

# Continuous Acid-Catalyzed Methylations in Supercritical Carbon Dioxide: Comparison of Methanol, Dimethyl Ether and Dimethyl Carbonate as Methylating Agents

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## Abstract:

The development of high-yielding, “greener” chemistry-based routes for the continuous synthesis of methyl ethers are reported in this study. Ethers have been efficiently produced using a methodology which eliminates the use of toxic alkylating agents and reduces the waste generation that is characteristic of traditional etherification processes. For the first time it is shown that the use of acidic heterogeneous catalysts can successfully achieve etherification when using scCO<sub>2</sub> as a reaction medium. Furthermore, the relative efficiencies of three alternative methylating agents, dimethyl carbonate, dimethyl ether and MeOH, have been compared and contrasted for the methylation of 1-octanol. Dimethyl carbonate has proven to be the superior methylating agent, demonstrating higher conversion and selectivity. Successful methylation of secondary alcohols, diols, carboxylic acids and amines using dimethyl carbonate in supercritical carbon dioxide has also been shown. Substrate structure was found to influence the temperature required to maximize the yield of the desired product, substrates with multiple hydroxyl groups requiring the highest temperatures.

## Introduction

Traditionally ethers are synthesised using the Williamson ether synthesis, which generates stoichiometric quantities of inorganic salt byproduct and uses toxic reagents such as alkyl halides.<sup>1,2</sup> However, we have previously reported a process by which cyclic and symmetrical ethers can be synthesised, in high yields, *via* the acid-catalysed bimolecular dehydration of alcohols in supercritical carbon dioxide (scCO<sub>2</sub>).<sup>3,4</sup> These studies demonstrated that the formation of unsymmetrical ethers *via* the simultaneous dehydration of two different alcohols leads to the formation of a mixture of products: the symmetrical ethers

of the two alcohols and the desired unsymmetrical ether with a relatively low yield.<sup>3</sup>

Although improved yields of methyl ethers of long-chain alcohols and diols can be obtained by using MeOH in large excess,<sup>4,5</sup> this route has two disadvantages: (i) the excess of MeOH used leads to formation of large amounts of dimethyl ether, and (ii) alkylation with methanol requires a relatively high temperature which also promotes alkene formation by unimolecular dehydration of the alcohols, thereby lowering the selectivity of the reaction. This is especially true for secondary or tertiary alcohols.

This paper reports the use of acid catalysts and two alternative methylating agents (MA), dimethyl ether (DME) and dimethyl carbonate (DMC), and compares their performance to that of MeOH for the formation of methyl ethers of long-chain alcohols. Although DME is extremely flammable, it is nontoxic and noncorrosive and does not generate inorganic waste, which makes it a cleaner alternative to traditional MAs such as methyl halides and dimethyl sulfate. DME has previously been reported to be more reactive than MeOH for the methylation of alkenes and arenes over acidic zeolites.<sup>6,7</sup>

DMC is often regarded as an environmentally benign MA because it is nontoxic and biodegradable.<sup>8–13</sup> DMC is currently manufactured *via* several routes including the catalytic oxidative carbonylation of MeOH.<sup>14–16</sup> 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.<sup>8,11</sup>

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(1) Williamson, A. W. *Liebigs Ann. Chem.* **1851**, 77, 37–49.

(2) Reed, C. J.; Gaskell, B. A.; Banger, K. K.; Lock, E. A. *Arch. Toxicol.* **1995**, 70, 51–56.

(3) Walsh, B.; Hyde, J. R.; Licence, P.; Poliakoff, M. *Green Chem.* **2005**, 7, 456–463.

(4) Gray, W. K.; Smail, F. R.; Hitzler, M. G.; Ross, S. K.; Poliakoff, M. *J. Am. Chem. Soc.* **1999**, 121, 10711–10718.

(5) Licence, P.; Gray, W. K.; Sokolova, M.; Poliakoff, M. *J. Am. Chem. Soc.* **2005**, 127, 293–298.

(6) Svelle, S.; Kolboe, S.; Swang, O.; Olsbye, U. *J. Phys. Chem. B* **2005**, 109, 12874–12878.

(7) Széchenyi, A.; Solymosi, F. *Catal. Lett.* **2009**, 127, 13–19.

(8) Tundo, P.; Selva, M. *Acc. Chem. Res.* **2002**, 35, 706–716.

(9) Tundo, P.; Trotta, F.; Moraglio, G.; Ligorati, F. *Ind. Eng. Chem. Res.* **1988**, 27, 1565–1571.

(10) Trotta, F.; Tundo, P.; Moraglio, G. *J. Org. Chem.* **1987**, 52, 1300–1304.

(11) Tundo, P.; Perosa, A. *Chem. Rec.* **2002**, 2, 13–23.

(12) Ono, Y. *Appl. Catal., A* **1997**, 155, 133–166.

