International Journal of Chemistry; Vol. 13, No. 2; 2021
ISSN 1916-9698 E-ISSN 1916-9701
Published by Canadian Center of Science and Education

Effect of Microwave Irradiation on the Fries Rearrangement Reactions of Acetyloxy- and Benzoyloxybenzenes

Yasutaka Iwata[1], Humiyoshi Ozaki[1], Yutaka Okada[1]

[1]Department of Applied Chemistry, Ritsumeikan University, Japan

Correspondence: Yutaka Okada, Department of Applied Chemistry, Ritsumeikan University, 1-1-1 Nojihigashi, Kusattsu, Shiga 525-8577, Japan.

Received: May 14, 2021 Accepted: June 12, 2021 Online Published: June 23, 2021

doi:10.5539/ijc.v13n2p11 URL: https://doi.org/10.5539/ijc.v13n2p11

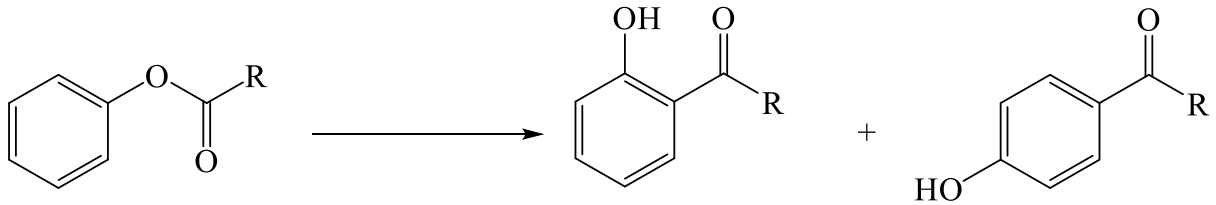
Abstract

The Fries rearrangement reactions of acetyloxy- and benzoyloxybenzenes were carried out both under microwave irradiation and conventional heating conditions, and the effect of microwave irradiation was examined. Acceleration of the reaction for the acetyloxy derivatives could not be confirmed, but was successfully demonstrated for the benzoyloxy derivatives. On the Fries rearrangement, the Lewis acid coordinates to the ester oxygens, but also coordinates to the aromatic rings. The microwave is efficiently absorbed by such an adduct between the Lewis acid and substrate, resulting in acceleration of the reaction.

Keywords: fries rearrangement, microwave irradiation, acyloxybenzene, Hammett rule, Lewis acid

1. Introduction

The Fries rearrangement reaction reported by Fries et al. in 1908 (Blatt, 1942; Clark, Dekamin, & Moghaddam, 2002; Fries & Finck, 1909; Martin, 2009) involves the heating of a phenolic ester of a carboxylic acid in the presence of a Lewis acid catalyst to promote rearrangement of the acyl group to give an aromatic hydroxyketone (Scheme 1). This rearrangement reaction has much in common with the Friedel-Crafts acylation reaction in terms of both the reaction conditions and the obtained product; both reactions are Lewis acid-catalyzed reactions that ultimately yield aromatic ketones.



Scheme 1. Fries rearrangement of acyloxybenzenes

Regarding the mechanism of the Fries rearrangement reaction, the pathway has been suggested, whereby the substrate and reaction conditions employed (i.e., reaction temperature, type and amount of catalyst, and solvent polarity) determine whether the Fries rearrangement reaction proceeds via an intermolecular or an intramolecular mechanism (Yamamoto, Ishikawa, & Okamoto, 1989).

If no substituents are present at either the *o*- or the *p*-position of the substrate aromatic ring, both the *o*- and *p*-rearranged products are formed. Usually, *p*-derivatives are mainly produced at low temperatures, while the *o*-derivatives are mainly produced at high temperatures. Generally, the *o*-rearrangement proceeds via the intramolecular mechanism, and the *p*-rearrangement is intermolecular. This is due to the fact that the *o*-derivatives are formed via chelate complexes that are stable at high temperatures. The isomerization of *p*-derivatives into *o*-derivatives is also known, and when the polarity of the solvent is high, the proportion of *p*-derivatives increases, since the polar solvent stabilizes the intermolecular mechanism (Dawson, Julia, Hart & Waddington, 1989; Munavalli, 1972).

