

9-1-2012

## Investigation of the Reactivity of Mildly Activated and Weakly Deactivated Substrates in Zinc Oxide-Catalyzed Friedel-Crafts Acylation

Gabriel Velez  
*Winona State University*

Alexandra Larrabee  
*Winona State University*

Thomas Nalli  
*Winona State University*

Follow this and additional works at: <https://openriver.winona.edu/studentgrants2013>

---

### Recommended Citation

Velez, Gabriel; Larrabee, Alexandra; and Nalli, Thomas, "Investigation of the Reactivity of Mildly Activated and Weakly Deactivated Substrates in Zinc Oxide-Catalyzed Friedel-Crafts Acylation" (2012). *Student Research and Creative Projects 2012-2013*. 47.

<https://openriver.winona.edu/studentgrants2013/47>

This Grant is brought to you for free and open access by the Grants & Sponsored Projects at OpenRiver. It has been accepted for inclusion in Student Research and Creative Projects 2012-2013 by an authorized administrator of OpenRiver. For more information, please contact [klarson@winona.edu](mailto:klarson@winona.edu).

## Introduction

Catalysis is a basis for more than 90% of all industrial processes<sup>1</sup> playing an essential role in the manufacture of a wide range of products.<sup>2</sup> Over the past generation major advancements in the area of catalysis has not only advanced the level of efficiency but also has simultaneously introduced great environmental benefits. By using catalysts chemists have found ways to remove the need to carry out transformations that would have ultimately contributed to the chemical waste stream for many reactions.<sup>3</sup>

Since the discovery of Friedel-Crafts acylation, many attempts have been made to produce novel "green" methods to carry out the reaction. Originally a Friedel-Crafts acylation involved the use of a Lewis acid catalyst (usually AlCl<sub>3</sub>) and an acylating agent. The negative aspects of AlCl<sub>3</sub> include the facts that the catalyst cannot be easily recovered and recycled and a large amount of toxic waste is typically generated.<sup>4</sup> New methods are aimed at producing efficient methods that are not only environmentally safe, but cost-effective. These new methods include using metal catalysts and metal- and halogen-free methodologies using methanesulfonic anhydride<sup>5</sup>. These strategies are attractive to chemists due to the growing concern over solvent waste effects on the environment and on human health.

Zinc oxide is a relatively inexpensive, commercially available inorganic solid<sup>6</sup> that is moisture-stable, reusable, environmentally benign, and it has distinctive surface properties.<sup>7</sup> As a catalyst for Friedel-Crafts acylation, zinc oxide has been reported to work well under solvent-free conditions.<sup>6</sup> After reaction completion, the catalyst can be washed in dichloromethane and then reused up to three times producing good yields.<sup>6</sup> The reaction was even reported to work well with weakly deactivated rings, such as chlorobenzene.<sup>6</sup> Since this report, zinc oxide has also been employed as a solvent-free catalyst for other types of reactions, including the acylation of alcohols, phenols, and amines<sup>8</sup>, Beckmann rearrangements, the synthesis of cyclic ureas<sup>9</sup> as well as many other types of reactions.<sup>10-12</sup>

However, one other attempt to use this catalyst for the Friedel-Crafts acylation of a deactivated substrate was reported in the literature to be poor yielding and full of impurities.<sup>13</sup> Additionally, the original manuscript describing this method<sup>6</sup> specified the use of large amounts of solvent (5 mL CH<sub>2</sub>Cl<sub>2</sub> per mmol) to extract the product.

Therefore, the objectives of this study were to further test the scope of substrates that react using this catalyst and to minimize the amount of solvent use upon scale-up of the final product.

