

Alkyl Methyl Carbonates as Methylating Agents. The *O*-Methylation of Phenols

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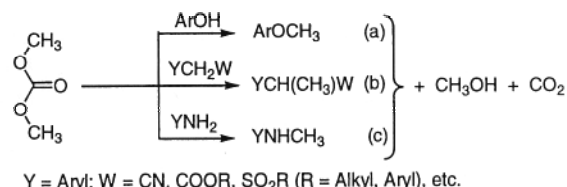
Abstract: The *O*-methylation reaction of a variety of phenols (ArOH: Ar = Ph, *p*-CH₃C₆H₄, *p*-ClC₆H₄, *o*- and *p*-CH₃COC₆H₄, and 2-naphthyl) can be conducted in a highly selective manner by using asymmetric alkyl methyl carbonates CH₃OCOOR (R = *n*-Pr, **3b**; *n*-Bu, **3d**; CH₃O(CH₂)₂O(CH₂)₂, **3e**) as alkylating agents. For example, at 150 °C, phenol can be quantitatively converted into anisole in 4.5 h, using 2-(2-methoxyethoxy)ethyl methyl carbonate **3e** in the presence of K₂CO₃ as a catalyst. Compared to the methylation reactions using dimethyl carbonate which require sealed pressurized reaction vessels, asymmetric alkyl methyl carbonates allow much simpler and safer alkylations at ambient pressure.

The selectivity towards *O*-methylation is scarcely affected by the temperature (in the range of 120–150 °C), while it depends on the nature and on the amount of the solvent. DMF and triglyme (triethylene glycol dimethyl ether) have proven to be the better reaction media.

Key words: alkyl carbonates, *O*-alkylation, methyl selectivity, anisoles, methylation

The methylating reactivity of dimethyl carbonate (DMC) has been studied by our group since the middle eighties. As a methylating reagent, DMC can replace undesirable and non-selective methyl halides (CH₃X; X = Cl, Br, I; **1**) and dimethylsulfate (CH₃OSO₂CH₃; DMS, **2**).^{1–5} With respect to these compounds, DMC has the great advantage of being environmentally benign, since it is: (i) non toxic, (ii) efficient and selective as methylating reagent, (iii) it originates only methanol as co-product which can be recycled for the production of DMC, and (iv) it is now synthesized from methanol rather than from hazardous phosgene.^{6–7} We have extensively reported that operating at high temperatures (≥ 160 °C), under both continuous-flow (c.-f.) and batch conditions, DMC allows the highly chemoselective methylation of phenols to yield the corresponding anisoles (Scheme 1; (a)).^{8–9} Even more importantly, DMC permits the highly selective mono-*C*-methylation of CH₂-acid compounds (i.e. aryl and aryl-oxy-acetic acid derivatives or benzylic sulfones), and the mono-*N*-methylation of primary aromatic amines (Scheme 1; (b) and (c), respectively).^{10–15}

The alkylations of Scheme 1 can be performed without solvent and with a catalytic amount of base (M₂CO₃; M = Li, Na, K, and Cs; Y zeolites). It was also shown, by us and by others,^{6, 10, 16} that the use of Cs₂CO₃ improves the rate of the reaction thanks to its higher solubility in DMC,¹⁰ though we still think that its cost is a limitation.

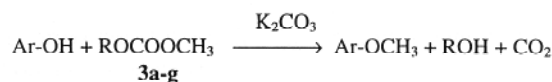


Methylation patterns with DMC

Scheme 1

However, a major operative drawback of DMC-mediated methylations, is determined by the reaction temperature (≥ 120 °C) which is well over the 90 °C boiling point of DMC. Consequently, pressurized vessels (autoclaves) fitted with CO₂ purging valves, are necessary under batch conditions;^{10–15} while, under c.-f. conditions, substrates must have a relatively high vapor tension in order to be fed into suitable plug-flow reactors.^{1, 2, 8} To overcome such difficulties, we conceived the use of asymmetric alkyl methyl carbonates (ROCOOCH₃, **3**) as possible methylating agents: a suitable R group would have increased the boiling point of the carbonate to allow reactions at ambient pressure, and simultaneously, the steric bulk of the R moiety would have favored anisoles towards the competitive formation of alkyl aryl ethers (ArOR).

We report here that a very good chemoselectivity (>99%) in the *O*-methylation of phenols can be obtained at atmospheric pressure with compounds **3**, provided that the R substituents are linear alkyl groups possessing at least 3 carbon atoms (Scheme 2).