It is known that many organic reactions are accelerated by microwave irradiation (Das, Banik, Kumar, Roy, Amhad, & Sukul, 2019), where in these reactions tend to proceed rapidly to give high product yields and selectivities. However, although the reaction rate is significantly accelerated, the higher rate can render it difficult to elucidate a detailed mechanism for the acceleration.

Thus, we herein report our investigation of the effects of microwave irradiation on the aforementioned Fries rearrangement reaction, and comparison of the obtained results with those obtained using a conventional heating method. The effects of microwave irradiation will be examined for both acetyloxy and benzoyloxy derivatives.

2. Experimental

The acyloxy benzene substrates were synthesized according to a well-known procedure (Sonntag, 1953).

The Fries rearrangement was carried out for all substrates as described below. In a 200 mL three-necked flask the substrate (3.45 mmol), aluminum chloride (460 mg, 3.45 mmol) and 1,1,2,2-tetrachloroethane (10 mL) were added. The reaction solution was sampled at regular intervals during heating and stirring. Heating was performed by microwave irradiation and conventional heating. A μ-reactor (Shikoku Keisoku. Ltd.) was used for microwave irradiation, and the temperature was measured using a fluorescent optical fiber thermometer. The microwave power eas 350 W. The ratio of substrate to product was measured by HPLC. For all substrates, the reaction temperature during microwave irradiation reached the reflux temperature 2 min after irradiation had commenced.

Separation of the rearranged products was performed as follows. When 4-substituted phenyl acetates were used, only the *o*-derivative was produced. Following completion of the Fries rearrangement, the reaction mixture was poured into ice water (100 mL), stirred well, and then extracted with toluene (100 mL). After washing the organic layer with water (100 mL × 2), the alkali-soluble components were extracted with a 10% aqueous sodium hydroxide solution (100 mL × 2). Following the addition of concentrated hydrochloric acid to the aqueous layer, it was extracted with 1,2-dichloroethane (100 mL × 2) and the solvent was distilled off.

When phenyl acetate and the 4-substituted phenyl benzoates were used, both the *o*- and *p*-derivatives were produced. After the Fries rearrangement, the reaction mixture was poured into 100 mL of ice water, stirred well, and then extracted with 100 mL of toluene. After washing the organic layer with water (100 mL × 2), the alkali-soluble component was extracted with a 10% aqueous sodium hydroxide solution (100 mL × 2). Following the addition of concentrated hydrochloric acid to the aqueous layer, it was extracted with 1,2-dichloroethane (100 mL × 2) and the solvent was distilled off. Toluene (20 mL) was added to the obtained mixture, and the insoluble matter was recovered by suction filtration to obtain the *p*-derivative. The filtrate was purified by column chromatography (eluent = toluene) using silica gel (50 g) to obtain the *o*-derivative.

3. Results and Discussion

Tables 1 and 2 show the results of the Fries rearrangement reactions carried out under both microwave irradiation and conventional heating conditions. The reaction rate constant was calculated as to be first-order reaction (Minami, 1962; Szell & Furka, 1960) for the substrate; k_{MW} and k_{CH} are the reaction rate constants under microwave irradiation and conventional heating conditions, respectively.

Table 1. Microwave irradiation effect on the Fries rearrangement of (4-substituted phenyl) acetates[a]

R	σ_m[b]	$k_{MW} \times 10^3$ /s^{-1}	$k_{CH} \times 10^3$ /s^{-1}	$k_{MW} \times k_{CH}$
H	0	5.41 ± 0.18	5.32 ± 0.09	1.02 ± 0.04
CH_3	-0.07	4.40 ± 0.07	4.43 ± 0.06	0.99 ± 0.02
OCH_3	0.12	1.55 ± 0.01	1.62 ± 0.01	0.96 ± 0.01
Cl	0.37	0.91 ± 0.07	0.86 ± 0.00	1.06 ± 0.08
NO_2	0.71	0.08 ± 0.01	0.10 ± 0.00	0.77 ± 0.06

[a] substrate: 3.45 mmol, aluminum chloride: 3.45 mmol, 1,1,2,2-tetrachloroethane: 10 mL. [b] (Jaffe, 1953)

Table 2. Microwave irradiation effect for the Fries rearrangement of phenyl (4-substituted benzoates)[a]

