.

3.6. Mechanism suggestion

At the temperature of the reaction (130 °C), ammonium quaternary salt would react with phenol to form a complex containing nucleophilic anion (PhO−). This phenolate reacts with DMC through B_{Al-2} mechanism to generate the phenolic ether (Scheme 2).

We observed on the Fig. 6, the OH deformation band at 1233 cm−1 has changed after heating to 130 °C with Bu4NBr. The same perturbation of OH band has been reported when zeolite was used as catalyst [36].

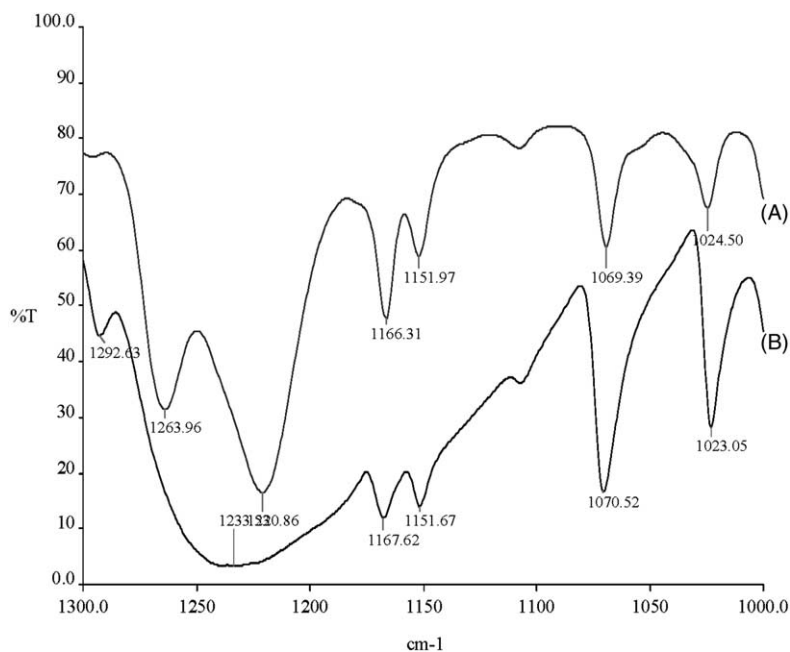Fig. 6. FT-IR spectra of phenol and phenol/Bu4NBr: (A) mixture of phenol and Bu4NBr after heating; (B) OH deformation of pure phenol.

Table 2
Results of the O-methylation of various phenols with DMC in the presence of Bu$_4$NBr

Substrate (S)	MHSV[S] (h^{-1})	MHSV[DMC] (h^{-1})	DMC:S (mol:mol)	Yield (%)	Selectivity (%)	V (h^{-1})
Phenol	2	3.2	1.6	100	100	2.00
o-Cresol	1.4	2.2	1.6	95	100	1.40
p-Cresol	1.8	2.9	1.6	100	100	1.82
4-Chlorophenol	2.2	3.7	1.7	98	100	2.13
2-Naphthol	1.0	2	2.0	94	98	1.04
4'-HAP[a]	1.0	5	5.0	67	93	0.75
2,6-DBMP[b]	1.0	3	3.0	97	100	1.09
Pentabromophenol[c]	0	2	–	41	100	0.21

At t_0, the reactor was loaded by 20 mmol of TBAB, 20 mmol of substrate and 40 mmol of DMC; $T = 130\,°C$; the mixture of substrate and DMC was fed into the reactor during 3.5 h, the reaction was kept continuing during 30 min. Thus, total reaction time was 4 h.

[a] 4'-Hydroxyacetophenone.

[b] 2,6-Di-tert-butyl-4-methylphenol.

[c] At t_0, the reactor was loaded by 20 mmol of TBAB, 40 mmol of pentabromophenol and 80 mmol of DMC; $T = 130\,°C$; DMC was fed into the reactor during 3.5 h with MHSV[DMC] $= 3\,h^{-1}$, the reaction was kept continuing during 30 min. Thus, total reaction time was 4 h.
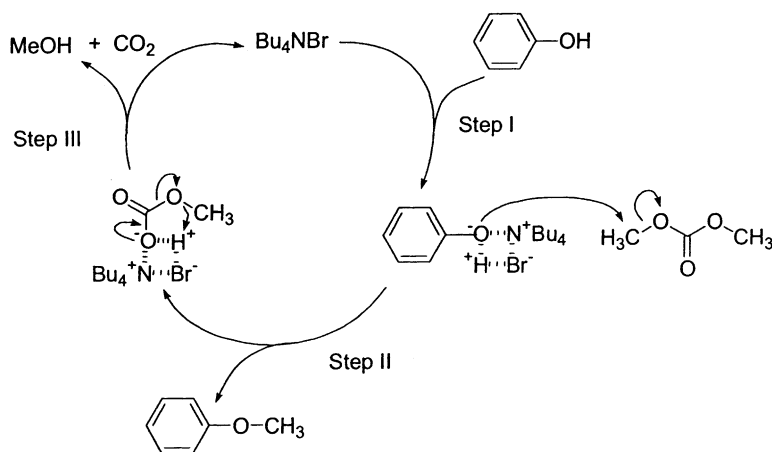
Scheme 2. Plausible catalytic cycle for phenol methylation.

This phenomena was explained as the result of deprotonation of phenol.

4. Conclusion

Through this process, DMC is an effective methylating agent for the O-methylation of phenols. Hundred percent of phenols conversion into their corresponding ethers can be selectively and rapidly reached. The reaction is performed in an economic and environmental concept as the pressure devices, large excess of DMC, and high temperature are not required. Moreover, catalyst can be easily separated from the reaction medium by water/MTBE (methyl tert-butyl ether) extraction and it can be regenerated. More importantly, This process is the fist ever which describes the O-methylation of sterically hindered phenols with DMC in mild conditions.

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