Selective Fries Rearrangement Catalyzed by Zinc Powder

Satya Paul,* Monika Gupta
Department of Chemistry, University of Jammu, Jammu-180 006, India
Fax +91(191)2505086; E-mail: paul7@rediffmail.com
Received 9 January 2004; revised 26 April 2004

Abstract: Zinc powder in the presence of N,N-dimethylformamide efficiently catalyzes the selective Fries rearrangement of acetylated phenols under microwave heating or with conventional heating using an oil bath. In some cases different products were obtained using microwave heating and conventional heating. Selective migration of the acyl group has been noted with good yields.

Keywords: acetylated phenols, zinc powder, Fries rearrangement, microwave activation, selectivity

Among Friedel–Crafts reactions,¹ the Fries rearrangement² is an important process for the conversion of acetylated phenols to hydroxy acetophenones. It is used in the manufacture of important pharmaceuticals including acetaminophen and salbutamol,³ UV adsorbents⁴ and pesticides.⁵

The Fries rearrangement is generally catalyzed by highly corrosive, hazardous and polluting Lewis acids, such as AlX₃ (X = Cl, Br or I), BF₃, TiCl₄, FeCl₃, ZnCl₂, ZrCl₄, SnCl₄, commonly employed in amounts of more than one equivalent. As water quenching is necessary at the end of the reaction, the process leads to large volumes of hazardous waste.¹,³ Some alternative solid acid catalysts including zeolites,⁶,⁷ transition metal triflates,⁸ sulfated zirconia,⁹ ionic melts,¹⁰ and solid sulfonated resins⁷,¹¹ have been reported for these reactions. These catalysts generally suffer from low activity, low selectivity and poisoning of the catalyst and its subsequent deactivation. Recently, some Fries rearrangements have been reported under microwave irradiation using AlCl₃–ZnCl₂ supported on silica gel,¹² aluminum chloride¹³ and K₁₀ montmorillonite.¹⁴ Thus, there remains a need to find a new environmentally benign procedure, which should be simple, safe and economic, for the Fries rearrangement.

The coupling of microwave irradiation¹⁵ with the use of catalysts or mineral-supported reagents provides chemical processes with special attributes such as enhanced reaction rates, higher yields, greater selectivity and improved ease of manipulation.

Zinc powder is non-toxic and inexpensive. It has been used for selective α-haloaclyation and gem-bisacylation of alkyl aldehydes,¹⁶ synthesis of o-arylenedizinc compounds,¹⁷ synthesis of benzhydrols,¹⁸ transesterification of β-ketoesters,¹⁹ acylation and sulfonation of pyrrole.²⁰

In our earlier communication,²¹ we have shown that zinc catalyzes acylation of aromatic substrates efficiently in solvent-free conditions under microwave irradiation. These findings encouraged us to study the Fries rearrangement of acetylated phenols, a reaction similar to above reaction using zinc powder in the presence of DMF under both microwave irradiation and oil-bath heating. A variety of acetylated phenols have been shown to undergo Fries rearrangement selectively at one position and we were able to isolate single isomer in quite a good yield. In some cases, different isomers (entries 1, 2, 4, 5, 9, 10) were formed using microwave and oil-bath heating. Although oil-bath heating takes longer time with comparable yields, yet the importance of zinc catalyst is reflected in the way that single isomer was obtained under both microwave and oil-bath heating.

Fifteen acetylated phenols (entries 1–15) were tested for Fries rearrangement using Zn powder as catalyst and DMF as energy transfer medium/solvent both under microwave irradiation as well as oil-bath heating (see the experimental section). The results are shown in Table 1. In case of phenyl acetate (entry 1), o-hydroxyacetophenone was obtained in 75% isolated yield when irradiated in a microwave oven for three minutes. However, when the reaction was carried out with same quantities in an oil-bath at 60 °C (temperature noted at the end of exposure during the microwave experiment) for six hours, p-hydroxyacetophenone was obtained in 70% isolated yield, whereas, a mixture of o- and p-hydroxyacetophenone was reported earlier under microwave irradiation. When the Fries rearrangement of phenyl acetate was attempted using Zn powder by stirring at 110 °C in toluene using oil-bath, no reaction was observed on TLC up to six hours. When (2-Methylphenyl) acetate (entry 2) was subjected to the microwave irradiation for five minutes using Zn powder and DMF, exclusive p-migration took place and 4-hydroxy-3-methylacetophenone was obtained in 74% isolated yield. However, when the same reaction was carried out in an oil-bath at 68 °C (temperature noted at the end of exposure during microwave experiment) for 45 minutes, exclusive o-migration took place with 70% isolated yield of 2-hydroxy-3-methylacetophenone. Earlier it was reported that when (3-methylphenyl) acetate was subjected to Fries rearrangement using K-10 montmorillonite under microwave irradiation, a mixture of ortho/para isomers was obtained in the ratio of 7:3. With anhydrous AlCl₃ at 165 °C, o-migration takes place exclusively.¹⁴ However, when (3-methylphenyl) acetate (entry 3) was irradiated in a microwave oven in the presence of zinc powder and N,N-di-
methylformamide for seven minutes, $o$-migration takes place exclusively. Same $o$-migration has been observed, when (3-methylphenyl) acetate was heated in an oil-bath at 48 °C (temperature noted at the end of exposure during microwave experiment) for 90 minutes. (2-Nitrophenyl) acetate (entry 4) undergoes exclusive $o$-migration with 75% isolated yield when irradiated in a microwave oven for 13 minutes, whereas, exclusive $p$-migration with 65% isolated yield has been noted when it was heated in an oil-bath at 60 °C (temperature noted at the end of exposure during microwave experiment) for one hour. In case of 1,2-diacetoxybenzene (entry 5) only one out of two $O$-
acetyl groups undergoes Fries rearrangement. Under microwave irradiation, p-migration takes place, whereas, under oil-bath conditions, o-migration has been noted. However, it was earlier reported that 1,2-diacetoxybenzene undergoes single Fries rearrangement at p-position when stirred for two hours at 75 °C using nitrobenzene as solvent. When 1,3-diacetoxybenzene (entry 6) was subjected to microwave irradiation for 15 minutes using Zn powder and DMF, the 2,6-diacetylated product was obtained in excellent yield. The same product has also been reported using AlCl₃, ZnCl₂ and FeCl₃ and also using oil-bath heating under the same conditions as those used in the microwave reaction. Further, in case of 1,4-diacetoxybenzene (entry 7), double Fries rearrangement (o-migration) has been observed under both microwave irradiation (six minutes) and oil-bath heating (45 minutes). Also, 1,3,5-triacetoxybenzene (entry 8) undergoes triple Fries rearrangement under both microwave irradiation (23 minutes) and oil-bath (two hours) heating.