**Table I. Reported yields of Friedel-Crafts acylation of 2-(2-butyl-1-benzofuran-5-yl)-1H-indole-1,3(2H) dione (12) with 4-(3-chloropropoxy) benzoic acid<sup>13</sup>**

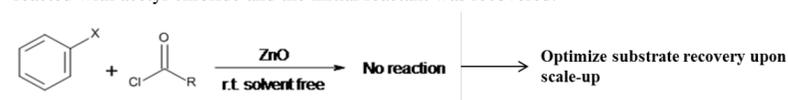
| Lewis Acid        | Conditions           | Results                              |
|-------------------|----------------------|--------------------------------------|
| ZnO               | DCM, 25 °C, 24 h     | No product formation observed by TLC |
| AlCl <sub>3</sub> | DCM, -20 °C, 1 h     | 68% isolated yield                   |
| SnCl <sub>4</sub> | DCM, 0 to 25 °C, 1 h | 88% isolated yield                   |

## Methods

**General Procedure** – An aromatic compound (5 mmol) was added to 2.5 mmol of ZnO (either 85% - 95% grade pellets or 99% grade powder) at room temperature. An acyl chloride (5 mmol) was added to the mixture and the reaction was mixed with a magnetic stirrer for 15 minutes. For entries 9 and 11, the acyl chloride was mixed with ZnO first. The product was then eluted with dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>, 5 mL per mmol of product) and the extract was washed with water and then an aqueous sodium bicarbonate solution (10%) and dried over anhydrous sodium sulfate. Solvent was evaporated using rotary evaporation or fractional distillation and the product was characterized using <sup>1</sup>H NMR. Percent recoveries were corrected for the presence of DCM using the <sup>1</sup>H NMR integrations.

## Results

**Figure I.** General experiment design for deactivated substrates. A deactivated compound was reacted with acetyl chloride and the initial reactant was recovered.



**Table II. Reactions of weakly deactivated and weakly activated substrates.<sup>a</sup>**

| Entry | Substrate         | ZnO               | Yield             | Recovery (%)    | Color Change |
|-------|-------------------|-------------------|-------------------|-----------------|--------------|
| 1     | PhBr              | Powder            | n.r. <sup>d</sup> | 33              | Colorless    |
| 2     | PhBr              | Pellets           | n.r.              | 43              | Colorless    |
| 3     | PhBr              | Pellets           | n.r.              | 59              | Colorless    |
| 4     | PhBr <sup>b</sup> | Pellets           | n.r.              | 66              | Colorless    |
| 5     | PhCl              | Pellets           | n.r.              | 55              | Colorless    |
| 6     | PhCl              | Pellets           | n.r.              | 63              | Colorless    |
| 7     | PhCl              | Powder            | n.r.              | 99 <sup>c</sup> | Colorless    |
| 8     | PhCl              | Powder            | n.r.              | 66 <sup>c</sup> | Colorless    |
| 9     | PhCl              | Powder            | n.r.              | 23              | Colorless    |
| 10    | PhCH <sub>3</sub> | Powder            | n.r.              | 5               | Light Yellow |
| 11    | PhCH <sub>3</sub> | Powder            | n.r.              | 50              | Light Yellow |
| 12    | PhCH <sub>3</sub> | Pellets           | n.r.              | 95              | Light Yellow |
| 13    | PhCH <sub>3</sub> | Pellets/Trace HCl | n.r.              | - <sup>e</sup>  | Light Yellow |

<sup>a</sup> All reactions were run at room temperature in solvent free conditions with a reaction time of approximately 15 minutes. DCM was used as the workup solvent unless indicated.

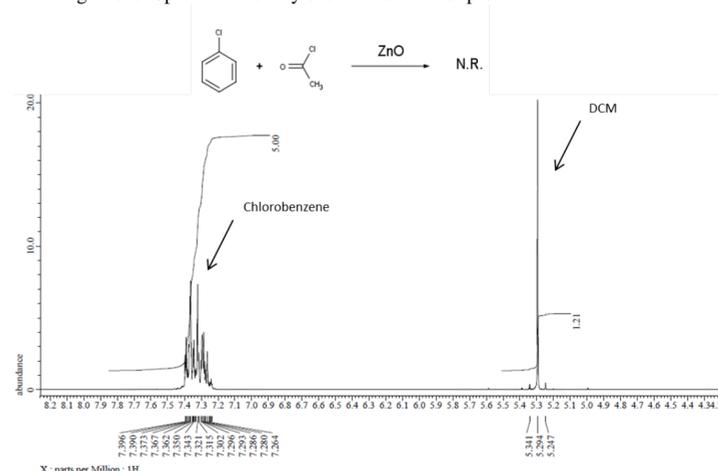
<sup>b</sup> Workup solvent – diethyl ether.

