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Graphite Oxide as an Auto-Tandem Oxidation–Hydration–Aldol Coupling Catalyst

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Abstract: Graphite oxide (GO) was found to function as an auto-tandem oxidation-hydration-aldol coupling catalyst for the formation of chalcones in a single reaction vessel. Various alkynes or alcohols were hydrated or oxidized *in situ* to their corresponding methyl ketones or aldehydes, respectively, which underwent a subsequent Claisen–Schmidt condensation. Each of the aforementioned reactions proceeded in the absence of metals (confirmed by inductively coupled plasma mass spectrometry, ICP-MS) and afforded a range of chalcone products in good to excellent yields from commercially available starting materials.

Keywords: chalcones; Claisen–Schmidt condensation; graphite oxide; heterogeneous catalysis; hydration; oxidation

Building on the recent discovery that graphite $oxide^{[1]}$ (GO) – a carbon-based material rich with oxygencontaining functional groups – and graphene oxide (its exfoliated counterpart) effectively facilitate the oxidation of alcohols and hydration of alkynes,^[2] we describe herein new methods for harnessing such broad reactivity to synthesize chalcones. As a motif commonly found in many natural products and often used as precursors in the preparation of flavonoids and isoflavonoids,^[3] chalcones are typically prepared *via* the Claisen–Schmidt coupling of methyl ketones and aldehydes. However, recent efforts have focused on combining multiple transition metal-based catalysts to expedite the synthesis of new derivatives, particularly by expanding the range of amenable starting materials.^[4]

We reasoned that GO, a 150-year-old material derived from graphite,^[1b] may be used to circumvent many of the limitations and drawbacks inherent to the synthetic approaches described above, and enable a metal-free synthesis of chalcones from a broad set of starting materials. GO is typically prepared using the Hummers method which involves adding KMnO₄ to graphite dispersed in concentrated H₂SO₄ followed by quenching with aqueous H₂O₂.^[5] Under these strongly oxidizing conditions, a variety of oxygen-containing functional groups (e.g., alcohols, aldehydes, and carboxylic acids) are introduced to the carbon surface (see Figure 1). Previously, we demonstrated



Figure 1. Structural model of graphene oxide, an exfoliated monolayer of graphite oxide (GO).^[1]

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Scheme 1. Summary of GO-catalyzed reactions explored.

that GO may be used to oxidize various alcohols or hydrate alkynes to their respective aldehydes and ketones.^[2] As shown in Scheme 1, we surmised that this reactivity may be harnessed to effect multiple mechanistically-distinct reactions in a single reaction vessel, without the use of additional reagents or isolation steps – a process known as auto-tandem catalysis^[6] – as a means to access chalcones (1) and other high value substrates.

Initial efforts sought to explore the acidic and hygroscopic properties inherent to GO^[7] as a means to effect C–C bond-forming reactions. As summarized in Table 1, a series of coupling reactions involving various acetophenones and benzaldehydes was performed neat by combining equimolar quantities of the aforementioned substrates with a fixed quantity of GO. After 14 h at 80 °C, the products as well as unreacted starting materials were dissolved in dichloromethane, the GO was removed *via* vacuum filtration and the corresponding chalcones were isolated by silica chromatography in good yields (66 to 85%).^[8] Although electron-poor as well as electron-rich aromatic com-

Table 1. Coupling of acetophenones to benzaldehydes.^[a]

| $R' \xrightarrow{+ H'} R'$ | | | | | |
|----------------------------|-----------------------|-----------------------------|-------------------------------|--|--|
| Entry | R-C(O)CH ₃ | R'-C(O)H | Isolated yield of 1 | | |
| 1 | R = Ph | R' = Ph | 81% | | |
| 2 | R = Ph | $R' = p - NO_2C_6H_4$ | 66% | | |
| 3 | R = Ph | $R' = p - CH_3OC_6H_4$ | 76% | | |
| 4 | R = Ph | $R' = p - CH_3C_6H_4$ | 80% | | |
| 6 | $R = p - NO_2C_6H_4$ | $\mathbf{R'} = \mathbf{Ph}$ | 85% | | |
| 7 | $R = p - CH_3OC_6H_4$ | $\mathbf{R'} = \mathbf{Ph}$ | 68% | | |
| 8 | $R = p - CH_3C_6H_4$ | $\mathbf{R'} = \mathbf{Ph}$ | 74% | | |