R	σ_p[b]	$k_{MW} \times 10^3$ /s^{-1}	$k_{CH} \times 10^3$ /s^{-1}	$k_{MW} \times k_{CH}$
H	0	6.14 ± 0.05	5.00 ± 0.09	1.23 ± 0.02
CH_3	-0.17	2.71 ± 0.02	1.73 ± 0.03	1.57 ± 0.03
OCH_3	-0.27	2.01 ± 0.01	1.35 ± 0.07	1.49 ± 0.08
Cl	0.23	1.39 ± 0.02	0.98 ± 0.02	1.42 ± 0.04
NO_2	0.78	0.75 ± 0.00	0.56 ± 0.01	1.34 ± 0.02

[a] substrate: 3.45 mmol, aluminum chloride: 3.45 mmol, 1,1,2,2-tetrachloroethane: 10 mL. [b] (Jaffe, 1953)

As in the case of the Fries rearrangement, the retro-Fries rearrangement is also known, in which the rearranged product returns to the substrate or undergoes isomerization (Effenberger, & Gutmann, 1982; Harmer, Junk, Rostovtsev, Carcani, Vickery, & Schnepp, 2007). When the reaction is reversible, even if the positive reaction is accelerated by some factor, the reversible reaction is also accelerated at the same time, and so the apparent reaction rate does not change. Therefore, to confirm the reversibility of the Fries rearrangement, we employed 4-hydroxybenzophenone, which is known to undergo both the retro-Fries rearrangement and the above-described isomerization process. The reaction was carried out under both microwave irradiation and conventional heating conditions. Since neither phenyl benzoate or 2-hydroxybenzophenone were produced under either conditions, it was considered that the Fries rearrangement was irreversible. As mentioned above, the substrate and the reaction conditions determine whether the Fries rearrangement is intermolecular or intramolecular.3 We therefore wished to investigate the effect of microwave irradiation on this mechanism. For this purpose, phenyl 4-methylbenzoate, which has a relatively high reactivity in terms of forming the *p*-intermolecular rearranged product, was used as the substrate. The Fries rearrangement was carried out in the presence of an equimolar quantity of naphthalene, which is activated against electrophilic attack. If the reaction proceeds intermolecularly, it should produce a naphthalene-substituted product. However, only the normal Fries rearranged product was produced, indicating that under the reaction conditions employed herein, the reaction was intramolecular.

To investigate the effect of the substituent on the Fries rearrangement, 4-substituted phenyl acetates bearing a substituent on the phenol moiety and 4-substituted phenyl benzoates bearing a substituent on the acyl group moiety were exampled. Four types of substituent were examined (i.e., methyl, methoxy, chloro, and nitro groups), which exhibit different electron-donating and electron-withdrawing properties.

The reactivities of the 4-substituted phenyl acetates matched the order of electron density at the position meta to the substituent, namely the order of the Hammett constants (σ_m) for the substituents. This is due to the fact that the Fries rearrangement involves electrophilic attack on the aromatic ring by the acylium cation, as in the case of the Friedel-Crafts acylation. However, the largest rate constant was observed for the unsubstituted substrate, since the rearrangement can be performed at the *p*-position, and so a greater degree of rearrangement occurs overall. When comparing only the amount of *o*-derivative, the methyl derivative underwent a greater degree of rearrangement than the non-substituted substrate.

Figure 1 shows the Hammett plot for the Fries rearrangements of the 4-substituted phenyl acetates. Regardless of the heating conditions employed, a linear plot with a downward slope was obtained in each case, as in the case of typical aromatic electrophilic substitution reactions. As mentioned above, under the reaction conditions employed herein, the Fries rearrangement was intramolecular. Thus, the intramolecular mechanism taking place via a π complex is shown in Scheme 2. The reaction constant ρ was negative, and so the reaction proceeded rapidly to yield the π complex, again, as in the case of a general aromatic electrophilic substitution reaction. However, the subsequent σ complex-forming step was slow, and so would be the rate-determining step.

