

Article

Microwave Assisted Esterification of Aryl/Alkyl Acids Catalyzed by *N*-Fluorobenzenesulfonimide

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Abstract: The susceptibility of the carbonyl group towards nucleophilic attack affords the construction of various organic compounds. Thus, investigations of carbonyl activation applying greener methodologies are highly important. In the present work, among the investigated *N*-halo compounds, *N*-fluorobenzenesulfonimide (NFSi) has been found as an efficient and selective catalyst in the reaction of direct esterification of aryl and alkyl carboxylic acids supported by microwave (MW) irradiation. The comprehensive esterification of different benzoic acids and mono-, di- and tri-carboxy alkyl derivatives was performed, whereby significant reaction time reductions were achieved. The presented method used NFSi as an easily manipulatable, non-metal, water- and air-tolerant catalyst, allowing simple synthetic and isolation procedures and energy saving, compared to conventional methodologies. Importantly, in contrast to esterification under thermal conditions, where *N*-halo compounds behave as pre-catalysts, in the MW-supported protocol, a distinct reaction mechanism has been proposed that assumes NFSi as a sustainable catalyst. Moreover, a scale-up of the industrially important derivative was performed.

Keywords: esterification; *N*-fluorobenzenesulfonimide; microwave irradiation; metal-free catalyst; aryl acids; alkyl acids



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1. Introduction

Esters represent highly valuable organic compounds exhibiting significant commercial potential. The importance of esters is reflected through their wide utilization in different industrial products such as perfumes, fine chemicals, cosmetics, electronics, plastics, coatings, paints, varnishes, solvents (ethyl/methyl acetate), preservatives in the food industry, herbicides, pesticides, biodiesel, etc. [1–7]. Ester functionality is renowned in biological systems, since it represents a key constituent of different metabolite classes [8]. Moreover, esters are found as a structural motif in different pharmaceuticals with a wide spectra of biological activities [9], whereby the fine tuning of physical-chemical drug properties can be achieved via the synthetic strategy of esterification.

Esters are generally produced in the direct reaction Fisher esterification [10] involving carboxylic acids and alcohols in the presence of different catalysts at elevated temperatures. Over the years, numerous catalysts and operating conditions have been employed in direct esterification and express different disadvantages, such as by-products and waste removal, as well as a solvent, energy, and time consumption [11]. Among commonly used protocols, different catalysts are used, which include: Brønsted acids [12], Lewis acids [13–15], metal catalysts [16,17], solid acids [18], solid-supported catalysts [19], ionic liquids [15], zeolites [20], enzymes [21], etc. The optimal esterification process should include easy process handling, an appropriate catalyst (low cost, recyclable, metal-free, water- and air-resistant), and moderate reaction conditions, as well as exclude water removal, excess reagents, and a stoichiometric

amount of activators. Moreover, it is desirable that the process ensures applicability to a wide range of reagents, an increase in product yield, and simple purification protocols. Despite ester's commercial importance and structural simplicity, the obstacles in esterification processes have not yet been fully resolved from industrial and environmental standpoints; hence, its further improvement is mandatory.

Ester synthesis by conventional heating shows unbalanced heat distribution and relatively slow heat transfer, making pre-heating and overall reaction time relatively long and energy demanding. On contrary, microwave (MW) irradiation, applied during different reactions, exerts its energy transfer effect via electromagnetic waves which require significantly lower energy input compared to conventional heating. Thus, MW irradiation has found broad application as a green source of energy applicable for different organic reactions [22–24], whereby numerous benefits compared to conventional strategy can be observed, and includereaction time reduction, higher yields, and increased purity of products [25,26]. All these benefits are consequences of both thermal and/or specific non-thermal effects of the MW radiation [27,28]. Special advantages of MW application can be achieved in reactions with polar functionalities where, along with the reaction coordinates, changes in the medium and transition states polarity can be significantly influenced and modulated by MW irradiation.