1-Naphthyl- (entry 9) and 2-naphthyl acetate (entry 10) undergo Fries rearrangement at o-position in 85% and 90% isolated yields, respectively, when subjected to microwave irradiation in the presence of Zn powder and DMF for ten minutes and eight minutes, respectively. However, when same reaction was carried out using oil-bath, deacetylation (1-naphthol, seven hours; 2-naphthol, eight hours) takes place. Deacetylation in the case of 1-naphthyl and 2-naphthylacetate has also been reported under microwave irradiation. In the case of other acetoxybenzenes (entries 11–15), the same rearranged products have been obtained under both microwave irradiation and oil-bath heating.

Since the reactions were not carried out under inert atmosphere and since unpurified commercially available zinc powder was used, there may be a possibility of formation of ZnO, which may catalyze the reaction. In order to see whether the reaction was catalyzed by Zn or ZnO, we carried out the Fries rearrangement in case of entries 1 and 3 using 0.25 equivalent of ZnO under the same conditions as described for microwave experiment. It has been found that after the complete work-up we were unable to get the desired products. This observation indicates that Fries rearrangement was catalyzed by Zn.

The zinc powder can be recovered and re-used after washing with Et₂O and dilute HCl. In case of phenyl acetate, zinc powder can be re-used up to six times without much loss of activity (Table 2), thereby making the process still more economic.

In conclusion, we have developed a selective procedure for Fries rearrangement of acetylated phenols using inexpensive and non-toxic zinc powder under microwave irradiation/oil-bath heating. Our method is superior to other existing methods as: i) there is no need of toxic and waste producing Lewis acids, ii) work-up is simply reduced to treatment with DMF, iii) pure isolated single isomers were obtained, iv) zinc powder can be re-used several times and, v) it falls within the domain of Green Chemistry.

Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 270-30 spectrophotometer using KBr discs. 1H NMR spectra in CDCl₃ were recorded on a Bruker DPX-200 (200 MHz) spectrometer using TMS as an internal standard. Mass spectral data were recorded on a JOEL D-300 spectrometer. The reactions were monitored by TLC. For the microwave irradiation experiments described below a conventional (unmodified) household microwave oven equipped with a turntable was used (LG Intello CHEF MS 257PL operating at 2450 MHz having a maximum output of 1300 W).

**Table 2** Results of Re-Use Studies on Fries Rearrangement of Phenyl Acetate (5 mmol), Zn Powder (5 mmol) and DMF (2.5 mmol) with MW Irradiation and Oil-Bath Heating

<table>
<thead>
<tr>
<th>No. of uses</th>
<th>MW Time (min)</th>
<th>Yield (%)</th>
<th>Oil-Bath Heating Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>75</td>
<td>1.5</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>72</td>
<td>2</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>65</td>
<td>2.5</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>3.5</td>
<td>61</td>
<td>2.5</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>58</td>
<td>2.5</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>53</td>
<td>2.5</td>
<td>50</td>
</tr>
</tbody>
</table>

*Time at which maximum yield was obtained.

Yield of isolated products.

**Microwave Irradiation Approach; General Procedure**

Substrate (5 mmol), zinc powder (0.15 g, 5 mmol) and N,N-dimethylformamide (0.18 mL, 2.5 mmol) were taken in a borosil beaker (50 mL). The mixture was mixed properly with the help of a glass rod (15 s) and then irradiated in a microwave oven at 480 W for the appropriate time (Table 1). The reaction mixture was cooled to r.t. and diluted with DMF (5 mL). It was filtered and ice-cold water (100 mL) was added to the filtrate. The product was obtained by extraction with EtOAc and removal of the solvent under reduced pressure after drying over anhyd Na₂SO₄. Finally the products were purified either by crystallization from EtOAc–petroleum ether or passing through column of silica gel and elution with petroleum ether (Table 1). The structure of the products were confirmed by 1H NMR, IR, mass spectral data and comparison with authentic samples available commercially or prepared according to literature methods.

**Oil-Bath Heating Approach; General Procedure**

Substrate (5 mmol), zinc powder (0.15 g, 5 mmol) and N,N-dimethylformamide (0.18 mL, 2.5 mmol) were taken in a borosil beaker (50 mL). The mixture was mixed properly with the help of a glass rod (15 s) and placed in a pre-heated oil-bath for the appropriate time and at the specified temperature (Table 1). The products were obtained by the same work-up procedure as for microwave-assisted method.

Synthesis 2004, No. 11, 1789–1792 © Thieme Stuttgart · New York
Acknowledgment

The authors thank to Council of Scientific and Industrial Research (CSIR), New Delhi, for awarding Junior Research Fellowship to Monika Gupta.

References and Notes