<sup>c</sup> Product purified using fractional distillation.

<sup>d</sup> n.r. = no acylated product are detected.

<sup>e</sup> product not isolated.

**Figure II.** Typical <sup>1</sup>H NMR spectrum of chlorobenzene recovery displaying substrate and solvent integrations. Spectra uniformly showed no trace of product.



**Table III. Reactions of strongly activated substrates.<sup>a</sup>**

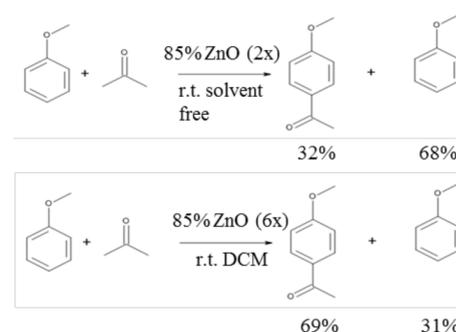
| Entry | Substrate                       | ZnO/Conditions           | Product Conversion (%) | Color Change              |
|-------|---------------------------------|--------------------------|------------------------|---------------------------|
| 14    | PhOCH <sub>3</sub>              | Powder                   | 13                     | Dark Green → Purple/Black |
| 15    | PhOCH <sub>3</sub>              | Pellets                  | 5                      | Light pink                |
| 16    | PhOCH <sub>3</sub> <sup>b</sup> | Pellets                  | 18                     | Orange                    |
| 17    | PhOCH <sub>3</sub>              | Pellets (2x)             | 32                     | Dark Green → Purple/Black |
| 18    | PhOCH <sub>3</sub>              | Pellets (6x)/DCM solvent | 69                     | Dark Green → Purple/Black |
| 19    | Furan                           | Pellets                  | 96                     | Dark Green → Purple/Black |

<sup>a</sup> All reactions were performed solvent free at room temperature with acetyl chloride being the acid chloride unless indicated.

<sup>b</sup> Reaction time of 1 hour/no workup.

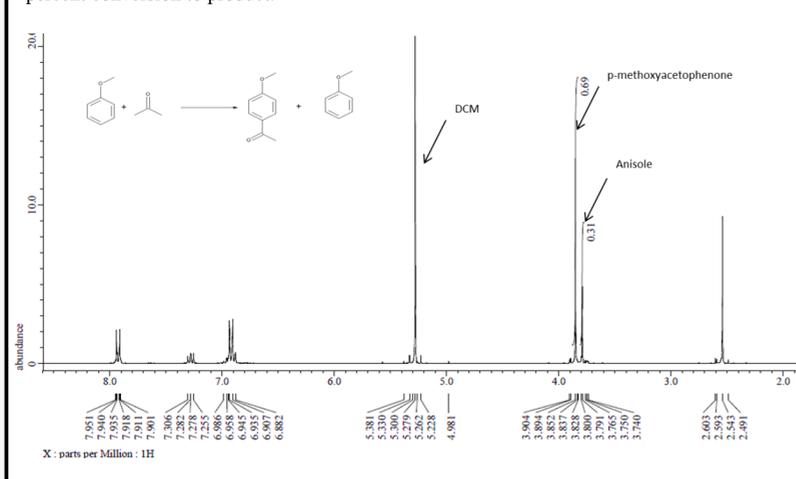
<sup>c</sup> Benzoyl chloride used.

**Figure III.** Increased surface area of ZnO pellets was shown to improve overall product conversion.



Recovery of unreacted substrate was optimized with increased use of dichloromethane (DCM) solvent in the work-up procedure. Additional washing of the leftover aqueous layer with DCM helped to substantially increase the recovery of substrate. Steps to minimize the amount of solvent were to stir the product with small amounts of solvent with each wash and to minimize the amount of solvent used per elution. The zinc oxide powder became a solid at the end of the reaction making it difficult to separate the product or unreacted substrate from the reaction mixture. The use of zinc oxide pellets instead of powder help to reduce the amount of solvent required upon scale-up. For chlorobenzene fractional distillation reduced the loss of recovery in the work-up procedure.