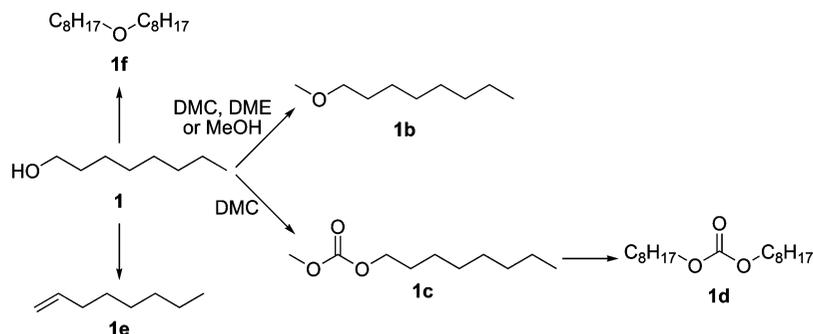
(13) Selva, M.; Perosa, A. *Green Chem.* **2008**, 10, 457–464.

(14) Romano, U.; Rivetti, F.; Di Muzio, N. Process for producing dimethylcarbonate. U.S. Patent 4,318,862, 1982.

(15) Delledonne, D.; Rivetti, F.; Romano, U. *J. Organomet. Chem.* **1995**, 488, C15–C19.

(16) Nishihira, K.; Mizutane, K.; Tanaka, S. Process for preparing diester of carbonic acid. EP425197, 1991.

### Scheme 1. Methylation of 1-octanol (1)



**Table 1.** Comparison of catalyst performance for the methylation of 1-octanol (1) using DMC in  $scCO_2$ <sup>a</sup>

catalyst	max. yield of <b>1b</b> (%)	temp. (°C) of max. yield of <b>1b</b>	max. yield of <b>1c</b> (%)	temp. (°C) of max. yield of <b>1c</b>	max. yield of <b>1e</b> (%)	temp. (°C) of max. yield of <b>1e</b>
Amberlyst 15	31	142	43	138	6	142
Amberlyst 70	54	168	53	131	62	188
Nafion SAC-13	54	191	66	161	68	207
Zeolite H-beta	56	202	58	167	94	298
basic alumina	75	270	73	179	11	330
acidic $\gamma$ -alumina	86	262	29	183	15	300

<sup>a</sup> Reaction Conditions:  $CO_2$  pumped at 1.0 mL/min (pump head at  $-10^\circ C$ , 56 bar), organic reactants (2:1 molar ratio of DMC:1) pumped at 0.2 mL/min, pressure 100 bar, 10 mL reactor packed with catalyst. Temperature linearly increased at a rate of  $10^\circ C/h$  over the operating temperature range of the catalyst.

Many reports exist of DMC being used to synthesize aryl ethers,<sup>12,17,18</sup> but few describe the synthesis of aliphatic ethers *via* this route.<sup>19,20</sup> Tundo et al.<sup>21</sup> have suggested that the aliphatic hydroxyl groups are hard nucleophiles which preferentially react at the carbonyl group, which is the harder of the two electrophilic centers in DMC. The result is the formation of methyl carbonates rather than methyl ethers, whatever the temperature. Methyl ethers can then be obtained *via* a second step where the methyl carbonate undergoes decarboxylation at high temperature over an amphoteric catalyst.<sup>19,22</sup> Selva et al.<sup>20</sup> have reported that sodium-exchanged NaY and NaX faujasites can be used to catalyze the reaction of aliphatic alcohols with DMC to form methyl ethers, where the more basic NaX faujasite possesses higher activity.

To the best of our knowledge there are no examples of DMC being used as a direct MA for aliphatic alcohols in  $scCO_2$ . As  $CO_2$  is inherently acidic, basic catalysts usually deactivate in the presence of  $scCO_2$  due to the reaction of  $CO_2$  with the active sites.<sup>23</sup> Therefore, it would be expected that acid catalysts would be preferable candidates for comparing the efficiency of MAs, when using  $scCO_2$  as the reaction medium. In this report, we describe the screening of a representative selection of heterogeneous acid catalysts, demonstrating that acidic catalysts can indeed be used in  $scCO_2$  to produce methyl ethers from aliphatic alcohols with DMC. We also compare the relative efficiencies of DMC, DME and MeOH as the MA in  $scCO_2$  and show that DMC is active at lower temperatures and achieves higher

conversions and selectivities than either DME or MeOH. Finally we extend the scope of this route by reacting DMC with a series of substrates that exhibit a variety of nucleophilic functionalities.