N-halo compounds (*N*-fluorobenzenesulfonimide—NFSi; 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2] octane bis (tetrafluoroborate)—SelectfluorTM; *N*-fluoropyridinium triflate, *N*-bromosuccinimide—NBS; *N*-iodosuccinimide—NIS, 1,3-dibromo-5,5-dimethylhydantoin—DBDMH; etc.), besides their traditional usage as halogenating and/or oxidizing agents, have found application during the last decade as (pre-)catalysts in a plethora of organic reactions [13,29–32]. This catalytic property has been manifested, most probably, due to their ability to act as Lewis acids, which is reflected through their possibility to establish noncovalent halogen bond interactions with electron-rich functionalities and thus facilitate nucleophilic attack. Generally, these *N*-halo compounds can be assumed as acid- and metal-free, low-priced, easy-to-handle molecules with significant (pre-)catalytic potential. Thus, investigations of their application in greener synthetic protocols are highly desirable.

In the context of our continuous interest to improve and develop environmentally acceptable synthetic protocols [13,31–33], and by comparing with the previously reported esterification protocols supported by MW irradiation [34–45], this paper, to the best of our knowledge, is the first to report direct esterification catalyzed by NFSi (easily manipulated, acid- and metal-free, water- and air-tolerant) and supported by MW irradiation.

2. Results and Discussion

The utilization of X_2 and/or $N-X$ compounds as (pre-)catalysts for the reaction of esterification under conventional heating conditions has been previously investigated [13,31]. However, the application of MW as the energy source for the esterification reaction in the presence of the aforementioned catalysts has not been previously developed; thus, the implementation of MW irradiation in the reaction of direct condensation between structurally different carboxylic acids and alcohols catalyzed by diverse $N-X$ compounds (Figure 1) has been investigated.

Initially, the aromatic acid benzoic acid (**1**) was chosen as a model molecule to test expectations and optimize the esterification protocol (Table 1). Generally, the mixture of **1** and methanol (MeOH) was MW irradiated in the presence of a substoichiometric amount of different catalysts (Table 1). Starting reaction conditions (temperature and amount of catalysts were 70 °C and 7 mol%, respectively) were set up as earlier, since they had been previously defined as optimal for conventionally heated reactions [13,31], with one exception—the time was significantly reduced from 20 h to 10 min. These preliminary results did not give the expected results (ester formation was not observed), thus, the temperature and reaction time were increased (120 °C and 15 min) in order to obtain the first positive signs of direct ester formation from **1** and MeOH (Table 1, Entries 1–5). Among

the investigated catalysts, NFSi and F-TEDA showed the highest efficiency (Entries 4 and 5, Table 1). These findings were completely different compared with our previous results, where conventional heating was applied and the most prominent catalysts were NBS and DBDMH, which suggests a different mode of catalytic activity under MW irradiation. Just as a note, based on our previous results [13], temperature increasement did not improve the conversion of ester during the conventional synthesis, while in the case of MW-supported esterification, the temperature had a significant role. Additionally, since the absorption of MWs is characteristic for polar functionalities, small quantities of water (50 μ L) were added to the reaction solution to try to promote thermal distribution over the system and consequently increase the ester formation. Although the presence of water is generally undesirable for the reaction of esterification, obtained results showed different trends towards ester formation, depending on the used catalyst (Table 1, Entries 6–10), which suggested different reaction mechanisms. This phenomenon will not be further discussed, since it will drag away investigation from the main course—esterification supported by MW irradiation in the presence of acid- and metal-free catalysts. Thus, additional experiments and optimization processes have been performed for the most prominent catalyst—NFSi (Table 1, Entry 5).