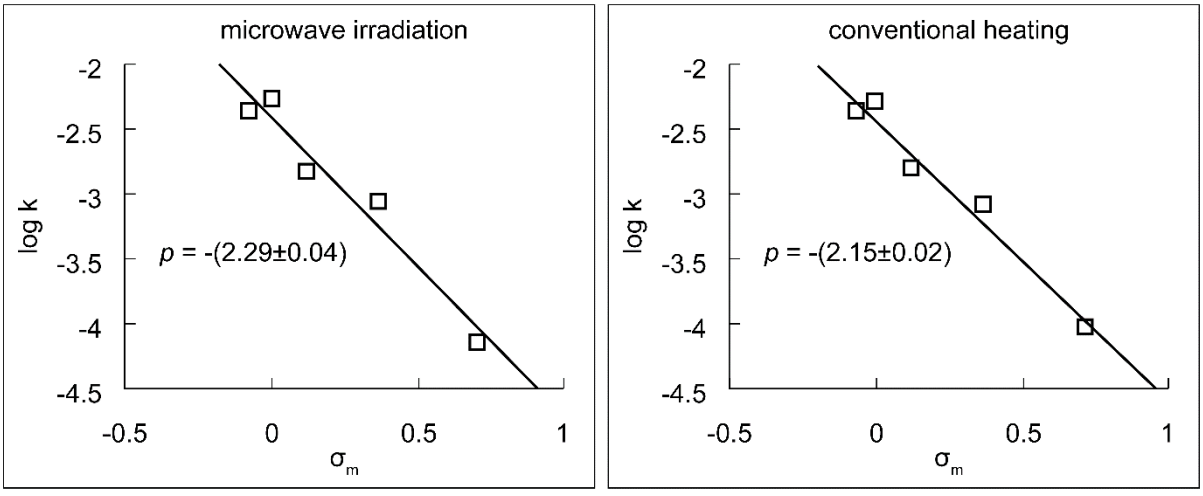


Figure 1. Hammett plot of the Fries rearrangement of (4-substituted phenyl) acetates

The reactivities of the 4-substituted phenyl benzoates matched the order of electron-donating substituents, namely the order of the Hammett constants for the substituents, σ_p. This could be explained by considering the stability of the acylium cation in the reaction intermediate. When an electron-donating group is introduced, the reaction rate increases as a result of stabilization through neutralization of the positive charge of the acylium cation. In contrast, when an electron-withdrawing group is introduced, the reaction rate decreases as a result of the positive charge of the acylium

cation becoming larger and destabilizing. In this case, the largest rate constant was observed once again for the unsubstituted substrate.

Upon comparison of the substituted substrates, the slowest reaction rate was observed when the strongly electron-withdrawing nitro group was introduced, while the fastest reaction rate was found when the weakly electron-donating methyl group was introduced. Despite being a strong donor group, the methoxy group was also examined, and was found to exhibit a lower reaction rate than the methyl group. This was partly attributed to the fact that the aluminum chloride, which was employed as a Lewis acid catalyst, coordinated to the methoxy group, thereby reducing its activity.

Figure 2 shows the Hammett plot for the Fries rearrangement of the 4-substituted phenyl benzoates. Inverse V-shaped plots were obtained in all cases, regardless of the heating conditions employed, thereby indicating that the rate-determining step may be different for substrates with electron-donating and electron-withdrawing groups. When the slope of the Hammett plot (i.e., the reaction constant ρ) is positive, the positive charge decreases or the negative charge increases at the reaction center of the rate-determining step. Conversely, when the reaction constant ρ is negative, the reaction center of the rate-determining step is characterized by an increase in the positive charge or a decrease in the negative charge (Scheme 2).