## Results and Discussion

**Acid-Catalyzed Methylation of 1-Octanol with DMC in  $scCO_2$ .** In all our experiments, reactions were carried out in an automated continuous reactor equipped with online gas liquid chromatography (GLC) analysis, described in the Experimental Section. To verify that DMC could be successfully used to produce methyl ethers using acid catalysis in  $scCO_2$ , a series of experiments was conducted in which the reaction of 1-octanol (1), Scheme 1, was carried out over six different heterogeneous acid catalysts, Table 1. Each catalyst was studied by pumping 1.0 mL/min  $CO_2$  (pump head at  $-10^\circ C$ , 56 bar) and 0.2 mL/min organic reactants (2:1 molar ratio of DMC:1) at 100 bar pressure over a fixed bed of the solid acid catalyst. The performance of each catalyst was monitored over its operating temperature range using the GLC to analyze the composition of the mixture emerging from the reactor.

Table 1 summarizes the results for all the catalysts studied, and plots containing details of the full temperature range are given in the ESI. It can be seen from this table that (i) by using acidic catalysts, the direct methylation of 1 to 1b with DMC is possible, (ii) that this approach is an improvement upon existing base catalysis which requires the use of large excesses of DMC,<sup>19</sup> (iii) this direct single step process has advantages over the two steps proposed by Tundo et al.,<sup>22</sup> which requires separation of the production of the dialkyl carbonate prior to the decarboxylation to the methyl ether, and (iv) comparing the performance of the acidic catalysts, it can be seen that the acid  $\gamma$ -alumina catalyst is the most effective, both in terms of high conversion of 1 and high selectivity towards 1b. The high yield is thought to be the result of the higher operating temperatures. We now look at the results in more detail.

(17) Ouk, S.; Thiebaud, S.; Borredon, E.; Legars, P.; Lecomte, L. *Tetrahedron Lett.* **2002**, *43*, 2661–2663.

(18) Fu, Y.; Baba, T.; Ono, Y. *Appl. Catal., A* **1998**, *166*, 419–424.

(19) Tundo, P.; Memoli, S.; Haurault, D.; Hill, K. *Green Chem.* **2004**, *6*, 609–612.

(20) Selva, M.; Militello, E.; Fabris, M. *Green Chem.* **2008**, *10*, 73–79.

(21) Tundo, P.; Rossi, L.; Loris, A. *J. Org. Chem.* **2005**, *70*, 2219–2224.

(22) Tundo, P.; Arico, F.; Rosamilia, A. E.; Memoli, S. *Green Chem.* **2008**, *10*, 1182–1189.

(23) Hattori, H. *Chem. Rev.* **2002**, *95*, 537–558.

**Amberlyst 15** is a supported Brønsted acid catalyst, and has been previously used by us to produce the cyclic and symmetrical ethers in  $\text{scCO}_2$ .<sup>3,5</sup> As the temperature was increased in the reaction of **1** over this catalyst ( $>80\text{ }^\circ\text{C}$ ), the initial product was methyl octyl carbonate (**1c**). The observation of this product was expected, as the transesterification of DMC with ethanol has previously been observed over acidic ion-exchange resins.<sup>24</sup> As the temperature was increased further ( $>110\text{ }^\circ\text{C}$ ), the desired methyl ether, 1-methoxyoctane (**1b**) was formed, reaching a maximum yield of around 30% at  $140\text{ }^\circ\text{C}$ . At these high temperatures octenes (**1e**) and dioctyl ether (**1f**) were also formed in small amounts respectively due to the unimolecular and bimolecular dehydration of **1**. However, the thermal instability of Amberlyst 15 precludes increasing the yield of **1b** by further raising the temperature.

**Amberlyst 70** and **Nafion SAC-13** are also supported Brønsted acid catalysts but possess greater thermal stability than Amberlyst 15, thus permitting higher reaction temperatures.<sup>25,26</sup> When using Amberlyst 70 and Nafion SAC-13 as catalysts, similar effects of temperature on product composition were observed; **1c** being formed at lower temperatures, followed by **1b** at increased temperatures with both catalysts having a maximum yield of 54%, achieved at  $168\text{ }^\circ\text{C}$  with Amberlyst 70 and  $191\text{ }^\circ\text{C}$  with Nafion. However, the competing dehydration reaction to form **1e** also occurs at these high temperatures and becomes the dominant process as the temperature is increased further. Additionally, at these elevated temperatures, small amounts of **1f** and dioctyl carbonate (**1d**), which is produced by the transesterification of **1c** with **1**, were also detected.

**Zeolite H-beta** is a protic zeolite related to the NaY and NaX faujasites used by Selva et al.<sup>20</sup> Again at lower temperatures the main product of the reaction is **1c** followed by **1b** at higher temperature with a maximum yield of 56% at  $200\text{ }^\circ\text{C}$ . Additionally, selectivity towards **1b** was generally observed to be poor with this catalyst, due to significant formation of **1f** and **1e** at temperatures above  $180\text{ }^\circ\text{C}$ .