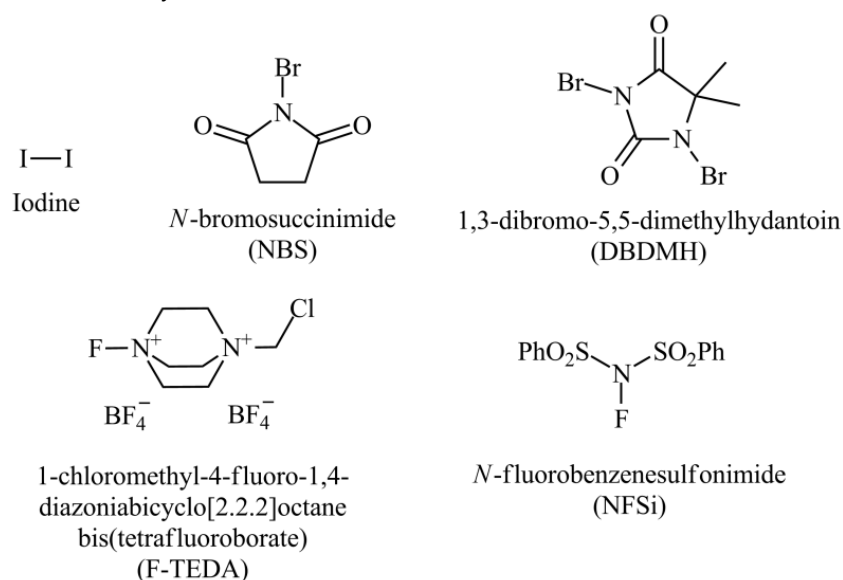
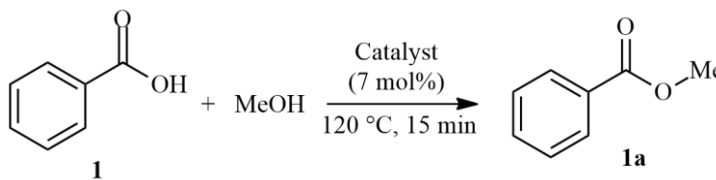


Figure 1. Structures of utilized molecules as putative catalysts for direct esterification under MW irradiation: molecular iodine— I_2 ; *N*-bromosuccinimide—NBS; 1,3-dibromo-5,5-dimethylhydantoin—DBDMH; *N*-Fluorobenzenesulfonimide—NFSi; 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis (tetrafluoroborate)—F-TEDA.

The optimization process for the formation of **1a** catalyzed by NFSi (Table 1, Entry 5) was performed applying RSM (Response Surface Methodology), where the analysis of the experimental data (SI, Table S1) allowed for the formation of quadratic equations (Equation (1), ANOVA: F -value = 189.30; $p < 0.0001$; Lack of Fit = 89.22) that significantly defined the dependence between ester formation (response— Y) and three independent variables (temperature, time, and amount of catalyst— X_1 , X_2 , X_3 , respectively, Table S2, Figure S1). The strong correlations between the experimental and the predicted data have been verified by a high R^2 and $adjR^2$ (0.9971 and 0.9918, respectively). One of the optimal conditions which predicted the quantitative conversion of **1** to **1a** were a temperature = 121.34 $^{\circ}C$, a time = 29.89 min, and an amount of catalyst = 6.99 mol%, and these conditions were chosen from 63 solutions proposed by numerical optimization. These proposed optimal reaction conditions were experimentally confirmed, and quantitative conversion was observed (Table 2). Finally, the optimal experimental conditions—temperature = 120 $^{\circ}C$; time = 30 min; amount of NFSi catalyst = 7 mol%—were set up as working conditions for all further experiments, except where it was noted differently. This optimal experimental condition of

1a production was additionally checked through two control experiments: (i) NFSi not present in the reaction mixture—formation of **1a** was not been observed; (ii) NFSi present in reaction mixture, but instead of MWs, conventional heating was applied—formation of **1a** was not been observed. Thus, based on the presented results, MW irradiation and the presence of a catalytic amount of NFSi in the reaction mixture can be assumed as crucial for the formation of **1a**.

Table 1. Initial screening of MW-irradiated esterification supported by different catalysts.

