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A Continuous Base-Catalyzed Methylation of Phenols with Dimethyl Carbonate

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ABSTRACT: We have found that the use of a conventional, heated, standard 316 stainless steel or steel-braided PTFE tube reactor is a good and easily scalable alternative to the use of continuous microwave-heated reactors. The heat-up is almost as fast as with microwave heating, and the reactors can easily be scaled towards large-scale production. The transfer of the reported microwave procedure to the continuous flow method went very smoothly, and we found that we could further optimize the reaction to a catalytic procedure where only 10 mol % of DBU is needed with only 3 equiv of DMC. The reaction can be run neat in cases where the starting material is soluble in DMC as phenol is, or with a small amount of DMF (2−3 vol). The reaction is efficient for different types of phenols, giving a clean reaction in high yields.

■ INTRODUCTION

Methylation of phenols is an important transformation that regularly employs toxic and hazardous reagents such as methyl iodide[1] or dimethyl sulfate.[2] Dimethyl carbonate (DMC) as a methylating reagent for phenols and NH-containing heteroaromatic compounds has recently been reported with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) under conventional thermal heating with long reaction times. These authors found that the change from conventional convection heating to microwave heating increases the speed of the reaction.[3] Later Rajabi and Saidi reported a similar methylation of phenols using microwave heating in a commercial microwave oven without temperature control. They also used DBU as base but in a catalytic amount.[4]

To speed up the reaction, autoclaves/sealed tubes[5] or asymmetrical carbonates[6] with a higher boiling point than that of DMC have also been employed. The exploration for milder and more practical conditions to accelerate the rate of methylation using DMC is important to minimize the use of hazardous reagents. DMC is a versatile reagent which, at temperatures around its boiling point of 90 °C, generally reacts to afford carbonate products via nucleophilic attack at the carbonyl group of DMC. However, at higher temperatures, 160 °C, DMC typically acts as a methylating reagent, with the nucleophile directly attacking the methyl group.[7]

Methylation of phenolic compounds is an industrially important chemical process.[8] Anisoles are widely utilized in different industrial branches. They find major applications as antioxidants in oils and greases manufacture, as stabilizers for plastics, and as starting materials in the production of agrochemicals and dyes.[9]

Since the use of bio-oil, it has become even more important to find efficient and economical processes for the methylation of phenolic compounds. Bio-oil has to be upgraded before it can be used as engine fuel, and this is done through methylation of phenolic groups. They are an important factor for the thermal instability of bio-oil.[10]

The enhancement of the methylation of phenols with DMC has been done with microwave heating also with extra enhancement through addition of tetrabutylammonium iodide[3] and in continuous reactors with thermal heating either in liquid phase in a continuously fed stirred tank reactor[11] or in the gas phase over a solid-supported catalyst.[12]

The continuously fed stirred tank reactor is filled to one-third with a mixture of PEG 1000 and solid potassium carbonate for the methylation of phenol. As the reactor is heated to 160−200 °C, the PEG 1000 melts and forms a film around the solid potassium carbonate. The so-obtained slurry is stirred, and the reactants, phenol and DMC, are fed into the reactor in such way that they continuously bubble through the stirred catalytic bed. After leaving the stirred tank reactor the gaseous product mixture is condensed and subsequently distilled.

The solid-supported catalyst for the continuous-flow gas-phase reaction consists of potassium carbonate supported on α-Al_2O_3 beads and is described for the methylation of 2-naphthol.[12] The catalyst is placed into a glass column, which constitutes the reaction chamber of the flow reactor. The reactor is heated to 180 °C, and the starting materials, 2-naphthol and DMC, are pumped into the reactor. At the end of the reaction the gaseous reaction mixture is cooled with a water condenser and collected.

■ RESULTS AND DISCUSSION

We have since some years worked with the use of simple tube reactors for the development and scale-up of various reactions. During this time we learned that it is a very easy transfer of a microwave protocol to a continuous flow protocol in a tube reactor. During a project with a customer we became interested in the methylation with DMC. On the basis of the microwave protocol for the DBU-promoted methylation of phenols and NH-heterocycles from Shieh et al.[3] and phenols and carboxylic acids from Rajabi and Saidi[4] we decided to study if this method could be converted into a continuous protocol. The intention was to run the reaction in a standard tube reactor, either 316