^[a] All reactions were performed neat in 1:1 stoichiometry (0.5 mmol each) of ketone:aldehyde using 50 mg of GO at 80 °C for 14 h.

pounds were successfully coupled,^[9] limited reactivities were observed when various aliphatic species (e.g., octanal, 2-pentanone, and hexane-2,5-dione) were explored as substrates. These results suggested to us that the GO was not merely functioning as an exogenous acid source^[10] and that aliphatics either do not possess sufficient rigidity required for an unencumbered approach to the GO surface or that a favorable arene-GO interaction is required.^[11]

We next focused on combining the ability of GO to facilitate oxidations (e.g., alcohols to aldehydes, a reaction shown to be catalytic in the presence of molecular oxygen)^[2] with its ability to promote acid-catalyzed condensations. As shown in Table 2, *in situ* oxidation of benzylic alcohols to their respective benzaldehydes in combination with coupling to acetophenones was explored. Treating equimolar quantities of various alcohols and ketones with GO under similar conditions as those described above afforded the expected chalcone products in isolated yields of up to 55% after 24 h, depending on the substrates em-

Table 2. Coupling of acetophenones to benzyl alcohols.^[a]



| Entry | R–C(O)CH ₃ | R'-CH ₂ OH | Isolated yield of 1 |
|-------|-----------------------|------------------------|-------------------------------|
| 1 | R = Ph | R' = Ph | 55% |
| 2 | R = Ph | $R' = p - NO_2C_6H_4$ | 36% ^b |
| 3 | R = Ph | $R' = p - CH_3OC_6H_4$ | с |
| 4 | $R = p - NO_2C_6H_4$ | R' = Ph | 55% |
| 5 | $R = p - CH_3OC_6H_4$ | R' = Ph | 48% |

[a] All reactions were performed neat in 1:1 stoichiometry (0.5 mmol each) of ketone:alcohol using 200 mg of GO^[14] at 80 °C for 24 h.

^[c] Not determined as *p*-methoxybenzyl alcohol was found to polymerize under these conditions.

^[b] Reaction performed at 100 °C.

ployed.^[12] While *in situ* oxidations of alcohols have been used previously in the synthesis of chalcones, metal-based catalysts were required and mixtures of products were obtained.^[4,13] Only a single product was observed in the crude NMR spectrum when GO was used to facilitate similar tandem oxidation–condensation reactions. To confirm that the reactivities observed were not metal-mediated, inductively coupled plasma mass spectrometry was performed on an aqueous dispersion of GO. The Mn content (KMnO₄ was used to prepare GO) was found to be <1 ppb, similar to other native metal contaminants such as Al (3 ppb), Pb (4 ppb), and Ba (1 ppb).

Building on these results, our attention shifted toward combining GO's ability to effect hydrations of phenylacetylenes to their respective acetophenones with GO's ability to facilitate acid-catalyzed condensations with aldehydes in a single reaction vessel.^[15] Combination of a 1:1 molar ratio of phenylacetylene and benzaldehyde with an equimass quantity of GO at 80°C afforded the desired chalcone product in 51% isolated yield (Table 3), which was increased to 79% (>98% conversion by NMR spectroscopy) when two equivalents of the aldehyde were used. We believe that some of the aldehyde was lost via oxidation to its carboxylic acid (observed via NMR spectroscopy), and that the use of excess substrate aided in driving the reaction toward formation of the targeted product. Regardless, a variety of alkyne and aldehyde derivatives were successfully coupled using this methodology (see Supporting Information, Tables S1–S3, S8).

Table 3. Coupling of arylalkynes to benzaldehydes.^[a]



| Entry | R−C≡CH | R′-C(O)H | Isolated yield of 1 |
|-------|-------------------------------|------------------------|-------------------------------|
| 1 | R = Ph | R' = Ph | 51% |
| 2 | R = Ph | $R' = p - NO_2C_6H_4$ | 63% |
| 3 | R = Ph | $R' = p - CH_3OC_6H_4$ | 43% |
| 4 | $R = p - t - BuC_6 H_4^{[b]}$ | R' = Ph | 55% |
| 5 | $R = p - NO_2C_6H_4$ | R' = Ph | 19% ^[c] |
| 6 | $R = p - CH_3OC_6H_4$ | R' = Ph | 50% |

[a] All reactions were performed neat in 1:1 stoichiometry of alkyne:aldehyde (0.5 mmol each) using 50 mg of GO at 100 °C for 14 h.

