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A Continuous Methylation of Phenols and *N,H*-Heteroaromatic Compounds with Dimethyl Carbonate

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ABSTRACT: The methylation of phenolic substrates has been reevaluated using sulfolane as solvent instead of DMF. The change of solvent gave in all cases cleaner production of the anisole products in very good yields. The reaction requires 0.1 equiv of DBU, 2−3 equiv of DMC, and 2−5 vols of sulfolane depending on the substrate. At 220 °C the reaction time is 10 min. Sulfolane is completely stable under the reaction conditions, excluding unwanted impurities from the solvent. The reaction could also be extended to NH-indole and NH-imidazole derivatives utilizing 0.1 equiv of DBU and 2−3 equiv of DMC in 2 vols of sulfolane. All NH-heteroaromatic compounds gave clean N-methylation.

INTRODUCTION

Methylation is an important transformation that regularly employs toxic and hazardous reagents such as methyl iodide[1] or dimethyl sulfate.[2] The use of alternative reagents has been scarce due to the harsh conditions required with dimethylcarbonate or methanol as methylating agents. Conditions reported herein are often gas phase reactions with low molecular weight substrates, but for large complex molecules this is not an option for N- or O-methylation. Recently dimethyl carbonate (DMC) as a methylating reagent for phenols and NH-containing heteroaromatic compounds has been reported in conjunction 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 energy increases the speed of the reaction.[3] Rajabi and Saidi reported a methylation of phenols and carboxylic acids using microwave energy in a commercial microwave oven without temperature control. They used DBU as base but in a catalytic amount.[4]

Methylation of phenolic compounds is an industrially important chemical process.[5] Anisoles are widely utilized in different industrial branches. They find major applications as antioxidants in oils and grease manufacture, as stabilizers for plastics, and as starting materials in the production of agrochemicals and dyes.[6]

Nitrogen-containing heterocycles, such as indoles, imidazoles, pyrroles, and lately, indazoles, are ubiquitous building blocks for the pharmaceutical chemistry. The N-methylation of such heterocycles is commonly accomplished using toxic reagents in the presence of a strong base.

The use of DMC for the N-alkylation of indole derivatives with DABCO catalysis has been reported. The reaction is performed in a mixture of DMC and *N,N*-dimethylformamide (DMF) under reflux conditions in a batch reactor for 5−24 h.[7] The authors also reported the methylation of indole-2-carboxylic acid to furnish the corresponding *N*-methylindole-2-carboxylic-methyl ester.

The use of DMC with potassium carbonate in refluxing DMF for the selective N-methylation of indoles has also been reported.[8] The method gave the N-methylated indoles in high yields. No C-alkylation was reported. The method was also evaluated for the N-methylation of 3-indolylacetonitrile to compare the N- and C-alkylation of an activated methylene compound. If potassium carbonate was replaced with tetrabutylammonium bromide, the N-selectivity went up to 93:2.5 in comparison to 89:8 with potassium carbonate.

Ouk et al. reported an N-methylation of nitrogen-containing heterocycles with DMC.[9] The authors found that imidazole was N-methylated in a selective reaction within a distillation setup at 170 °C. Other heterocycles such as 1,2 pyrazole, mono- and dimethylated pyrazoles, and pyrrole could be N-methylated with this procedure although in low to good yields (60−90%).

Zhao et al. reported an N-methylation procedure with DMC catalyzed by TMEDA.[10] The reaction was performed in a mixture of DMC and DMF with a catalytic amount of TMEDA in the case of indole (10 mol %) at 95 °C for 8 h. Also other NH-heterocycles and secondary amines were N-methylated using this method. The reaction was performed with phthalimide, benzotriazole, carbazole, 10*H*-phenothiazine, 1-benzoylpiperazine, and benzoimidazole in yields between 60 and 90%.

Quaranta et al. reported the N-methoxycarbonylation and the N-methylation of pyrrole with DMC with (*tert*-butylimino-tris(dimethylamino)phosporane (P_1-t-Bu) or *tert*-butylimino-tris(pyrrolidino)-phosphorane (BTPP) catalysis.[11] The authors commented that with the phosphazenes as well as with DBU the only reaction at room temperature is the carbamation reaction. At higher temperatures and higher loadings of the phosphazene the main pathway is the N-methylation of pyrrole. At 150 °C, in the presence of 10 mol % of BTPP, pyrrole can be quantitavely methylated with DMC to 1-methylpyrrole within 3 h.