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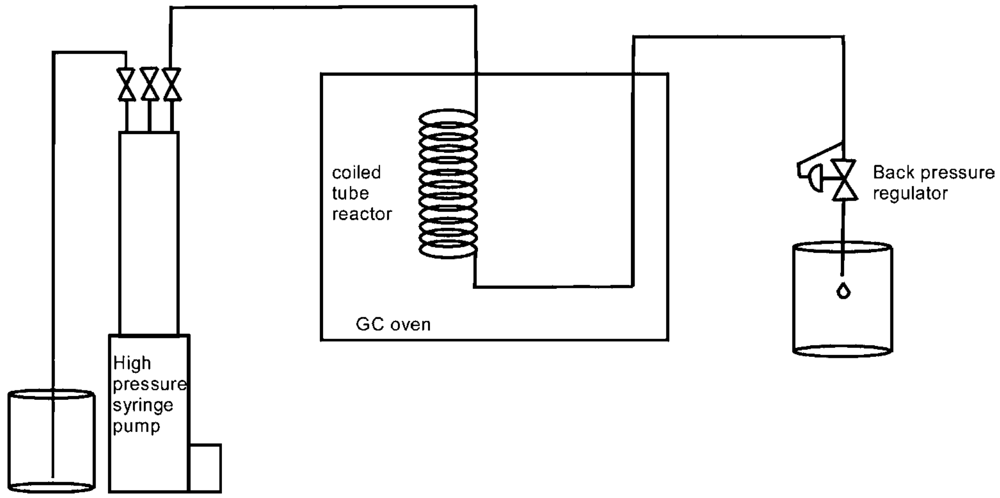
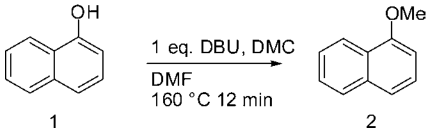


Figure 1. Schematic description of the continuous tube reactor setup.

stainless steel or steel-braided PTFE. We decided to use a 2 m long 1/8 in. steel-braided PTFE reactor for the first test runs with an internal volume of 15.8 mL. The needed temperature is below the recommended highest temperature of 240 °C for the use of steel braided PTFE tubes. We have previously used these types of reactors with amine bases at elevated temperatures and have not observed any problems of leaching or decomposition of the PTFE. The formation of carbon dioxide during the reaction and the high temperature above the boiling point of DMC cause the need to equip the reactor with an inline back-pressure regulator. We used a preset 500 psi back-pressure regulator from Upchurch Scientific. In the front end of the reactor setup we used a Teledyne Isco syringe pump 500 D. The hot zone of the reactor is placed in a GC oven (see Figure 1).

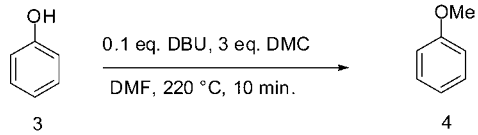
The conditions that were reported by Shieh et al. were 12 min at 160 °C with 1 equiv of DBU, 10 vol of DMC, and 10 vol of *N*,*N*-dimethyl formamide/DMF as solvent (Scheme 1). We choose to use these reaction conditions as our startup conditions. Under the described conditions in the microwave reactor, Shieh et al. obtained an isolated yield of 99% of 1-methoxy-naphthalene (**2**).

Scheme 1. Transformation of 1-naphthol to 1-methoxy-naphthalene



We set the oven temperature to 160 °C, mixed all reactants and the solvent in a round-bottom flask, and fed the clear solution into the pump. The flow through the 15.8 mL reactor was set to give a residence time in the hot zone of 12 min. After line out we analyzed a sample. According to HPLC a complete conversion of the 1-naphthol (**1**) to 1-methoxy-naphthalene (**2**) was made. After workup of the complete reaction mixture we obtained a yield of 98% of 1-methoxy-naphthalene (**2**). This encouraging result made us run the same reaction with phenol (**3**). With phenol we also received a complete conversion to anisole (**4**) within 12 min (Scheme 2).

Scheme 2. Transformation of phenol to anisole



To make the protocol valuable for the methylation of phenols on large scale the amount of DMC and DMF need to be reduced. Due to the high costs of DBU it will be important to use only a catalytic amount of base as described by Rajabi and Saidi.[4] The further development of the process was hereafter conducted with phenol (**3**) as substrate. First we reduced the amount of solvent to 3 vol. This gave a complete conversion of the starting material (Table 1, entry 2).