		
Entry	Catalyst	Conversion ^a (%)
1	I ₂	<1
2	NBS	8
3	DBDMH	25
4	F-TEDA	58
5	NFSi	71
6	I ₂	6.5 *
7	NBS	13 *
8	DBDMH	35 *
9	F-TEDA	37.5 *
10	NFSi	59 *

^a Conversions have been determined by ¹H NMR analysis of the crude reaction mixtures; * 50 µL of water was added to the reaction mixture.

Table 2. The effect of alcohol structure on esterification of benzoic (**1**) and stearic acid (**2**) ^{a,b}.

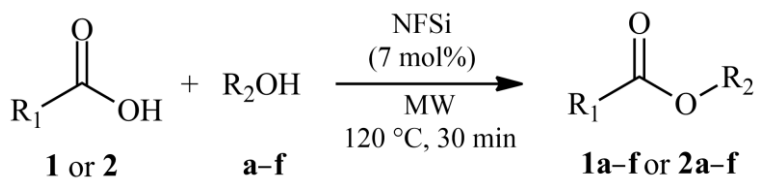
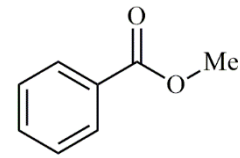
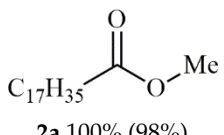
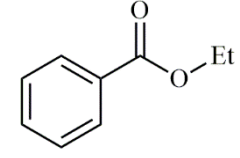
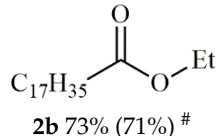
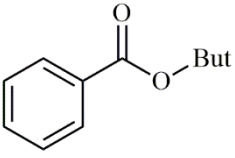
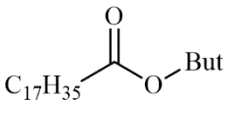
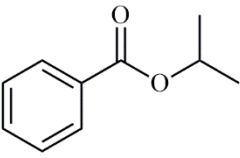
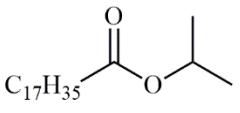
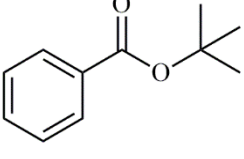
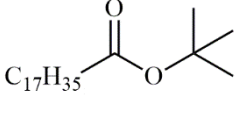
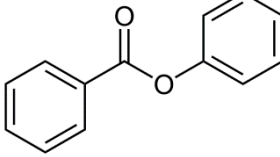
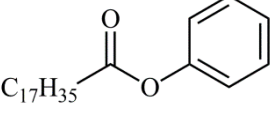
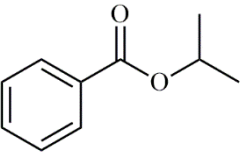
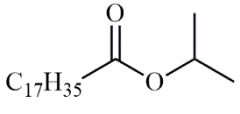
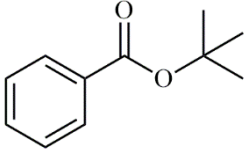
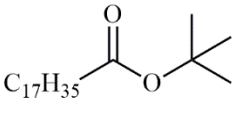
		
R ₂ OH	R ₁ = Ph	R ₁ = C ₁₇ H ₃₅
MeOH (a)	 1a 100% (97%)	 2a 100% (98%)
EtOH (b)	 1b 13% 63% ^c ; 95% ^d (94%)	 2b 73% (71%) [#] 100% ^d

Table 2. Cont.

$ \begin{array}{c} \text{O} \\ \parallel \\ \text{R}_1-\text{C}-\text{OH} + \text{R}_2\text{OH} \xrightarrow[\text{120 } ^\circ\text{C, 30 min}]{\text{NFSi (7 mol\%) MW}} \text{R}_1-\text{C}(=\text{O})-\text{O}-\text{R}_2 \\ \text{1 or 2} \qquad \text{a-f} \qquad \qquad \qquad \text{1a-f or 2a-f} \end{array} $		
R ₂ OH	R ₁ = Ph	R ₁ = C ₁₇ H ₃₅
1-ButOH (c)	 1c 14% (10%) 57% ^d	 2c 35% (32%) [#] 100% ^e
2-PrOH (d)	 1d 0%	 2d 18% (16%) ^{c,#}
tert-ButOH (e)	 1e 0%	 2e 0%
Phenol	 1f 0%	 2f 0%
Transesterification		
MeOH/2-PrOH ^f	 1d 12%	 2d 12%
MeOH/tert-ButOH ^f	 1e 0%	 2e 0%