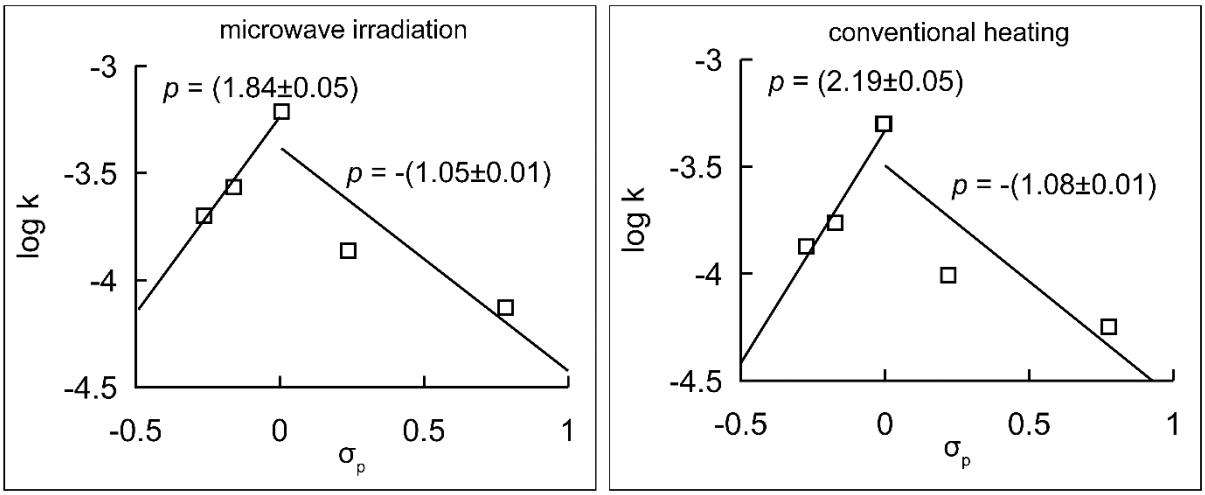
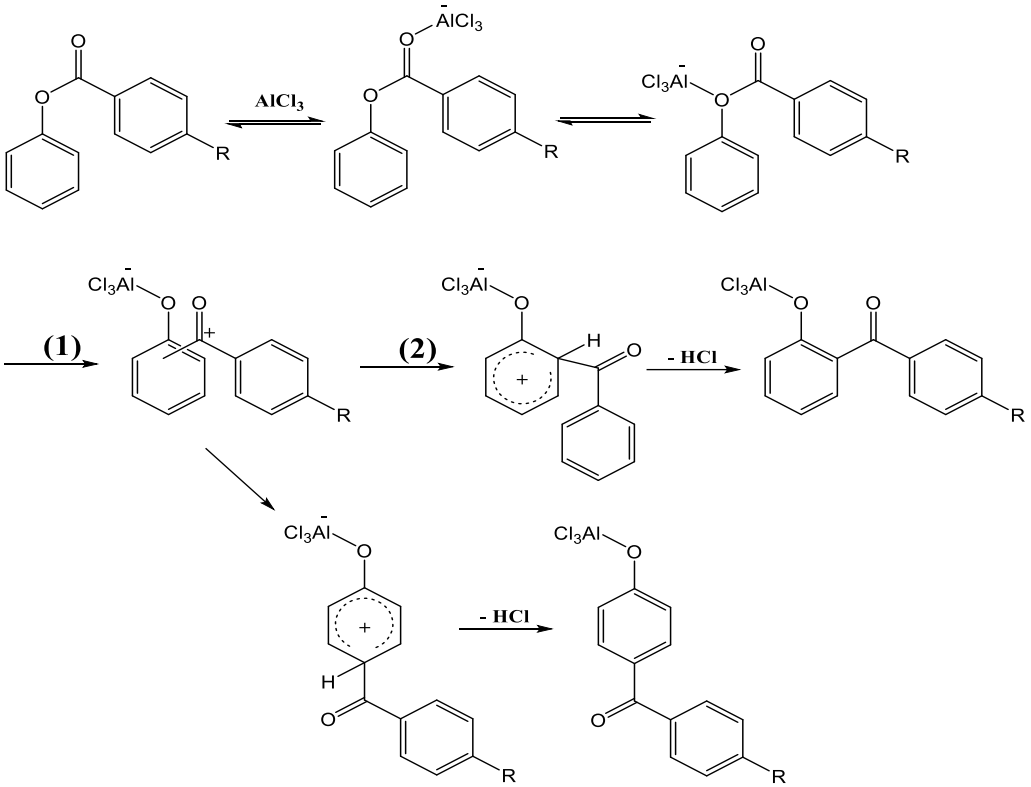


Figure 2. Hammett plot of the Fries rearrangement of phenyl (4-substituted benzoates)

When the substituent constant σ was negative, i.e., when an electron-donating group was present, the reaction constant ρ was positive. This was attributed to the fact that during step (2) of the mechanism shown in Scheme 2, where the σ complex is formed, the positive charge of the carbonyl carbon atom is canceled by the electron-donating group, which renders this step the rate-determining step. In this step, the positive charge on the carbonyl carbon (i.e., the reaction center) decreases, and this is consistent with the fact that when the reaction constant ρ is positive, the positive charge decreases at the reaction center in the rate-determining step.

