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O-Methylation of phenolic compounds with dimethyl carbonate under solid/liquid phase transfer system

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Abstract—The industrially important alkyl aryl ethers, of which anisole is the simplest form, can be synthesized by reacting the corresponding phenols with the environmentally benign dimethyl carbonate (DMC). The reaction is carried out under mild conditions of temperature and pressure. Excellent yields and selectivity of product were obtained after a few hours of reaction.

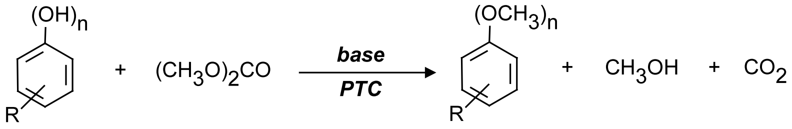
In organic synthesis, dimethyl carbonate (DMC) is considered as an alternative methylating reagent to replace hazardous compounds such as methyl halides or dimethyl sulfate.[1–4]

The *O*-methylation of phenols leads to alkyl aryl ethers, useful as starting materials for the preparation of fragrances, dyes and pesticides, as antioxidants in oils and fats or as stabilisers of plastics.[5]

It has been found that the reaction of methylation of phenols with DMC can be carried out in an autoclave at 160°C with a catalyst system composed of an alkaline base or a tertiary amine in association with an iodide.[6] Tertiary amines or phosphines,[7] or nitrogen-containing heterocyclic catalysts (4-[dimethylamino]-pyridine),[8] penta-alkylguanidines,[9] cesium carbonate,[10] have been used as catalysts to prepare phenolic ethers by reaction of phenols with a dialkyl carbonate at a temperature between 120 and 200°C under autogenous pressure. Notari et al. described how 2-hydroxy-4-alkoxybenzophenone was synthesised by selective mono-methylation of 2,4-dihydroxybenzophenone in an autoclave at the temperature ranges between 140 and 180°C in the presence of alkaline base.[11]

Recently, alkyl methyl carbonate was used to accomplish the *O*-methylation of phenols in the presence of potassium carbonate and a polar solvent. Due to the high boiling point of carbonate, the reaction can be conducted under atmospheric pressure.[12] The reaction of hydroquinone with alkyl carbonates in the presence of an alkaline base takes place in a soxhlet extractor at 170–200°C; the presence of a solvent such as pyridine or an alkyl formamide is vital.[13]

Basic zeolites, alumina or alumina-silica, were also described as good catalysts in a continuous flow process. The reaction was conducted in the vapour phase at high temperature range from 180 to 300°C. High yields of aryl methyl ether were obtained but by-products of *C*-methylation were observed.[14,15] Fu et al. described the vapour-phase *O*-methylation of catechol with DMC over alumina. The alumina loaded with



Scheme 1.

Keywords: alkyl aryl ether; anisole; dimethyl carbonate; phase transfer catalyst; environmentally safe.

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lithium hydroxide was found to provide an excellent selectivity toward guaiacol, whereas alumina loaded with potassium nitrate is selective for the synthesis of veratrole.[16–18]

Gas/solid phase transfer methods using polyethylene glycol (PEG) as phase transfer catalyst (PTC) and potassium carbonate as base have been widely reported.[19–24] The reaction was conducted at high temperature (180°C). The authors described that the reaction is *O*-selective and resulted in good yields of phenolic ethers. For some phenols, this procedure seems to be restrictive due to their high boiling point that creates difficulties in feeding the reactor.

Lissel et al. have reported the *O*-methylation of *p*-cresol, *t*-butyl-phenol and phenol with DMC using crown ether (18 crown 6) as PTC and potassium carbonate as base. After 8 h at 100°C only 23, 36 and 40% yields were, respectively, obtained. Under the same conditions, the *O*-methylation of 2-naphthol yielded 82% of 2-methoxynaphtalene.[25] It should be noted that crown ethers are very expensive and toxic.

Table 1. Effect of catalyst system on the yield of the reaction of 2,4-DHB ($R=C_6H_5(CO)-$; $n=2$) with DMC[a]

No	Base	PTC	Yield[b] (%)
1	K_2CO_3	$(Et)_4NBr$	8.5
2	”	**$(Bu)_4NBr$**	**12**
3	”	$(Octyl)_4NBr$	4
4	”	$(Bu)_4NOH$	11
5	”	$Ph_3(CH_2CH_2OH)PCl$	1.5
6	”	CHBG, HCl[c]	8.5
7	”	$(Bu)_4PCl$	11
8	$KHCO_3$	$(Bu)_4NBr$	2.5
9	Cs_2CO_3	$(Et)_4NBr$	5.5
10	”	$(Et)_3BzNBr$	4.5
11	KOH	$(Bu)_4NBr$	1

[a] *T*: 93°C; molar ratio DMC/base/PTC/2,4-DHB: 16/1.5/0.05/1; time: 9 h.