^a Conversions have been determined by ¹H NMR spectroscopy. ^b The values in brackets stand for yields of isolated products. ^c Conversion after 2 h of the reaction. ^d Conversion after 4 h of the reaction. ^e Conversion after 6 h of the reaction. ^f Reaction conditions: 120 °C, 120 min, 7 mol% NFSi, MeOH (1 mL) and 2-PrOH (1 mL), or tert-ButOH (1 mL). [#] Flash chromatography employed silica gel 60 (230–400 mesh) with an elution system hexane: diethyl ether (9:1). Thin layer chromatography was carried out using alumina plates with a 0.25 mm silica layer (Kieselgel 60 F254, Merck). Compounds were visualized by staining with potassium permanganate solution.

Being encouraged by the obtained results, the scope of alcohols appropriate for esterification supported by MW irradiation was investigated (Table 2). General assumptions, as well as previous findings regarding the higher reactivity of alkyl acid compared to aromatic acid, have also been confirmed in our experiments (Table 2). Stearic acid (**2**) was used as a model molecule of alkyl acid. Since nucleophilic characters and steric properties of alcohols have a significant impact on the reaction kinetics, different alcohols were used (**a–f**, Table 2). In the presence of methanol, quantitative conversion of both model aromatic and alkyl acids (**1** and **2**, respectively) was observed (Table 2). Going further towards longer chain n-alcohols, compared to methanol, the lipophilicity ($\log P$) of alcohols was manifested as crucial for corresponding ester formation, since MWs exhibit a higher impact on the more polar molecule. Thus, a decrease in the conversion of both model acids (**1** and **2**) in the presence of ethanol (**b**) and 1-butanol (**c**) was observed (**1b–c**, **2b–c**, Table 2). This conversion reduction was more expressed for aromatic acid (**1**), while for stearic acid, linear function between the $\log P$ of n-alcohols and their corresponding ester formation was observed (conversion (%) = $-41.718 \cdot \log P + 67.915$; $R^2 = 0.9835$). However, this limitation could be overcome by increasing the reaction time (Table 2 (c) and (d)). Furthermore, the effects of steric changes of the nucleophilic alcohol component were investigated by varying the bulkiness of the alcohol from primary to tertiary structures (**a**, **d**, and **e**). Interestingly, in the presence of the secondary alcohol 2-PrOH, the low yield esterification reaction was only observed for stearic acid, while the transformation of benzoic acid to the corresponding ester was not observed, even when the time of reaction was been significantly increased up to 6 h. Unfortunately, the limitation of the method was also observed in reactions with bulky tertiary alcohol—tert-ButOH and aromatic alcohol—phenol, where no products were detected for either model acid. Moreover, transesterification was applied as a possible solution for increasing the ester production when bulky alcohols were used. The expected results of transesterification were missed, since the mixtures of esters were found, although a small amount of isopropyl benzoate was detected (Table 2).