In contrast, when the substituent constant σ is positive, i.e., when an electron-withdrawing group was present, the reaction constant ρ was negative. This was attributed to the fact that step (1), which involves formation of the π complex, is the rate-determining step since the electron density of the carbonyl carbon atom is lowered by the presence of an electron-withdrawing group. In this step, the positive charge on the carbonyl carbon increases, which is again consistent with the fact that there is an increase in the positive charge at the reaction center in the rate-determining step when the reaction constant ρ is negative.

In general, if there is no substituent at either the *o*- or *p*-position of the phenol moiety of the phenyl ester, both *o*- and *p*-rearranged products are formed, with their ratio depending on the type of substrate and the reaction conditions employed. In our all examples studied herein, both products were produced. Interestingly, for all substrates, the isomer ratio remained relatively constant under both microwave irradiation and conventional heating conditions. This indicates that microwave irradiation did not affect the regio-isomer ratio of the Fries rearrangement; in most cases, the *o*-rearranged product was the main product. This was attributed to the fact that the *o*-derivative forms stable chelate complexes at high temperatures.



Scheme 2. Reaction mechanism of the intramolecular Fries rearrangement via a π complex (Yamamoto, Ishikawa, & Okamoto, 1989)

For the 4-substituted phenyl benzoates, the presence of methyl and methoxy groups (i.e., electron-donating groups) yielded the *o*- and *p*-rearranged products in almost the same ratio. When an electron-donating group is introduced, the formation of the σ complex was considered to be the rate-determining step. However, this does not proceed rapidly following the intramolecular formation of the π complex, and so it was apparent that both the *o*-rearrangement and *p*-rearrangement processes occurred.

Conversely, when chloro and nitro groups were introduced (i.e., electron-withdrawing groups), the ratio of *o*-rearranged products increased. When an electron-withdrawing group is introduced, π complex formation is considered to be the rate-determining step. However, since formation of the σ complex followed by intramolecular π complex formation proceeded rapidly, the *o*-rearrangement would be prioritized.

In the case of the 4-substituted phenyl acetates, no change in the reaction rate was observed under the different the heating conditions regardless of the properties of the substituent, thereby indicating that microwave irradiation did not show any specific effect on the Fries rearrangement of these substrates.

In the case of the 4-substituted phenyl benzoates, the reaction rate constant under microwave irradiation was larger than that under conventional heating for all substrates, regardless of the substituent properties. These results indicated that microwave irradiation accelerated the Fries rearrangement of these substrates.

From the above results, it is apparent that when the acyl group of the substrate is an acetyl group, the reaction rates are similar under both microwave irradiation and conventional heating conditions. However, in the case of a benzoyl group, the reaction rate constant under microwave irradiation was larger than that under conventional heating. More specifically, it was confirmed that the reaction rate ratio (k_{MW}/k_{CH}) was ~1.5 only for the benzoyl-based substrates, and therefore that the rearrangement reaction was accelerated by microwave irradiation. As indicated in the proposed reaction mechanism, the Lewis acid coordinates to the ester oxygens, but also coordinates to the aromatic rings (Kokui, China, & Okada, 2018; Okada & Nakano, 2009). Since it is known that Lewis acid-coordinated aromatic rings can efficiently absorb microwave irradiation, it appears that in our reaction system, the Lewis acid catalyst coordinates to the rearranging group to promote the absorption of microwave irradiation, resulting in acceleration of the reaction.

4. Conclusion

Following our examination of the effects of microwave irradiation on the Fries rearrangement reactions of acetyloxy-

and benzoyloxybenzenes, it was found that under both microwave irradiation and conventional heating conditions, the Fries rearrangement was intramolecular and irreversible. When the acyl group of the substrate was an acetyl group, the reaction rate remained constant under the two heating conditions examined herein, regardless of the type of substituent on the benzene ring. In contrast, when the acyl group was a benzoyl group, the reaction rate was higher under microwave irradiation than under conventional heating conditions, regardless of the type of substituent on the benzene ring of the benzoyl group.