The methylation of electron-deficient pyrrole derivatives with DMC has also been reported by Magnus et al.[12] The authors found that electron-deficient pyrroles can be methylated with an excess of DMC and a small amount of DMF under DABCO catalysis (10 mol %) at 90−95 °C after 23 h reaction time.

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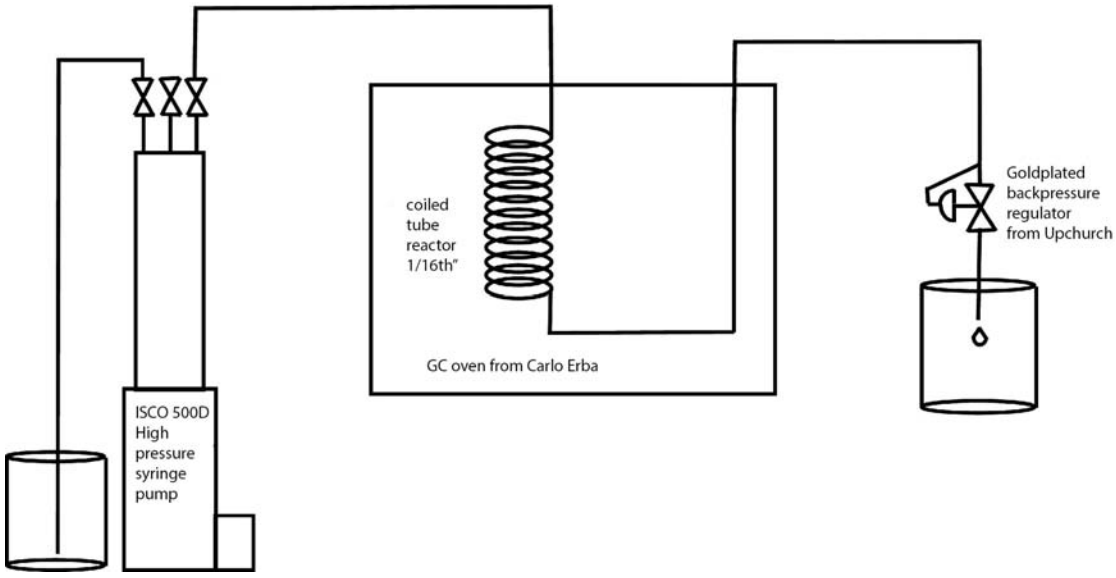


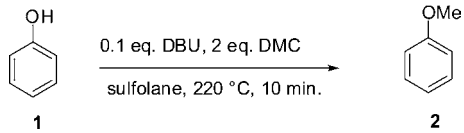
Figure 1. Schematic description of the continuous tube reactor setup.

RESULTS AND DISCUSSION

We have worked for some years using simple tube reactors for the development and scale-up of various reactions. We became interested in the methylation with DMC. We developed a continuous process for the methylation of phenols based on the protocol from Shieh et al.[3] using a catalytic amount of DBU in DMF with 3 equiv of DMC.[13] During this study we observed a rather large amount of an impurity. Originally we believed that this was related to the use of DBU, but we and others[14] have lately found out that amide dipolar aprotic solvents such as DMF, DMAC, and NMP are not stable at elevated temperatures under either acidic or alkaline conditions. During our previous study we used steel-braided PTFE, but as 316 stainless steel worked as well, we decided to use a 316 stainless-steel reactor for this study. The 316 stainless-steel reactors can be easily scaled. We decided to use a 6 m long, 1/16̀ 316 stainless-steel reactor for the test runs with an internal volume of 6.5 mL. The formation of carbon dioxide during the reaction and the high temperature above the boiling point of DMC causes the need to equip the reactor with an in-line back-pressure regulator. We used a preset 500 psi back-pressure regulator from Upchurch Scientific as during several years of development of lab-scale continuous processes we have always had a good experience with these small back-pressure regulators. In the front end of the reactor setup we used a Teledyne Isco syringe pump 500 D, a reliable high-pressure pump. The hot zone of the reactor is placed in a GC oven (see Figure 1). We decided to use our standard GC oven for small scale, but any oven can be used. We have rebuilt our oven so that it can be purged with nitrogen gas when needed. This can of course be done with any type of high-temperature oven. For larger scale it would be better to use a liquid transfer of the heat instead of air convection to ascertain uniform temperature through the whole reactor in the hot zone. The use of a GC oven is also not optimal for large-scale reactions as it produces a lot of heat that is wasted. For very high temperatures >300 °C it is better to use a more insulated furnace. To follow the reactions in the continuous setup we used a standard HPLC method and sampled after the reaction mixture has come to steady state. Recently, Nijhuis et al.[15] published a review article on the integration of microreactors for online reaction monitoring with spectroscopic detection and the possibility to do catalyst characterization.