Scheme 2

The required alkyl methyl carbonates **3** were synthesized according to established procedures, by reacting the appropriate alcohols with methyl chloroformate (compounds **3a-c**),¹⁷ or DMC (compounds **3d-g**).^{18, 19}

Phenol was chosen as the model nucleophilic substrate based on our earlier reports of carbonate-mediated alkyla-

tions.⁸⁻⁹ The reactions were carried out at 120 °C, using phenol, carbonate **3**, and potassium carbonate in a 1: 5: 1.1 molar ratio, and DMF as the solvent (100 mL/g phenol). The results are reported in Table 1.²⁰

In the case of compounds **3a-e**, the reported methylating reactivity and selectivity seem to be well explainable by steric factors:²¹⁻²³ in fact, although the reaction of phenol with carbonates **3b-d** affords anisole with a very high yield (95-97%, entries 2-4), the methyl chemoselectivity is even more improved (>99%), using compound **3e** with the more hindered oxyethylene chain (entry 5). While in the case of compounds **3f-g**, the observed drop in the *O*-methylation selectivity (PhOR: 16 and 17% for **3f** and **3g**, respectively; entries 6-7), is likely ascribable to resonance effects which favor S_N2 displacements for both allylic and benzylic systems.²⁴

Table 1 Reactions of Phenol with Different Alkyl Methyl Carbonates^a

Entry	R =	ROCOOCH ₃	Time (h) ^c	Products ^d (%)	
				PhOCH ₃	PhOR
1	Et	3a	15	90	10
2	<i>n</i> -Pr	3b	17	95	5
3	<i>i</i> -Pr	3c ^b	40	73	2
4	<i>n</i> -Bu	3d	15	97	3
5	CH ₃ O(CH ₂) ₂ O(CH ₂) ₂	3e	20	>99	-
6	Bn	3f	5	84	16
7	Allyl	3g	21	83	17

^a T = 120 °C, phenol (0.3 g; 3.3 mmol)/K₂CO₃ / **3** = 1 : 1.1 : 5. DMF (30 mL) was used as solvent.

^b Conversion of phenol stopped at 75%.

^c Time for complete conversion of the substrate.

^d Determined by GC, referred to the internal standard.

In the case of **3c**, the obtained *O*-methyl selectivity is high, but the reaction stops at a 75% conversion of phenol even after prolonged reaction times (entry 3). We suggest that such a behavior is due to the co-product *i*-propyl alcohol (Scheme 2) which, rather than undergoing transesterification with the organic carbonate (slower for secondary alcohols²⁵), presumably inhibits anisole formation by limiting the availability of phenoxide through solvation.

As we already observed for DMC-mediated mono-*C*-methylations,¹⁰ also the outcome of the investigated reaction is affected by the solvent polarity: under the conditions of entry 5 of Table 1, by increasing the amount of DMF from 2 to 10 mL, the formation of anisole increases as well from 90 to >99%, respectively. Instead, the *O*-methyl selectivity shows no dependence from the reaction temperature: by progressively raising it from 120 to 150 °C, the reaction rate increases as well (complete phenol conversion is achieved after 20 and 4.5 h, respectively), but anisole is the sole product in any case. The effect of solvent polarity is also evident by using different solvents, such as diglyme (**5a**), triglyme (**5b**), diethylene glycol diethyl ether (**5c**), and polyethylene glycol 250 dimethyl ether

(**5d**) which are suitable anion activating media to perform the present alkylation reactions,^{9,25,26} and allow to operate at higher temperatures in the 140-170 °C range (except for **5a**, bp = 162 °C).²⁷ With respect to DMF, a decrease in the *O*-methyl selectivity is observed for glycols **5a**, **5c,d** (anisole/PhOR in 9:1 molar ratio at complete conversion); only **5b** (triglyme) affords good selectivity, yielding 98% anisole after 10 h at 140 °C.

To extend the synthetic applicability of the investigated methylation procedure, **3e** was treated with different phenols **6**, on a larger scale (2-5 g) than that considered previously (PhOH: 0.3 g). All reactions were carried out at 140 °C in the presence of triglyme, using the substrate, K₂CO₃, and **3e** in a 1: 1.1: 5 molar ratio, respectively. Only for the case of phenol, the reaction was also performed using DMF as the solvent. Table 2 shows the results.²⁸

Table 2 *O*-Methylation of Different Phenols **6** by Methyl 2-(2-Methoxyethoxy)ethyl Carbonate (**3e**)^a

Entry	Ar	ArOH (g)	Conv (%)	Solvent (50 mL)	Yield (%) ^c	Purity (%)
1	Ph	6a (3.8)	97	DMF	86	91 ^d
2	Ph	6a (3.8)	100	Triglyme	81	>99
3	<i>p</i> -MePh	6b (4.0)	100	"	79	>99
4	<i>p</i> -ClPh	6c (4.0)	98	"	60	>99
5	2-naphthyl	6d (4.0)	100	"	83	>99
6	MeCOPh	6e (2.0) ^b	100	"	81	>99

^a T = 140 °C, substrate/K₂CO₃/**3e** = 1 : 1.1 : 5.

