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Graphene-catalyzed transacetalization under acid-free conditions

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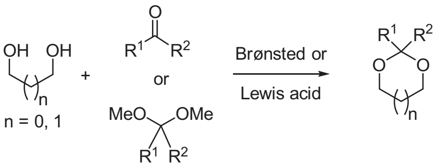
ABSTRACT

1,2- and 1,3-Diols are readily protected as cyclic acetals and ketals through a graphene-catalyzed transacetalization process. The methodology features an atom economic procedure since quasi-stoichiometric conditions have been developed. Unlike prior systems, the graphene-catalyzed transacetalization is performed under Brønsted and Lewis acid-free conditions and without solvent. Our method has been applied to several volatile compounds that are unsuitable for complex work-up and extensive purification steps. The very unusual catalytic properties of graphene for transacetalization reactions are ascribed to molecular charge transfer between graphene and substrates.

The formation of cyclic acetals and ketals for the transient protection of 1,2- and 1,3-diols has been massively employed in multi-step synthesis and many well established methods are now routinely used by synthetic chemists.[1] Methods for the protection of diols as cyclic acetals and ketals are traditionally executed with acetone, benzaldehyde, or their dimethyl acetal derivatives (Scheme 1). All variations of these methods usually require the use of homogeneous Brønsted or Lewis acid catalysts such as *p*-TsOH and $BF_3{\cdot}Et_2O$ under anhydrous conditions.

While homogeneous catalysts usually provide high selectivities and excellent reaction yields, extra neutralization steps and both recovery and corrosive issues are prohibiting for sustainable and/or large scale processes. These last years, environmental concerns have led to the resurgence of this transformation in order to find active catalyst systems compatible with the principle of green chemistry, especially through the use of heterogeneous catalysts.[2–5] Moreover, acetalization reactions are key transformations for the preparation of biodiesel additives from glycerol[6] and many heterogeneous catalysts have shown great potential as traditional homogeneous acid surrogates.[7–10] The catalytic activity of most heterogeneous catalysts reported in the literature, results from non-easily quantifiable contributions of both Brønsted and Lewis acid properties complicating the fine-tuning of catalytic properties and corrosion issues cannot be addressed with heterogeneous acid catalysts. While a few homogeneous neutral catalysts based on the use of molecular iodine have been reported,[11–13] we reasoned that discovering a heterogeneous neutral catalyst showing strong activities for (trans)acetalization processes would be of great interest.



Scheme 1. General equation for cyclic acetals or ketals formation from diols.

We recently unveiled the peculiar properties of graphene that promoted the acetalization of glycerol without any external source of Brønsted or Lewis acid.[14] Graphene being a non-Lewis and non-Brønsted acid platform, the unprecedented catalytic activity recorded for the acetalization of glycerol was attributed to the peculiar electronic properties of the honeycomb-structured 2D material.[15–19] This acid-free process was successfully developed for the valorization of glycerol with a variety of carbonyl compounds including ketones and aldehydes, giving the corresponding cyclic ketal or acetal in high yields. However, a large excess of the

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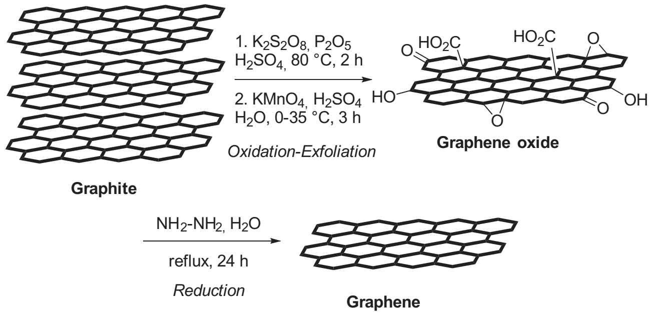
carbonyl source (10 equiv) with respect to glycerol was used and a more atom-economic process is therefore required for increasing its practical usefulness. In this Letter we describe an optimized process whose scope was extended to several 1,2- and 1,3-diols leading to five- and six-membered acetals respectively. We especially explored the synthesis of volatile cyclic acetals which are unsuitable for complex work-up and column chromatography purification, and therefore require a procedure generating minimum amounts of by-products and waste.

The graphene catalyst used in this study was prepared from commercially available and inexpensive graphite following a scalable procedure recently developed in our laboratory (Scheme 2).[20] Briefly, graphite was oxidized into graphene oxide following a two-step approach. A first pre-oxidation was carried out with potassium persulfate in sulfuric acid at 80 °C for 2 h followed by a second and stronger oxidation step using potassium permanganate in aqueous sulfuric acid at 35 °C for 3 h. The oxidized graphite was exfoliated under ultrasound into isolated sheets of graphene oxide. The exfoliated sheets of graphene oxide were then reduced to graphene by hydrazine. The successful exfoliation was assessed by XRD, and we determined that graphene contained an average of only four stacked sheets while 85 stacked sheets were determined for graphite. This parameter is crucial for the success of our methodology, since more exfoliated the graphene is, more important its electronic properties increase with respect to charge transfer.