**Base-activated alumina and acidic  $\gamma$ -alumina** were studied as a comparison to the basic and acidic aluminas used by Tundo et al.<sup>19</sup> Acidic  $\gamma$ -alumina is a well-known catalyst for the formation of ethers *via* the dehydration of alcohols,<sup>27–30</sup> which we have also demonstrated in a  $\text{scCO}_2$  environment.<sup>31</sup> Whilst both these aluminas are believed to be somewhat amphoteric in nature, there is a clear difference in their performance in this reaction. The basic alumina exhibited a marked selectivity for the undesired **1c** at  $\sim 180\text{ }^\circ\text{C}$ . However, high yields of **1b** were achieved at temperatures in excess of  $220\text{ }^\circ\text{C}$ , with a maximum yield of 75% obtained at  $270\text{ }^\circ\text{C}$ , and an operating window of

$>70\%$  yield between  $260$  and  $290\text{ }^\circ\text{C}$ . By contrast, the acidic  $\gamma$ -alumina exhibited a much higher selectivity toward the formation of **1b** over a larger temperature range than the basic alternative. The acidic catalyst produced  $>80\%$  yield of **1b** over a temperature window that extended from  $220$  to  $280\text{ }^\circ\text{C}$ , with a maximum yield of 86% at  $262\text{ }^\circ\text{C}$ . In a separate experiment, this catalyst showed no decline in activity over a period of 20 h at a constant temperature of  $250\text{ }^\circ\text{C}$ .

As a result of these initial screening studies, the acidic  $\gamma$ -alumina was chosen as the catalyst to be used in further MA comparison studies, because of its wide temperature range, high catalytic activity and good selectivity.

**Comparison of the Performance of DMC, DME and MeOH as Methylating Agents.** The relative performance of each of these MAs, were compared by mixing solutions of **1** and each MA (6:1 molar ratio of MA to **1**) with  $\text{scCO}_2$  (11:1 molar ratio of  $\text{CO}_2$  to MA) and passing the resulting mixture over the acidic  $\gamma$ -alumina. The molar ratio of **1** to MA was raised from the 1:2 used in the screening studies because it was known from previous work that greater ratios of MeOH were needed to achieve etherification at significant yield. The reactor temperature was gradually increased from  $100$  to  $350\text{ }^\circ\text{C}$ , while the system pressure was maintained at a constant 100 bar. The variations in product distribution with temperature for all three reactions are shown in Figure 1. The key results, summarized in Table 2, show that the formation of **1b** proceeded in higher yield with DMC than with either DME or MeOH, and that DMC required significantly lower operating temperatures than MeOH.

Furthermore, from Figure 1a, it can also be seen that the undesired byproduct, **1c**, was the major product when using DMC at lower temperatures ( $<150\text{ }^\circ\text{C}$ ), presumably resulting from the direct attack of **1** at the carbonyl group of DMC. At higher temperatures ( $160\text{--}250\text{ }^\circ\text{C}$ ), the selectivity of the reaction rapidly switched to favor the formation of the methyl ether, **1b**, to a maximum yield of 96%. Figure 1b shows that, when using DME as the MA, ether formation is favored over a much narrower temperature range ( $170\text{--}275\text{ }^\circ\text{C}$ ) and the yield is consistently lower (75%) than that of the comparable reaction with DMC.

The methylation of **1** using MeOH, shown in Figure 1c, required much higher catalyst bed temperatures than with either DMC or DME. Significant ether formation was not observed until the temperature was in excess of  $280\text{ }^\circ\text{C}$ . With all three MAs, temperatures  $>300\text{ }^\circ\text{C}$  led to dehydration of **1**, resulting in the production of the alkene **1e**. This is consistent with previous reports for the dehydration of **1** over alumina catalysts.<sup>32</sup> The dehydration reaction places an upper limit on the temperature range over which etherification can be carried out. Overall, our results show that DMC has a significantly wider operating temperature range than either DME or MeOH due to the enhanced reactivity of DMC at lower temperatures.

It was observed that during the reaction of **1** with DMC, a proportion of DMC underwent catalytic thermal decomposition to form DME and  $\text{CO}_2$ , Scheme 2. This decomposition has been

(24) Zielinska-Nadolska, I.; Warmuzinski, K.; Richter, J. *Inz. Chem. Procesowa* **2004**, *25*, 1861–1866.

(25) Siril, P. R.; Cross, H. E.; Brown, D. R. *J. Mol. Catal. A: Chem.* **2008**, *279*, 63–68.

(26) Harmer, M. A.; Sun, Q. *Appl. Catal., A* **2001**, *221*, 45–62.

(27) Sohlberg, K.; Pennycook, S. J.; Pantelides, S. T. *Chem. Eng. Commun.* **2000**, *181*, 107–135.