The reduction of DMC to 3 vol gave a conversion of 80% at 160 °C (entry 3). An increase of the temperature gave at 180 °C a conversion of 88% (entry 4). At 200 °C the conversion of the starting material was 95% (entry 5), and at 220 °C no starting material could be detected entry 6). In all of these reactions with stoichiometric amounts of DBU the reaction is not clean although the initial reaction at 160 °C gave high yield of the wanted product. We decided to use a smaller amount of DBU as it might be that DBU is not stable under the reaction conditions. The first step was to run the reaction with 0.5 equiv of DBU under the same conditions. In the reaction mixture no phenol (**3**) could be detected, and the impurity was reduced from 17.9% to 14.5%. Further reduction of the amount of DBU to 0.2 equiv also showed an absence of the starting material. The level of the impurity was reduced to 6.7%. At 0.1 equiv the level of the impurity was down to 4.3% with no starting material. It seems that the formation of this unknown impurity is related to the amount of DBU. To understand the problem with the impurity we ran one reaction with 1-naphthol at 220 °C with 0.1 equiv of DBU with 3 equiv of DMC in 3 vol of DMF with a reaction time of 12 min. Also in this case we observed the same impurity as with phenol as substrate and at the same level of 4.4%. The isolated yield from this reaction was 96%. From this we believe that the impurity is due to a reaction of DBU with DMC or a byproduct as carbon dioxide. Due to the high isolated yields of the different products the impurity cannot be formed from the phenol or the anisole.

Table 1. Optimization of the continuous methylation

entry	temperature, °C	amount DMC	amount DBU	amount DMF	phenol %	impurity
1	160	10	1	10	(**3**) 0[a]	14.5
2	160	10	1	3	(**3**) 0	13.9
3	160	3	1	3	(**3**) 20	13.8
4	180	3	1	3	(**3**) 12	15.8
5	200	3	1	3	(**3**) 5	16.5
6	220	3	1	3	(**3**) 0	17.9
7	220	3	0.5	3	(**3**) 0	14.5
8	220	3	0.2	3	(**3**) 0	6.7
9	220	3	0.1	3	(**3**) 0	4.3
10	220	3	0.1	3	(**1**) 0[b]	4.4
11	220	3	0.05	3	(**3**) 20	4.5
12	220	3	0.01	3	(**3**) 34	4.2
13	220	2	0.1	3	(**3**) 9	4.5
14	220	1.5	0.1	3	(**3**) 21	4.1

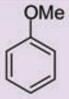
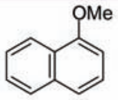
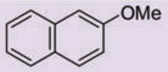
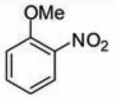
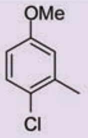
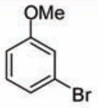
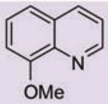
[a] Isolated yield of anisole (**4**) 94% [b] Isolated yield of 1-methoxy-naphthalene 96%.

Further reduction of the amount of DBU gave at 0.05 equiv 80% conversion, and at 0.01 equiv we reached only 66% conversion. We decided to remain at 0.1 equiv of DBU and looked at lowering the equivalents of DMC. At 2 equiv the reaction gave at 220 °C 91% conversion and with 1.5 equiv only 79% conversion. We repeated this experiment with a residence time of 30 min in the hot zone. Also in this reaction we did not reach complete conversion of the starting material. In this case 19% of phenol was found after the reaction. For the moment the use of 3 equiv of DMC is needed to get a complete conversion of the starting material in the wanted residence time in the hot zone of the reactor. The residence time at 220 °C was also evaluated; at 8 min the conversion of the starting material was complete, but at 6 min the conversion of the starting material was only 95%. It was decided to use a longer residence time of 10 min for the screen of different substrates.

With this optimized catalytic protocol we ran one reaction with phenol (**3**) at 50 mmol scale. From this reaction we obtained a 96% isolated yield of anisole (**4**, see Table 2, entry 1). With 1-naphthol (**1**) we obtained complete conversion and a 97% isolated yield of 1-methoxy-naphthalene (**2**, entry 2); we also obtained a high yield of 2-methoxy-naphthalene (**5**, 95%, entry 3). We were able to obtain from a deactivated phenol as 2-nitrophenol an isolated yield of 92% of 2-nitro anisole (**6**, entry 4). We also obtained in 93% yield 4-chloro-3-methyl anisole (**7**, entry 5). 3-Bromo-anisole (**8**, entry 6) was also obtained in a high yield (94%). 8-Methoxy-quinazoline (**9**, entry 7) was only obtained in 88% yield although we had a complete conversion of the starting material.