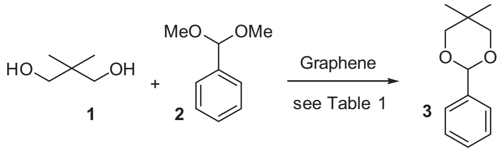
The two main aims of this work with respect to our previous research results were to significantly reduce the carbonyl-to-diol molar ratio and optimize the mass loading of graphene. We reasoned that the need for a large excess of carbonyl compounds to reach high conversion of the acetalization could be attributed to the formation of water, allowing the reaction to reverse. To address this point we reasoned that performing the process with carbonyl dimethyl acetals as carbonyl surrogates will suppress the formation of water, avoiding the reaction to reverse. In order to settle this hypothesis, we optimized a benchmark reaction involving the transacetalization of 2,2′-dimethylpropan-1,3-diol with benzaldehyde dimethyl acetal **2** using graphene as catalyst under solvent-free conditions. The expected cyclic acetal **3** being rather volatile and unsuitable for extended work-up manipulations, the transacetalization process must minimize the formation by- and side-products. As expected, when using a 10:1 **2**-to-**1** molar ratio at 100 °C with graphene as catalyst (25 mg per mmol of diol **1**), a quantitative yield of the corresponding acetal **3** was obtained but the remaining starting material **2** was almost impossible to remove from **3** either under vacuum or by column chromatography due to their similar volatility and polarity (entry 1). Interestingly, the decrease of the **2**-to-**1** molar ratio from 10:1 to only 1.25:1 did not affect the reaction yield at 100 °C and a quantitative yield for **3** was obtained, indicating that after a simple filtration to remove the graphene catalyst, cyclic acetal **3** was obtained with an excellent purity (>95%) with only a trace amount of remaining **2** as detected by ^{1}H NMR (entry 4). By contrast, reducing the temperature to 80 °C significantly altered the reaction conversion suggesting that this parameter could not be modulated (entry 5). The reaction time was also optimized and we were able to preserve the reaction yield within 10 hours of stirring (entry 6), but upon a further decrease an incomplete conversion was obtained (entry 7). The mass loading of graphene was also significantly reduced from 25 to 6 mg of graphene per mmol of diol **1** without affecting both the reaction yield and rate (entry 9). The background reactions showed that the transacetalization marginally occurred in the absence of graphene, leading to the corresponding acetal **3** in 22% yield (entry 10) while graphite and graphene oxide catalyzed the transacetalization with a reduced efficiency, highlighting the peculiar properties of graphene (entries 12–13). The activity of graphene oxide is not surprising since this material possesses significant Brønsted acid properties due to the presence of carboxylic acid functions. We also confirmed that under optimized conditions, the use of benzaldehyde instead of benzaldehyde dimethyl acetal **2** significantly altered the reaction yield (77%), confirming the detrimental effect of water that favors the reaction to reverse and decrease the conversion (entry 11) (Table 1).

With these optimized conditions in hand, we set out to explore the scope of this process (Table 2). The transacetalization of 1,2- and 1,3-diols with benzaldehyde dimethyl acetal **2** proceeded in high yields, providing the corresponding five- and six-membered cyclic acetal respectively (compounds **3**–**9**). Both, primary and secondary alcohols were well tolerated but steric hindrance might require a slightly higher loading of graphene (12.5 mg/mmol vs 6 mg/mmol) for reaching a high yield of the cyclic acetal (compounds **4** and **7**). Beside benzaldehyde dimethyl acetal **2**, cyclohexane dimethyl acetal and 2,2′-dimethoxypropane were also successfully involved in the graphene-catalyzed transacetalization reaction (compounds **9**–**12**). The inertness of 1,2-hexadecanediol required an excess of 2,2′-dimethoxypropane for reaching a



Scheme 2. Synthesis of graphene.

Table 1
Optimization studies



Entry[a]	Compound **2** (equiv)	Graphene (mg/mmol)	Time (h)	Temp (°C)	Yield[b] (%)
1	10	25	14	100	>97
2	5	25	14	100	>97
3	2.5	25	14	100	>97
4	1.25	25	14	100	>97
5	1.25	25	14	80	90
6	1.25	25	10	100	>97
7	1.25	25	6	100	94
8	1.25	12.5	10	100	>97
9	1.25	6	10	100	>97
10	1.25	0	10	100	22
11[c]	1.25	6	10	100	77
12[d]	1.25	6	10	100	86
13[e]	1.25	6	10	100	85

[a] Optimized reaction conditions: Diol **1** (1 mmol), benzaldehyde dimethyl acetal **2,** (1.25 mmol) and graphene (6 mg) were stirred for 10 hours at 100 °C in a sealed tube.