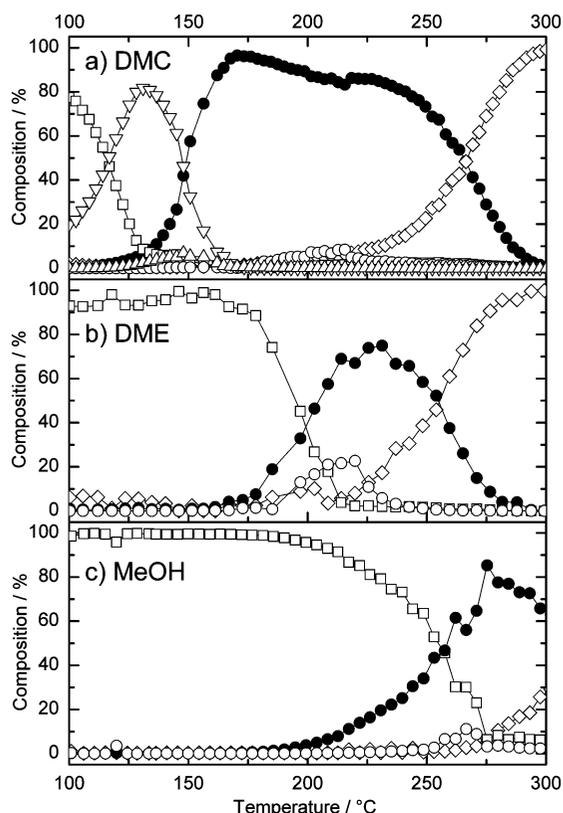
(28) Knözinger, H. *Angew. Chem., Int. Ed.* **1968**, *7*, 791–805.

(29) Shi, B. C.; Davis, B. H. *J. Catal.* **1995**, *157*, 359–367.

(30) Seo, C. W.; Jung, K. D.; Lee, K. Y.; Yoo, K. S. *Ind. Eng. Chem. Res.* **2008**, *47*, 6573–6578.

(31) Amandi, R.; Hyde, J. R.; Ross, S. K.; Lotz, T. J.; Poliakov, M. *Green Chem.* **2005**, *7*, 288–293.

(32) Makgoba, N. P.; Sakuneka, T. M.; Koortzen, J. G.; van Schalkwyk, C.; Botha, J. M.; Nicolaidis, C. P. *Appl. Catal., A* **2006**, *297*, 145–150.



**Figure 1.** Results of methylation of **1** using (a) DMC, (b) DME and (c) MeOH. Filled circles ● indicate the desired product, **1b**. Other species are labeled as follows: □**1**, ▽**1c**, Δ**1d**, ◇**1e**, ○**1f**. Note the desired product **1b** is observed at a lower temperature with DMC than with either DME or MeOH. Reactions were performed in continuous flow with *sc*CO<sub>2</sub> as the reaction media. Solution of the methylating agent and **1** (6:1 molar ratio) pumped at 0.2 mL/min; CO<sub>2</sub> flow rate 1.0 mL/min; system pressure 100 bar; tubular reactor internal volume 10 mL used throughout.

**Table 2.** Comparison of methylating agents in the methylation of **1** to form **1b**, in *sc*CO<sub>2</sub>

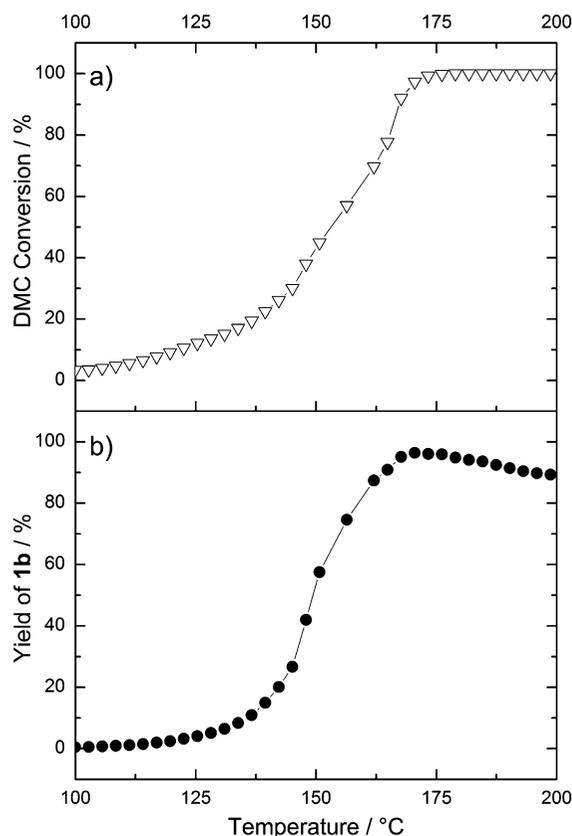
	methylating agent		
	MeOH	DME	DMC
yield of <b>1b</b> (%) at 150 °C	<1	33	58
yield of <b>1b</b> (%) at 175 °C	1	69	96
max. yield (%) of <b>1b</b>	85	75	96
temp. (°C) of max. yield of <b>1b</b>	275	230	170