As all the test runs have been done with a stainless steel-braided PTFE reactor, we wanted to evaluate if a 316 stainless steel 1/8 in. tubing could be used as the reactor for this reaction. A reactor with the same volume as the PTFE reactor was constructed. In this reactor we ran a reaction with phenol (**3**) as substrate under the same conditions that had been used in the steel-braided PTFE reactor. We obtained a 95% isolated yield of anisole (**4**). A comparison of the impurity profile from the reaction in the two different reactors did not show any difference. This result shows that steel-braided PTFE or 316 stainless steel reactors can be used for the reaction.

Table 2. Screen of various substrates using the best conditions developed

Entry	Product[1]	Compound No.	Yield
1		4	96 %
2		2	97 %
3		5	95 %
4		6	92 %
5		7	93 %
6		8	94 %
7		9	88 %

[1] The methylated products gave the same spectral data as commercial samples.

We also evaluated if the reaction can be run without solvent. Due to the low solubility of the salts of the phenolic compound with DBU it will not be possible for all substrates. We picked phenol as our candidate. The experiment gave a complete conversion with an isolated yield of 95%.

To show the potential of the procedure a small-scale production run was performed. The oven was heated to 220 °C and the reactor was prefilled with DMC. The pump was filled with the premade reaction mixture containing 2 mol of phenol (**3**), 6 mol of DMC, and 0.2 mol of DBU in DMF. The pump is subsequently started to ascertain a 10 min residence time in the hot zone. The prefill and the reaction mixture as well as the washing with methanol are captured in a collection flask. The impurity profile of this larger-scale reaction corresponds to the previous small-scale reaction. From the collected reaction mixture, methanol and DMC were distilled off. From the distillation of anisole (**4**) we obtained 207 g corresponding to an isolated yield of 96%.

■ SUMMARY

We have found that the use of a conventional, heated, standard 316 stainless steel or steel-braided PTFE tube reactor is a good and easily scalable alternative to the use of continuous microwave-heated reactors. The heat-up is almost as fast as with microwave heating, and the reactors can easily be scaled towards large-scale production. The transfer of the reported[3] microwave procedure to the continuous flow method went smoothly, and we found that we could further optimize the reaction to a catalytic procedure with 10 mol % of DBU and 3 equiv of DMC. The reaction can be run neat in cases where the starting material is soluble in DMC as phenol (**3**) is, or with a small amount of DMF (2−3 vol). The reaction is efficient for different types of phenols giving a clean reaction in high yields.

■ EXPERIMENTAL SECTION

All solvents were purchased as anhydrous and used as received. All reagents were used as received. All manipulations were performed under nitrogen atmosphere. Reactions were monitored with reversed phase HPLC on a Waters instrument with a photodiode array detector using a Waters Sunfire (4.8 mm × 50 mm C8 3.5 μm). The mobile phase (water/acetonitrile/phosphoric acid (0.1%), 85:5:10 in 0 min to 0:90:10 in 3.3 min; 3.3 min to 0:90:10 in 5.0 min; 0:90:10 in 5 min to 85:5:10 in 5.1 min with a flow rate of 3.0 mL/min.

The reactor setup (see Figure 1): Connect the pump with the coiled tube reactor at the front end. Connect the back end of the coiled steel-braided PTFE reactor (internal volume 15.8 mL) to a T-joint. To the T-joint is a pressure gauge connected at one end and to the other a back-pressure regulator prior to the outlet into the collection flask. Insert the coiled reactor part into the GC-oven. Fill the reactor with DMC and heat the oven for the hot zone to 220 °C

A typical experimental procedure is here described for phenol without solvent. Dissolve phenol (188 g, 2 mol) in DMC (540 g, 6 mol). Add DBU (30.4 g, 0.2 mol). Fill the mixture into the syringe pump. Start the pump with a flow rate of 1.6 mL/min. As the pump empties, refill with 60 mL of DMC and continue to pump. At the end collect a sample to verify that the complete reaction mixture has left the reactor. Stop the pump and refill the collection flask into a round-bottom flask. Distill off the methanol and the DMC at reduced pressure. Thereafter, distill the anisole at 11 mbar into a collection flask. After distillation is finished, the obtained yield of anisole is 207 g (96%). After the distillation, no analysis of the small amount of residue was performed.

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Notes

The author declares no competing financial interest.

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