Conditions that we had found in our earlier communication[13] were 10 min at 220 °C with 0.1 equiv of DBU, 3 equiv of DMC, and 10 vols of DMF as solvent. We decided to use these conditions but changed the solvent from DMF to sulfolane. The decision not to use DMF and DBU in the reaction was made on the basis that with more complex starting materials the formation of an impurity coming from the starting material or the product could disturb the reaction. At that time it seemed obvious the combination of DBU with DMF was the source for the formation of the impurity peak in the HPLC chromatogram. The structure of the impurity is still unknown. As substrate for the experiments in sulfolane we chose phenol (**1**). We used phenol (**1**) as the test substrate although we proved in the earlier communication[13] that, for phenol (**1**) and a few other derivatives, there is no need for a solvent, as the starting material dissolves in DMC. We let the reaction flow through the reactor for 20 min before we took the first sample. From the HPLC analysis we had a 100% conversion of the starting material to anisole (**2**) (Scheme 1). In the first

Scheme 1. Transformation of phenol to anisole



experiment where we used sulfolane, no impurity peak was observed. On the basis of this observation we believe that it is not useful to use DMF with amidine bases at high temperatures. We re-ran the reaction with 1 equiv of DBU as in this case even larger amounts of the impurity had been formed in DMF as solvent. Again in this case we could not detect the impurity. Our conclusion is that it is not useful to use DMF for high-temperature reactions with strong amidine bases such as DBU.

We evaluated the potential for the reduction of sulfolane and DMC. Using 5 volumes still did not cause a problem with

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solubility of the starting material (**1**), and the conversion was complete in a clean reaction (Table 1, entry 3). Reduction to 2 vols of sulfolane gave the same result (Table 1, entry 4). With 2 vols of sulfolane and 2 equiv of DMC the conversion of the starting material was complete (Table 1, entry 5). Further reduction of DMC to 1.5 equiv gave only a 90% conversion of the starting material (Table 1, entry 6). To finalize the evaluation we made a small production run on 50 mmol scale (Table 2, entry 1). The obtained yield after workup was 97%.

Table 1. Optimization of the continuous methylation of phenol in sulfolane

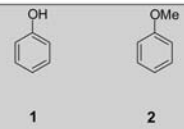
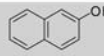
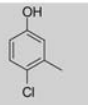
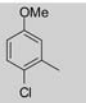
Entry	Temperature, °C	Amount DMC	Amount DBU	Amount sulfolane	Conversion %	Comment
1	220	3	0.1	10	100	No impurity detected
2	220	3	1	10	100	No impurity detected
3	220	3	0.1	5	100	No impurity detected
4	220	3	0.1	2	100	No impurity detected
5	220	2	0.1	2	100	No impurity detected
6	220	1.5	0.1	2	90	No impurity detected

With the new protocol we evaluated other phenols. With 1-naphthol (**3**) we obtained complete conversion and a 96% isolated yield of 1-methoxynaphthalene (**4**) (Table 2, entry 2). We obtained a high yield of 2-methoxynaphthalene (**6**, 97%, entry 3). With the deactivated 2-nitrophenol (**7**) we had to use 5 vols of sulfolane to obtain a clear solution at room temperature, and for a complete conversion, 3 equiv of DMC were necessary. Under these conditions we were able to obtain an isolated yield of 95% of 2-nitro-anisole (**8**, entry 4). We also obtained in 93% yield 4-chloro-3-methyl anisole (**10**, entry 5) from the starting material **9**. 3-Bromo-anisole (**12**, entry 6) was also obtained in a high yield (95%) from the corresponding phenol **11**.