**Scheme 2.** Decomposition of DMC to form DME and CO<sub>2</sub>



reported previously over solid catalysts such as quartz<sup>33,34</sup> and zeolites.<sup>35,36</sup> Fu et al.<sup>37</sup> have also studied the thermal decomposition of DMC over solid acid and base catalysts, including alumina, and have claimed that it was due to the presence of both acidic and basic sites in alumina that led to complete decomposition of DMC at lower temperatures than over either solely strongly acidic or basic catalysts.

- (33) Wijnen, M. H. *J. Chem. Phys.* **1961**, *34*, 1465–1466.  
 (34) Thynne, J. C. J.; Gray, P. *Trans. Faraday Soc.* **1962**, *58*, 2403–2409.  
 (35) Beutel, T. J. *Chem. Soc., Faraday Trans.* **1998**, *94*, 985–993.  
 (36) Anderson, S. A.; Manthata, S.; Root, T. W. *Appl. Catal., A* **2005**, *280*, 117–124.  
 (37) Fu, Y.; Zhu, H.; Shen, J. *Thermochim. Acta* **2005**, *434*, 88–92.



**Figure 2.** Plots showing (a) the percentage conversion of DMC and (b) the corresponding percentage yield of **1b** in the same experiment. Note that the two plots exhibit a very similar temperature dependence. Reactions were performed in continuous flow with *sc*CO<sub>2</sub> as the reaction media. A solution of DMC and **1** (6:1 molar ratio) was pumped at 0.2 mL/min; CO<sub>2</sub> flow rate 1.0 mL/min; system pressure 100 bar; tubular reactor internal volume 10 mL.

Closer study of the results from our automated reactor suggested that the extent of DMC decomposition is related to the yield of **1b**. Figure 2 shows that the onset of the decomposition reaction and the increase in ether formation occur at very similar temperatures. However, as shown in Figure 1b, DME is a less active methylating agent for the etherification of **1** than DMC. One possible explanation for these observations is that the decomposition of DMC may leave adsorbed reactive species on the surface of the catalyst, thus increasing its potential to methylate the substrate. This hypothesis is supported by previous spectroscopic studies by Beutel<sup>35</sup> and suggests that direct methylation by nucleophilic attack on the methyl groups of DMC may not be occurring with this catalyst.

**Methylation of Other Substrates with DMC.** A series of experiments were performed to examine the potential applications of DMC as a methylating agent. A range of substrates, Scheme 3, were reacted with DMC under conditions similar to those described above, and the results are summarized in Table 3.

Table 3 shows that (i) all of the substrates can be methylated with a good or high yield using DMC, (ii) the temperature at which the maximum yield is observed is different for different substrates ranging from 170 to 270 °C, (iii) the formation of ethers from secondary alcohols is lower yielding than that from primary, reflecting the greater stability of the secondary car-

### Scheme 3. Methylation of various substrates with DMC

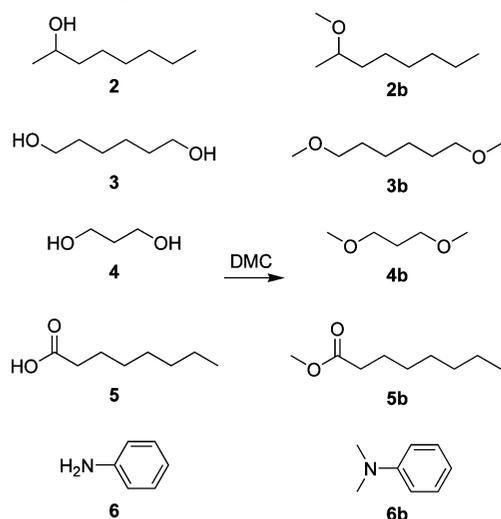


Table 3. Results of methylation experiments using DMC<sup>a</sup>

substrates, <i>n</i>	max. yield (%) of products, <i>nb</i>	temp. (°C) of max. yield
1	96	170
2	90	180
3	84	175
4	68	270
5	94	205
6 <sup>b</sup>	>99 (46)	250 (205)

<sup>a</sup> Reaction conditions: Substrate solution pumped at 0.2 mL/min, CO<sub>2</sub> pumped at 1.0 mL/min, system pressure 100 bar. Fixed catalyst bed (tubular reactor, internal volume 10 mL) temperature ramped linearly between 100–350 at 0.3 °C/min. A 6:1 molar ratio of DMC:substrate was used, except for experiments with substrates 3, 4 and 5, where a 30:1 molar ratio was applied. <sup>b</sup> Formation of *N,N*-dimethylaniline proceeds *via* the monomethylated intermediate *N*-methylaniline. Figures in parentheses indicate the relevant values for this intermediate species.

bocation, which increases the likelihood of alkene formation, and (iv) methylation of aniline requires a relatively high temperature.