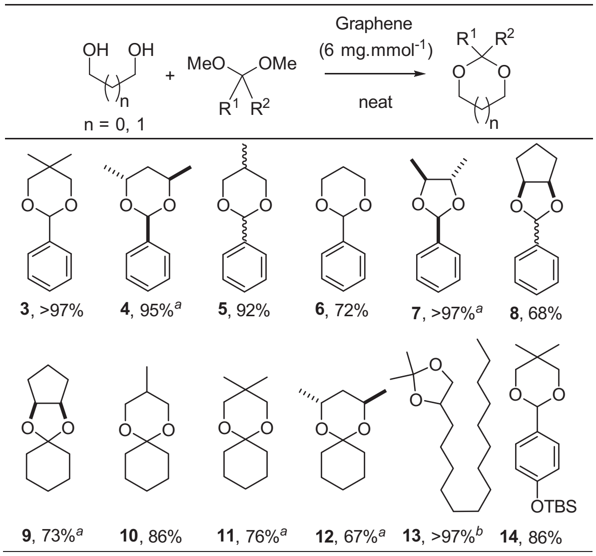
[b] Yield determined by ^{1}H NMR using 1,2,4-trimethylbenzene as internal standard.

[c] Benzaldehyde was used instead of benzaldehyde dimethyl acetal.

[d] Graphite was used instead of graphene.

[e] Graphene oxide was used instead of graphene.

Table 2
Scope of the reaction



[a] 12 mg of graphene per mmol of diol were used.
[b] 12 mg of graphene per mmol of diol were used and 10 equiv of 2,2-dimethoxypropane.

quantitative yield due to its very low solubility and high crystallinity. With the exception of **12**, most acetals prepared in this study were quite volatile and unsuitable for purification by column chromatography. However, it must be mentioned that even for acetals not produced in quantitative yields, unreacted diols were not detected in the crude mixture after filtration, suggesting that it might be stacked on graphene and the cyclic acetals were obtained with ~95% purity as determined by ^{1}H NMR.[21] Importantly, the methodology is compatible with acid-sensitive substrates as highlighted in the preparation of acetal **14** bearing a silyl ether protecting group. While at this stage it is premature to definitively conclude on a reaction mechanism, the unusual activity of graphene for the transacetalization of diols might result from charge transfer between graphene and reacting molecules; graphene having ambivalent properties since it can receive and donate electrons.[22–24]

The recycling of graphene was also studied on the benchmark reaction allowing the transacetalization of 2,2′-dimethylpropan-1,3-diol with benzaldehyde dimethyl acetal **2**. After each run the catalyst was recovered by filtration, thoroughly washed with acetone, and dried under *vacuum* before being reengaged in a further cycle. We observed a slight decrease of the reaction yield upon successive reuses since 93 and 87% yield were obtained after the 2nd and 3rd reuses respectively. This decrease was attributed to the surface graphene poisoning by starting materials as we previously observed on related transformations.[14]

In summary, we described a graphene-catalyzed transacetalization process for the formation of cyclic acetals from 1,2- and 1,3-diols. The methodology features an experimentally simple protocol under solvent-free conditions and does not require Bronsted or Lewis acid; this latter point is of synthetic relevance for acid-sensitive substrates. The quasi-stoichiometric carbonyl dimethyl acetal-to-diol molar ratio and the heterogeneous nature of graphene simplify the work-up and purification steps since they allow recovering the reaction product with a high purity. We believe that such a methodology will be of great interest for synthetic chemists working with acid-sensitive substrates and/or volatile intermediates that are not suitable for purification by column chromatography.

Acknowledgments

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21. *For a representative procedure:* A mixture of diol **1** (1 mmol), benzaldehyde dimethyl acetal (1.25 mol) and graphene (6 mg) were stirred for 10 h at 100 °C. The resulting mixture was filtered on a nylon membrane, washed with a minimum amount of acetone and the crude was carefully concentrated under vacuum giving the corresponding cyclic acetal in excellent purity (>90%) without further purification. IR (KBr) ν 1100, 1216, 1389, 1455, 1469, 2844, 2953 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 0.81 (s, 3H), 1.31 (s, 3H), 3.66 (d, 2 H, $J = 9$ Hz), 3.78 (d, 2H, $J = 12$ Hz), 5.41 (s, 1H), 7.34–7.42 (m, 3H), 7.51–7.54 (m, 2H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 21.8, 23.0, 30.2, 77.6, 101.7, 126.1, 128.2, 128.8, 138.4. MS (CI/NH$_3$): 193 (M+H$^+$), 210 (M+NH$_4^+$).
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