**Figure IV.** Typical <sup>1</sup>H NMR spectrum of anisole and acetyl chloride reaction displaying percent conversion to product.



## Discussion

**Deactivated compounds** – Weakly activated (PhCH<sub>3</sub>) and deactivated (PhBr, PhCl) rings uniformly failed to react contrary to the results reported in reference 6. These results are somewhat inconclusive since total recovery was not accomplished in most of the experiments (Table II), but they strongly suggest that there is no reaction with deactivated substrates. We had originally been adding the reactants in the opposite order according to the general procedure described in reference 6, so to test the possibility that the order of addition of reactants was crucial to success, the prescribed procedure was followed in entries 9 and 11 (Table II). No reaction was detectable using this method. In entry 13, trace amounts of HCl were added to the reaction mixture in attempt to generate the proposed ZnCl<sub>2</sub> catalyst *in situ*<sup>6</sup>. This resulted in the HCl dissolving both the ZnO catalyst and loss of product.

**Activated compounds** – Strongly activated compounds did react in the presence of ZnO (both 85% and 99% grade) to give conversions of 5-69% (Table III). Product conversion in the reaction of anisole and acetyl chloride is maximized with increased surface area of catalyst (Figure IV). However, full conversion to product was not achieved using zinc oxide pellets or powder. In contrast, furan did react in the presence of pelletized ZnO to form 2-acetylfuran in an NMR yield of 96% (entry 19).

## Conclusion

Zinc oxide was examined as a catalyst in the Friedel-Crafts acylation of varying activated and deactivated compounds. Despite a literature report that ZnO functions very well with weakly activated rings such as chlorobenzene to give excellent yields<sup>6</sup>, we found no detectable product was formed in the reactions of PhCl and PhBr. Moreover, no product was detected for the attempted acylation of toluene, a weakly activated substrate. Recovery of the unreacted substrate was optimized using additional solvent and fractional distillation instead of rotary evaporation. In addition, we can report that this reaction recovers in good to excellent recoveries. Our attempts to reduce solvent requirements for activated rings through use of pelletized ZnO were unsuccessful, resulting in uniformly incomplete conversion to product. With activated substrates, the reaction is not as green as implied in reference 6 because despite the solvent-free nature of the reaction, very large amounts of solvent were required for workup. Strongly activated compounds such as anisole and furan were found to react in the presence of the ZnO catalyst, but not to completion in the short times reported in the original report<sup>6</sup>

## References

- Anastas, P. T., Kirchoff, M. M. & Williamson, T. C. *Applied Catalysis A: General*. **2001**, 221, 3-13.
- Carley, A., Davies, P., Hutchings, G. & Spencer, M. *Surface Chemistry and Catalysis*. (Kluwer Academic/Plenum Publishers: New York, **2002**).
- Anastas, P. & Warner, J. *Green Chemistry: Theory and Practice*. (Oxford University Press: New York, **1998**).
- Wilkinson M.C.; *Org. Lett.* **2011**, 13, 2232-2235
- Tamaddon, F., Amrollahi, M. A. & Sharafat, L. *Tetrahedron Lett.* **2005**, 46, 7841-7844.
- Hosseini-Sarvari M.; Sharghi H. *J. Org. Chem.* **2004**, 69, 6953-6956.
- Hosseini-Sarvari M.; Sharghi H. *Tetrahedron* **2005**, 61, 10903-10907.
- Hosseini-Sarvari M. *Green Chemistry* **2012**, 6, 103-120.
- Hosseini-Sarvari M.; Sharghi H. *J. Org. Chem.* **2006**, 71, 6652-6654.
- Wang R.; Hong X.; Shan Z. *Tetrahedron Lett.* **2008**, 49, 636-639.
- Tamaddon F.; Amrollahi M.A.; Sharafat L. *Tetrahedron Lett.* **2005**, 46, 7841-7844.
- Brown H.C.; Marino G. *J. Org. Chem.* **1961**, 84, 1658-1661
- Hivarekar R. et al. *Org. Process Res. Dev.* **2012**, 16, 677-681.

## ACKNOWLEDGEMENTS:

WSU for undergraduate and travel grants and the WSU Chemistry department for lab facilities and equipment.