^b *Ortho/para* = 4.5 : 5.5.

^c Isolated yields of *O*-methylated derivatives.

^d Residual DMF in the distilled product.

In all cases, the reaction proceeds with a very high methyl chemoselectivity (95-99%), and good yields in isolated products (80-86%), except for *p*-chloroanisole (60%, entry 4). Entry 6 refers to a mixture of a *o*- and *p*-acetylphenol **6e** (in a 4.5: 5.5 ratio, respectively) and the yield is that of the isolated mixture of *o*- and *p*-acetyl anisoles.

In conclusion, alkyl methyl carbonates ROCOOCH₃ **3**, efficiently perform the *O*-methylation of phenols under very simple conditions and at ambient pressure. In particular:

At T ≥ 120 °C, the reaction of **3** with phenols affords the corresponding anisoles with a methyl chemoselectivity > 95%, provided that a bulky linear R group with at least 3 carbon atoms is present.

The solvent polarity has a significant effect on the reaction selectivity: better reaction media have proven to be polar aprotic compounds such as DMF and triglyme.

The described methylation procedure is intrinsically environmentally benign since it employs new cleaner and safer reagents, derived from DMC, in place of hazardous existing ones.

Acknowledgement

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- (19) 2-(2-Methoxyethoxy)ethyl methyl carbonate **3e**: $^1\text{H NMR}$ (CDCl_3): δ ppm 4.13 (m, 2H), 3.65 (s, 3H), 3.55 (m, 2H), 3.47 (m, 2H), 3.19 (s, 3H); Mass spectrum (70 eV): m/z (%): 178 (M^+ , < 1), 103 ($[\text{M} - \text{CH}_3\text{OCH}_2\text{CH}_2\text{O}]^+$, 10), 59 ($[\text{M} - \text{CH}_3\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{O}]^+$, 100), 58 (58). Bp = 48-50 °C/0.1.
- (20) A general procedure for the *O*-alkylation of phenol using the asymmetric organic carbonates **3a-3g** is as follows: a 25 mL flask, fitted with a reflux condenser, a rubber septum, a thermometer, and a nitrogen inlet, was charged with phenol (0.30 g, 3.2 mmol), K_2CO_3 (0.6 g, 4.5 mmol), the organic carbonate (2.8 g, 16 mmol), DMF (30 mL), and *n*-tetradecane as the internal standard (0.07 mmol). The mixture was stirred under N_2 at the chosen temperature (120, 130, 140, 150 °C) until complete phenol conversion was observed, as monitored by GLC. All reactions were repeated twice to assure reproducibility. Both phenol conversion and anisole yield were determined by comparison to the internal standard. Reactions were also run using different volumes of DMF (2, 4, 6, 8, and 10 mL) or **3e** as the solvent (5.7 g, 32 mmol).
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- (27) Since anisole boils at 154 °C, reactions were followed by monitoring the phenol concentration. Once the reaction mixture was cooled at room temperature, the mass balance between phenol and anisole was determined by GC.
- (28) Procedure for the *O*-alkylation of different phenols using the organic carbonate **3e** and triglyme as solvent (Table 2): a mixture of the appropriate phenol (2-5 g, see Table 2 for amounts), K_2CO_3 , and carbonate **3e**, in a 1:1.1:5 molar ratio, was dissolved in 50 mL of triglyme and heated at 140 °C under N_2 , until complete substrate conversion. After cooling, 150 mL of diethyl ether were added, and the solution was washed with water (5 x 50 mL). The organic phase was dried over Na_2SO_4 , filtered, and the solvent was removed under reduced pressure. The product was either distilled under reduced pressure (anisole, yield 81%; *p*-methyl anisole, 79%; *p*-chloroanisole, 60%); or flash-chromatographed on a column of silica gel (2-methoxynaphthalene, 83%; *o*- and *p*-acetylanisole, 81% combined), eluting with a 1 to 1 mixture of ethyl ether and petroleum ether. All products were identified by comparing spectroscopic data with those of authentic samples. The 45 to 55 mixture of *o*- and *p*-acetylphenol used in the above procedure was prepared by a Friedel-Crafts acylation of phenol with acetyl chloride, followed by a Fries rearrangement.²⁹
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