References

Blatt, A. H. (1942). Organic Reactions. I: Fries reaction. *Organic Reactions, 1*, 342-369. https://doi.org/10.1002/0471264180.or001.11

Clark, J. H., Dekamin, M. G., & Moghaddam, F. M. (2002). Genuinely catalytic Fries rearrangement using sulfated zirconia. *Green Chem.*, *4*, 366-368. https://doi.org/10.1039/B203943P

Das, S., Banik, R., Kumar, B., Roy, S., Amhad, K., & Sukul, P. K. (2019). A Green Approach for Organic Transformations Using Microwave Reactor. *Current Organic Synthesis, 16*, 730-764. https://doi.org/10.2174/1570179416666190412160048

Dawson, I. M., Julia, L., Hart, L. S., & Waddington, C. R. (1989). Aromatic rearrangements in the benzene series. Part 5. The Fries rearrangement of phenyl benzoate: the rearranging species. The effect of tetrabromoaluminate ion on the ortho/para ratio: the noninvolvement of the proton as a cocatalyst. *Journal of the Chemical Society, Perkin Transactions 2: Physical Organic Chemistry*, 2133-2139. https://doi.org/10.1039/p29890002133

Effenberger, F., & Gutmann, R. (1982). Electrophilic aromatic substitution. 23. The Fries rearrangement as an equilibrium reaction. *Chemische Berichte, 115*, 1089-1102. https://doi.org/10.1002/cber.19821150325

Fries, K., & Finck, G. (1909). Homologues of Cumaranone and their Derivatives. *Berichte der Deutschen Chemischen Gesellschaft., 41*, 4271-4284. https://doi.org/10.1002/cber.190804103146

Harmer, M. A., Junk, C., Rostovtsev, V., Carcani, L. G., Vickery, J., & Schnepp, Z. (2007). Synthesis and applications of superacids. 1,1,2,2-Tetrafluoroethanesulfonic acid, supported on silica. *Green Chemistry, 9*, 30-37. https://doi.org/10.1039/B607428F

Jaffe, H. H. (1953). A reëxamination of the Hammett equation. *Chemical Reviews, 53*, 191-261. https://doi.org/10.1021/cr60165a003

Kokui, T., China, H., & Okada, Y. (2018). Microwave Irradiation Effect on Friedel-Crafts Type Cyclization Reaction. *Current Microwave Chemistry, 5*, 32-38. https://doi.org/10.2174/2213335604666171111112801

Martin, R. (1992). Uses of the Fries rearrangement for the preparation of hydroxyaryl ketones. *Organic Preparations and Procedures International*, *24*, 369-435. https://doi.org/10.1080/00304949209356226

Minami, M. (1962). Fries reaction. I. Determination of *o*- and *p*-hydroxyacetophenone with 2,4-dinitrophenylhydrazine. *Nippon Kagaku Zasshi, 83*, 1268-1270. https://doi.org/10.1246/nikkashi1948.83.12_1268

Munavalli, S. (1972). Mechanism of Fries rearrangement. Intermolecular versus intramolecular acylation. *Chemistry & Industry*, 293-294.

Okada, Y., & Nakano, S. (2009). Studies on ferrocene derivatives. Part XVIII. Microwave irradiation effect on the ligand exchange reaction between ferrocene derivatives and aromatic compound. *Inorganica Chimica Acta, 362*, 4853-4856. https://doi.org/10.1016/j.ica.2009.07.014

Sonntag, N. O. V. (1953). The reactions of aliphatic acid chlorides. *Chemical Reviews, 52*, 237-416. https://pubs.acs.org/doi/10.1021/cr60162a001

Szell, T., & Furka, S. (1960). Fries reaction. II. Effect of HCl on the isomerizat`ion of thymyl acetate. *Journal of the Chemical Society*, 2321-2328. https://doi.org/10.1039/JR9600002321

Yamamoto, J., Ishikawa, Y., & Okamoto, Y. (1989). Studies on the Fries rearrangement. V. The Fries rearrangement of phenyl *p*-nitro-, *p*-chloro-, and *p*-methylbenzoates. *Nippon Kagaku Kaishi*, 1870-1875. https://doi.org/10.1246/nikkashi.1989.1870

Copyrights