As in the reaction of 1, the methylation of 2-octanol (2) results in the desired methyl ether, 2-methoxyoctane (2b), in high yield. Dehydration of 2 to form octenes was observed at lower temperatures than for 1; this precludes effective methylation being achieved with MeOH, which requires higher temperatures than DMC. 1,6-Hexanediol (3) reacts to form the bis-methylated analogue (3b) with selectivity of up to 80%; as with the reaction of 1, small amounts of carbonate byproduct are detected below the temperature of DMC decomposition. At higher temperatures intramolecular dehydration of 3 forms the cyclic ether, hexamethylene oxide, which has been observed previously over alumina.<sup>38</sup> 1,3-Propanediol (4) showed an increased propensity to form dimer or trimer species and appeared to hinder the decomposition of DMC, with higher temperatures (>290 °C) being required to achieve complete decomposition. This is possibly due to diol molecules interacting more strongly with the active sites, potentially *via* both hydroxyl groups, leading to increased catalyst crowding and/or catalyst site deactivation/inaccessibility. As a result higher temperatures are required to overcome this 2-fold interaction in order to allow methylation to occur. Under conditions at which DMC decom-

poses, it was found that both free hydroxyl groups of 4 were fully methylated to produce the bis-methylated analogue (4b).

The versatility of this methylation route was explored further by reacting solutions of DMC with octanoic acid (5) and aniline (6) over  $\gamma$ -alumina in scCO<sub>2</sub>. The esterification of 5 proceeded in excellent yield to the corresponding methyl ester (5b). The *N*-methylation of 6 proceeded initially to *N*-methylaniline, and subsequently to *N,N*-dimethylaniline (6b) quantitatively, as the temperature was increased. Interestingly, above 325 °C, significant amounts (~75%) of *C*-methylated products of *N,N*-dimethylaniline were observed.

### Conclusion

This study has described a high-yielding, chemically greener route for the continuous synthesis of methyl ethers from primary and secondary alcohols using DMC in scCO<sub>2</sub>. In so doing, ethers have been produced efficiently without the use of toxic alkylating agents or the inorganic waste generation that is characteristic of traditional etherification processes. It has shown, we believe for the first time, that it is possible to use DMC with acidic catalysts to obtain high yields of target ethers, when using scCO<sub>2</sub> as the reaction medium.

The relative efficiencies of three known methylating agents (DMC, DME and MeOH) have been compared, and it is clear that DMC is the most efficient within this system. DMC gave the highest yields of the desired ethers over the widest temperature range, thereby allowing the greatest flexibility over the choice of reaction conditions. Furthermore, the greater reactivity of DMC leads to successful conversions with a much lower substrate:methylating agent molar ratio than the reactivity of either DME or MeOH.

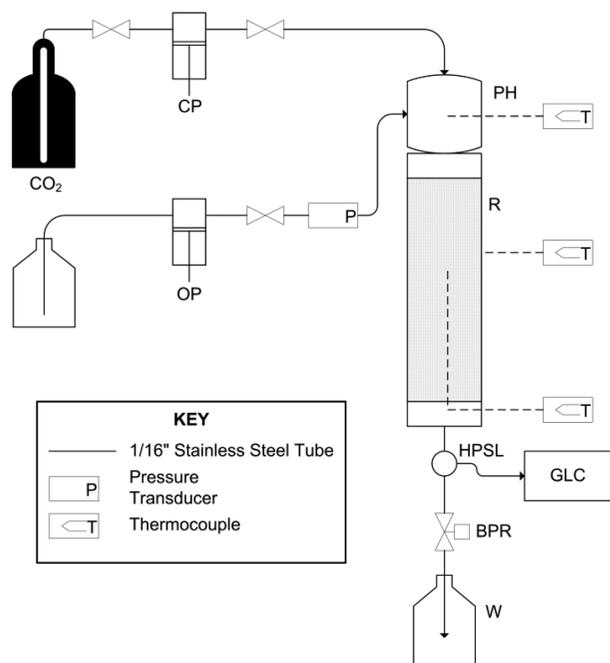
Additionally, it has been shown that the decomposition of DMC and formation of the desired methylated product occur at similar temperatures. Thus, we postulate that the decomposition of DMC generates reactive methylating species on the catalyst surface, and it is these species that participate in the methylation reaction.

However, substrate structure has also been found to influence the conditions under which this reaction has to be run to maximize the yield of the target product. Diols require higher temperatures to promote the desired reaction, perhaps because of stronger binding between the catalyst and the diol which reduces the availability of sites for DMC to interact with the catalyst. Thus, higher temperatures are required to overcome this increased substrate association. DMC was also shown to be high yielding for clean esterification and *N*-methylation reactions.