We next turned our attention to the N-methylation of indoles to determine whether our protocol could be used for the N-methylation of NH-heteroaromatic compounds. We first used the protocol with phenol with 0.1 equiv of DBU and 2 equiv of DMC in 2 vols of sulfolane. This gave a 95% conversion of indole (**13**) to 1-methylindole (**14**) (Table 3, entry 1). We then extended the reaction time to 20 min. In this case the conversion was 98% (Table 3, entry 2). As we raised the temperature to 240 °C while retaining the 20 min reaction time, we obtained the 1-methylindole (**14**) in a clean reaction with complete conversion of the starting material (**13**) (Table 3, entry 3). This protocol gave an isolated yield of 1-methylindole (**14**) in 93% yield at 20 mmol scale (Scheme 2).

5-Methoxyindole (**15**) with the same protocol gave 5-methoxy-1-methylindole (**16**) in 88% yield after a clean conversion (Table 3, entry 4, Scheme 3).

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

Entry	Starting material	Product[1]	Yield	Comments
1	 **1**	**2**	97 %	2 eq. DMC 2 vol. sulfolane
2	 **3**	 **4**	96 %	2 eq. DMC 2 vol. sulfolane
3	 **5**	 **6**	97 %	2 eq. DMC 2 vol. sulfolane
4	 **7**	 **8**	95 %	3 eq. DMC 5 vol. sulfolane
5	 **9**	 **10**	93 %	3 eq. DMC 5 vol. sulfolane
6	 **11**	 **12**	95 %	3 eq. DMC 5 vol. sulfolane

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

With 5-fluoroindole (**17**) the reaction did not go to completion (80% conversion) (Table 3, entry 5). With 0.2 equivalents of DBU we did not observe a change (Table 3, entry 6). With 3 equiv of DMC, however, we did observe a 96% conversion and could isolate the product 5-fluoro-1-methyl-indole (**18**) in 84% yield (Table 3, entry 7, Scheme 4). Under identical conditions, 5-chloro indole (**19**) gave a complete conversion, and the product, 5-chloro-1-methylindole (**20**), was obtained in 86% yield (Table 3, entry 8).

We studied thereafter the N-methylation of imidazole (**21**) and used the conditions that we had developed for indole (**13**): 0.1 equiv of DBUand 2 equiv of DMC in 2 vols of sulfolane at 240 °C for 20 min (Scheme 5). This gave a complete conversion in a selective reaction to 1-methylimidazole (**22**) in an isolated yield of 84% (Table 3, entry 9).

SUMMARY

We have developed a new, reliable, DBU-catalyzed protocol for the methylation of phenols with DMC in sulfolane. This solvent remains stable under the reaction conditions thus preventing the formation of an unwanted impurity. The reactions are done within 10 min at 220 °C in high yields (93−97%) using different phenolic substrates with 2−3 equiv

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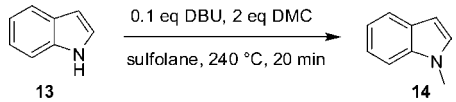
Table 3. Screen of various NH-heteroaromatic substrates[a]

Entry	Temperature, °C	Substrate	Amount DBU	Amount DMC	Conversion %	Comment
1	220	**13**	0.1	2	95	2 vol. sulfolane 10 Min
2	220	**13**	0.1	2	98	2 vol. sulfolane 20 Min
3	240	**13**	0.1	2	100 Yield 93%	2 vol. sulfolane 20 Min
4	240	**15**	0.1	2	100 Yield 88%	2 vol. sulfolane 20 Min
5	240	**17**	0.1	2	80	2 vol. sulfolane 20 Min
6	240	**17**	0.2	2	82	2 vol. sulfolane 20 Min
7	240	**17**	0.1	3	96 Yield 84 %	2 vol. sulfolane 20 Min
8	240	**19**	0.1	3	100 Yield 86 %	2 vol. sulfolane 20 Min
9	240	**21**	0.1	2	100 Yield 84%	2 vol. sulfolane 20 Min

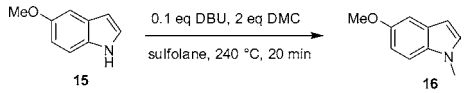
[a]The spectral data from all isolated products correspond to those of commercial samples.

Scheme 2. N-Methylation of indole



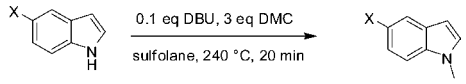
13 → 14, 93 %

Scheme 3. N-Methylation of 5-methoxyindole



15 → 16, 88 %

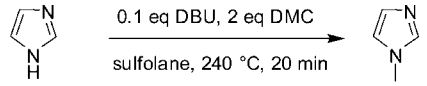
Scheme 4. N-Methylation of 5-halogenated indoles



X = F 17, X = Cl 19 → X = F 18, X = Cl 20

of DMC and 0.1 equiv of DBU. We were able to extend the reaction to NH-indole derivatives and to NH-imidazole with 0.1 equiv of DBU and 2−3 equiv of DMC in 2 vols of sulfolane All NH-heteroaromatic compounds gave clean N-methylation. The yields of the different N-methylated heteroaromatic products were between 84 and 93%.