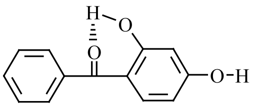
[b] Yield of 2-H-4-MB; no trace of 2,4-dimethoxybenzophenone (2,4-DMB) was observed.

[c] Hydrochloride of hexabutylguanidinium chloride.

To overcome these problems, we have studied the reaction of phenol derivatives with DMC under solid/liquid phase transfer conditions (Scheme 1). The reaction was carried out at 90–100°C under atmospheric pressure in a reactor equipped with a stirrer and a reflux condensator for DMC. At the end of the reaction, the base (K_2CO_3) was simply recovered by filtration and the PTC was separated from the reaction medium by liquid/liquid extraction with an aqueous hydrochloric acid (pH 1) and *tert*-butyl methyl ether (MTBE). The organic phase, containing methylated products, was analysed by gas chromatography. The PTC recovered in the aqueous phase can be regenerated.[26]

Among various catalyst systems tested, the couple of K_2CO_3 (base)/tetrabutylammonium bromide (PTC) was shown to be the most effective catalyst for the *O*-methylation of 2,4-dihydroxybenzophenone (2,4-DHB) (Table 1). Under such conditions, the reaction is regioselective as 2-hydroxy-4-methoxybenzophenone (2-H-4-MB) is exclusively obtained.

In order to improve the yield of the reaction, the PTC/2,4-DHB ratio was modified. Increasing this ratio from 0.05 (entry 2, Table 1) to 0.5 and 1.0 (entries 12 and 13, Table 2) resulted in a good yield. We have observed that the mono-methylation on the OH group at position 4 took place first. The hydroxy group at position 2 may be protected by a hydrogen bond with a carbonyl group (Scheme 2).



Scheme 2.

Table 2.

No	Substrate (S)	PTC[a]/S[b]	DMC/S[b]	K_2CO_3/S[b]	Time (h)	Yield (%)
12	2,4-DHB	0.5	16	1.5	9	34/3[c]
13	”	1	”	”	”	6/72[c]
14	Phenol	0.2	”	0.75	5	31
15	”	”	”	”	10	64
16	”	”	”	”	13	80
17	”	0.6	”	”	5	96
18	”	”	30	”	”	99
19	*p*-Cresol	0.3	16	1.5	4	25
20	”	0.4	”	”	”	48
21	”	0.5	”	”	5	99
22	”	0.6	”	”	4	97
23	”	0.5	8	0.75	5	95
24	”	”	10	”	”	99
25	”	1	”	0	”	45
26	”	0	”	1	”	0

All reactions were conducted at 93°C.

[a] PTC = Bu_4NBr.

[b] mol/mol.

[c] Yield 2-H-4MB/yield 2,4-DMB.

When this catalyst system (K_2CO_3/Bu_4NBr) was used with phenol and *p*-cresol, 100% conversion and selectivity to *O*-methylated products was achieved only after a few hours (entries 17–18 and 21–24, Table 2). The attempt to reduce the PTC amount led to a poor yield (entries 14–16 and 19–20, Table 2), but longer reaction times can improve the reaction yield (entries 15–16, Table 2).

The different reactivity between phenols can be explained by the negative inductive effect (I− effect) of the $(C_6H_5)CO$ group of 2,4-DHB, which creates difficulty in the reaction between the phenoxy ion with DMC. The negative charge on the oxygen atom of the phenoxy ion formed in situ by the reaction of the base with 2,4-DHB is weakened by the attraction of this effect. On the contrary, the I+ effect of the methyl group of *p*-cresol accelerates the reaction kinetics.

Although we note that tetrabutylammonium bromide alone can act as a catalyst (entry 25, Table 2), the yield of the reaction is reduced to 45%, even if the molar ratio is doubled. Moreover, the base alone is unable to make the reaction take place (entry 26, Table 2).

In conclusion, we have presented an efficient method to synthesise aryl methyl ethers by using the environmental safe, DMC as reagent. The reaction takes place under mild conditions of temperature and pressure, while good to excellent yields (95–99%) are obtained. Furthermore, the catalysts (base and PTC) can be easily recovered and regenerated.

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