Of course, the disadvantage of scCO<sub>2</sub> on the large scale is the energy cost associated with generating high pressures of CO<sub>2</sub>. Unfortunately, CO<sub>2</sub> cannot be totally eliminated from the reaction since it is a decomposition product of DMC. However, we are currently exploring the possibility of using DMC at lower pressures, for example with gas-expanded liquids, which are already proving useful for a wide variety of reactions.<sup>39</sup>

(38) Costa, A.; Riego, J. M. *Synth. Commun.* **1987**, *17*, 1373–1376.

(39) Akien, G. R.; Poliakoff, M. *Green Chem.* **2009**, *11*, 1083–1100.



**Figure 3.** Schematic of the automated supercritical flow reactor developed at the University of Nottingham. The reactant solution and CO<sub>2</sub> are pumped by a HPLC pump (OP) and a chilled CO<sub>2</sub> pump (CP) respectively. The two streams are then mixed in a heated mixing unit (PH) and passed over a heated fixed catalyst bed (R). The system pressure is controlled by a back pressure regulator (BPR), and the products are collected once the pressure is released in a collection vessel (W). Whilst the product stream is flowing from the exit of R to the BPR, the high pressure sample loop (HPSL) can remove aliquots of the product mixture and introduce them directly into the carrier gas stream of the gas liquid chromatograph (GLC) for analysis.

### Experimental Section

**CAUTION!** The experiments described in this paper involve the use of relatively high pressures and require equipment with the appropriate pressure rating.

Figure 3 shows a simplified schematic of the automated supercritical flow reactor. This system has been described in more depth previously<sup>3</sup> and only a brief overview of the equipment will be provided here. A programmable HPLC CO<sub>2</sub> pump (Jasco PU-1580-CO<sub>2</sub>) and HPLC pump (Jasco PU-980) were connected to a 1/4 in. cross-piece, packed with glass beads. The cross-piece acts as both mixer and preheater, heated by cartridge heaters within an aluminium heating block. The fixed bed reactor consists of a 10 mL 316 stainless steel tube (156 mm × 12 mm OD) packed with catalyst and heated by cartridge heaters in an aluminium heating block, controlled *via* a programmable heating controller (Eurotherm 2216 L). The pressure is controlled by a BPR (Jasco BP-1580-81). The setup utilizes an online sample loop (Valco VICI microvolume, 0.06

mL, electronically actuated, 250 ms switching time) which is positioned upstream of the expansion system to allow direct sampling of the product stream *via* GLC analysis using a Shimadzu GC-17A equipped with a RTX-5 column (30 m, 0.25 mm ID, 0.25 μm FT), using He carrier gas and a FID detector. This sampling provides a method to obtain an instantaneous ‘snapshot’ of the reaction products at the current reactor conditions. The identities of compounds were confirmed by injection of authentic samples and by GLC-MS using a Thermo-Finnigan Polaris-Q instrument fitted with a RTX-1MS column (30 m, 0.25 mm ID, 0.25 μm FT). Reaction conditions are monitored using a PicoLog TC-08 connected to thermocouples positioned internally and externally on the reactor and to the pressure transducers located within both the HPLC pumps and the BPR.

In a typical experiment, the catalyst was loaded in the reactor and sealed into the apparatus. The initial conditions for the experiment were set at the pumps, BPR and temperature controllers, and the system was allowed to equilibrate over at least 30 min. The experimental parameters were then programmed into pumps, BPR, temperature controllers and GLC such that samples are injected into the GLC periodically as one or more reaction parameters (e.g., temperature and pressure) were varied. Commercially available catalysts were employed: acidic NWA-150 γ-alumina (Supplied by SI group; powder, 150 m<sup>2</sup>/g surface area and containing trace impurities of SiO<sub>2</sub>, Fe<sub>2</sub>O<sub>3</sub> and Na<sub>2</sub>O), basic alumina Brockmann I (Sigma-Aldrich), Amberlyst 15 (Lancaster Synthesis), Amberlyst 70 (Rohm and Haas), Nafion SAC-13 (Sigma Aldrich), and Zeolite H-Beta (research sample from University of Manchester). Dimethyl carbonate 99% (Sigma-Aldrich), 1-octanol 99% (Sigma-Aldrich), 2-octanol 97% (Sigma-Aldrich), 1,6-hexanediol 99% (Sigma-Aldrich), 1,3-propanediol 98% (Fisher Scientific Ltd.), octanoic acid 99% (Sigma-Aldrich), aniline 99% (Fisher Scientific Ltd.) and CO<sub>2</sub> 99.9% (Cryoservice) were used without further purification.

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### Supporting Information Available

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