- ^[b] Reaction of this substituted phenylacetylene derivative with benzaldehyde was used to help elucidate the coupling mechanism.¹⁵
- ^[c] The high melting point $(150 \,^{\circ}\text{C})^{[16]}$ of *p*-nitrophenylacetylene limited miscibility, and ultimately reactivity, under the conditions explored.

Based on the results obtained above, we lastly explored the ability of GO to catalyze the aforementioned hydration and oxidation reactions in a single reaction vessel, and then facilitate an acid-catalyzed Claisen-Schmidt type condensation coupling of the respective products formed in situ. As shown in Table 4, the combination of various phenylacetylenes and benzyl alcohols (1:2 molar ratio) with GO under conditions similar to those described above afforded the desired chalcone products in up to 61% isolated yields (94% conversion by NMR spectroscopy) (see Supporting Information, Tables S4–S6). To the best of our knowledge, these reactions are the first examples of coupling alkynes and alcohols in a single vessel for the direct formation of chalcones. Beyond demonstrating the ability to facilitate multiple, mechanistically-distinct reactions in an auto-tandem fashion and uncovering new transformations enabled by GO, this methodology may prove useful in syntheses where methyl ketones are inaccessible, or unwanted side reactions (e.g., irreversible formation of ketols or Michael addition products) are observed.^[17]

In conclusion, we have shown that GO effects multiple mechanistically-distinct oxidation, hydration, and C–C bond forming reactions and is capable of doing so in an auto-tandem fashion. This unique combination of reactivities from a readily available carbon material facilitated access to substituted chalcones from a wide range of commercially available starting materials, and in the absence of metal catalysts. Moreover, these transformations underscore the ability of GO to function as a carbocatalyst,^[2] and offer signifi-

Table 4. Coupling of arylalkynes to benzyl alcohols.^[a]



| Entry | R−C≡CH | R'-CH ₂ OH | Isolated yield of 1 |
|-----------------------|---|--|--|
| 1 2 3 4 5 | $R = Ph$ $R = Ph$ $R = Ph$ $R = p-NO_2C_6H_4$ $R = p-CH_3OC_6H_4$ | $R' = Ph$ $R' = p-NO_2C_6H_4$ $R' = p-CH_3OC_6H_4$ $R' = Ph$ $R' = Ph$ | $\begin{array}{c} 61\%^{[b]}\\ 34\%^{[c]}\\ _^{[b,d]}\\ 10\%^{[e]}\\ 50\%^{[b]}\end{array}$ |

 [a] All reactions were performed neat in 1:2 stoichiometry (0.5 mmol of alkyne; 1 mmol of alcohol) using 200 mg of GO^[14] at 80 or 100 °C for 24 h.

- ^[b] Performed at 80 °C.
- ^[c] Performed at 100 °C.
- ^[d] Not determined as *p*-methoxybenzyl alcohol was found to polymerize under these conditions.
- [e] Performed at 150 °C. The high melting point (150 °C)^[16] of *p*-nitrophenylacetylene limited miscibility, and ultimately reactivity, under the conditions explored.

cant modularity with respect to the reactive functional groups of the reagents while requiring little change to the reaction conditions employed (temperature, time, catalyst loading, etc.) Numerous combinations for directly coupling alkynes or methyl ketones with alcohols and aldehydes are now possible and the methodologies reported herein are expected to be of value for the preparation of chalcones and related compounds, particularly in a combinatorial manner.^[18] In a broader perspective, these results establish GO's potential for use in synthetic chemistry, especially in the development of metal-free methodologies, rather than simply as a precursor to graphene and derivatives thereof.^[1] Future efforts will be directed toward optimizing the reactions described herein and further exploring the as yet unknown factors that contribute to GO's remarkable reactivity (e.g., extent of oxidation, surface area, etc.)

Experimental Section

General Procedure for the Synthesis of 1 from a Methyl Ketone or Alkyne and an Aldehyde or Alcohol

In a typical preparation, a 7.5-mL vial was charged with 50–200 mg of GO, methyl ketone or alkyne (0.5 mmol), aldehyde or alcohol (0.5 or 1 mmol) and a magnetic stir bar. The vial was then sealed with a Teflon-lined cap under ambient atmosphere and heated at 80–150 °C for 14–24 h. Afterward, the reaction mixture was cooled to room temperature and washed with 50 mL of CH_2Cl_2 . The filtrate was collected and the solvent was evaporated to obtain the crude product. Following purification of the crude product by column chromatography on silica gel, the desired product was dried under vacuum and characterized.

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