Scheme 5. Methylation of imidazole



21 → 22, 84 %

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 column (4.8 mm × 50 mm C8 3.5 μm). The mobile phase used was water/acetonitrile/phosphoric acid (0.1%), from 85:5:10 at 0 min to 0:90:10 at 3.3 min.; keep 0:90:10 from 3.3 to 5.0 min.; 0:90:10 at 5 min to 85:5:10 at 5.1 min with a flow rate of 3.0 mL/min.

The reactor setup (see Figure 1) consisted of the following: Connect the pump with the coiled tube reactor at the front end. Connect the back end of the coiled 316 stainless steel reactor (internal volume 6.5 mL) to a T-joint. At the T-joint is a pressure gauge connected at one end and to the other a back-pressure regulator prior to the outlet of the collection flask. Insert the coiled reactor part into the GC-oven. Add sulfolane to the reactor and heat the oven for the hot zone to the desired temperature.

A Typical Experimental Procedure for Phenolic Compounds. Phenol (4.7 g, 50 mmol) was taken up in 9 mL of sulfolane. DMC (9.0 g, 100 mmol) was added followed by the addition of 0.760 g of DBU (5 mmol). The syringe pump was filled with the mixture. The pump was started with a flow rate of 0.2 mL/min. As the pump emptied, it was refilled with 10 mL of sulfolane and continued to pump. At the end a sample was collected to verify that the complete reaction mixture had left the reactor completely. The pump was stopped, and the contents of collection flask were transferred into a round-bottom flask. The methanol and the DMC were distilled off at reduced pressure. Then the anisole product was distilled at 11 mbar into a collection flask. After the distillation finished, the yield of anisole was 5.24 g (97%). The residue remaining was mainly sulfolane contaminated with DBU.

A Typical Experimental Procedure for Indole Compounds. Indole (2.34 g, 20 mmol) was taken up in 5 mL of sulfolane. DMC (3.6 g, 40 mmol) was added followed by the addition of 0.304 g of DBU (2 mmol). The contents were transferred into the syringe pump. The pump was started with a flow rate of 0.1 mL/min. As the pump emptied, 7 mL of sulfolane was transferred to the pump that continued to pump. At the end a sample was collected to verify that the complete reaction mixture had left the reactor. The pump was stopped, and the contents were transferred from the collection flask into a round-bottom flask. Distill off the methanol and the DMC at reduced pressure. Added to the solution were 0.1 equiv of 1 N hydrochloric acid (0.2 mL) and MTBE ether (15 mL). The phases were separated, and the aqueous phase was extracted twice with MTBE ether (5 mL). As sulfolane is not soluble in MTBE ether, it will remain completely in the aqueous phase. The combined organic phases were washed twice with water (5 mL). The solvent was removed by vacuum distillation using a rotary evaporator. The crude product was redissolved in one

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volume of MTBE, and hexane was slowly added under stirring until the product started to crystallize. The mixture was cooled in the freezer overnight to complete the crystallization. The product was filtered off and washed with hexane. The product was dried under vacuum. Indole (2.4 g, 93%) was obtained. The purity of the crystalline product was 98%. Spectroscopic data were in accordance with reported data.

An Experimental Procedure for Imidazole. Imidazole (1.36 g 20 mmol) is taken up in 3 mL of sulfolane. DMC (3.6 g 40 mmol) is added followed by the addition of 0.304 g DBU (2 mmol). Fill the mixture into the syringe pump. Start the pump with a flow rate of 0.1 mL/min. As the pump is emptying, refill with 7 mL of sulfolane 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 transfer the contents of the collection flask into a round-bottom flask. Distill off the methanol and the DMC at reduced pressure. Subsequently, the product distills at 11 mbar into a collection flask. After the distillation is completed, the obtained yield of *N*-methylimidazole is 1.4 g (84%). After the distillation no analysis of residual sulfolane solution is performed.

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Notes

The authors declare no competing financial interest.

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