Since the commercial significance of different methyl esters has been previously noted (Introduction section), the esterification of structurally different carbocyclic acids (**3–30**) with MeOH under previously determined optimal reaction conditions was additionally examined (Table 3). As can be seen from Table 3 (Methyl Benzoates), the substituents' electronic effects exhibited a significant impact on the conversion of acids (**3–11**) to their corresponding methyl esters. Substituent patterns on the phenyl ring of the investigated aromatic acids exhibited a negligible influence on the conversion of aromatic acids. Compared to our previous results [13] encompassing conventional heating esterification catalyzed by NBS, in the presented investigation, opposite trends were observed. All substituents with a positive resonance effect (+R) did not significantly affect acid conversion compared with benzoic acid. In all examined cases, near quantitative conversion was observed. On the contrary, strong electron-withdrawing groups (4-NO₂, 2-NO₂, 2-COOH—**9a**, **10a**, **11a**, respectively) significantly inhibited the reaction, with exception of the 4-CHO group with moderate electron-withdrawing effect, where excellent yield was observed (**8a**). Additionally, nicotinic acid was used as heteroaromatic acid, but no conversion was observed, as well as in the case of the previously defined conventional heating protocol [13]. On the other hand, in the case of aliphatic carboxylic acids, a wide scope of different (poly-)acids could be exploited, and excellent yields were obtained (Table 3—Methyl Alkanoates). The exemptions were oxalic acid and glycine, for which no conversions were observed, most probably due to intramolecular interactions which hinder access of the NFSi to the carboxyl group, and thus inhibit its catalytic properties. Also, a lower conversion towards methyl indol-2-formate (**18a**) formation was observed. Furthermore, ibuprofen (propanoic acid derivative), due to its commercial importance, was used as a drug-model molecule for the esterification of drugs, and quantitative conversion was observed (**16a**), thereby ensuring the proposed protocol as a promising solution for the fine physico-chemical tuning of pharmaceuticals.

Table 3. Esterification of substituted benzoic and different alkyl carboxylic acids with MeOH under previously defined optimal reaction conditions for benzoic acid (**1**).

$\text{R-C}_6\text{H}_4\text{-COOH} + \text{MeOH} \xrightarrow[\text{MW, 120 } ^\circ\text{C, 30 min}]{\text{NFSi (7 mol\%)}} \text{R-C}_6\text{H}_4\text{-COOMe}$ 3-11 3a-11a		
Methyl Benzoates		
3a 94% (91%)	4a 100% (98%)	5a 100% (96%)
6a 100% (97%)	7a 95% (91%)	8a 92% (87%)
9a 36% (34%)	10a 17% (12%)	11a 35% (32%)
$\text{Alkyl-COOH} + \text{MeOH} \xrightarrow[\text{MW, 120 } ^\circ\text{C, 30 min}]{\text{NFSi (7 mol\%)}} \text{Alkyl-COOMe}$ 12-30 12a-30a		
Methyl Alkanoates		
12a 100% (99%)	13a 100% (97%)	14a 100% (95%)
15a 100% (96%)	16a 100% (98%)	17a 100% (98%)

Table 3. Cont.

$\text{Alkyl}-\text{C}(=\text{O})\text{OH} + \text{MeOH} \xrightarrow[\text{MW, 120 } ^\circ\text{C, 30 min}]{\text{NFSi (7 mol\%)}} \text{Alkyl}-\text{C}(=\text{O})\text{OMe}$		
12-30		12a-30a
Methyl Alkanoates		
	18a 18% (13%)	
	21a 100% (97%)	
	24a 81% (77%)	
	27a 100% (97%)	
		29a 0%
		30a 100% (99%)

To gain better insight into the possible reaction pathway, ^{19}F NMR spectra of the crude reaction mixture were recorded, and from the obtained results, it was concluded that NFSi did not degrade during the reaction. This result was very informative and indicates that NFSi can be promoted as a promising acid- and metal-free catalyst for direct esterification supported by MW irradiation. This finding is opposite to our previous ones, wherein the pre-catalytic activity of NBS and DBDMH was observed, but their activities were associated with their degradation products during the reaction [13,31]. It can be hypothesized that the process of esterification is provided by the classical Fischer esterification mechanism, where the initial step—activation of the carbonyl group—is achieved by halogen bonding [46]. Although the strength of the sigma hole on fluorine from the NFSi was generally neglectable compared with Br or I derivatives, it can be proposed that the increase in positive charge of the sigma hole could be achieved by MW irradiation i.e., N–F bond elongation, which provides optimal interaction compared to other investigated N–X derivatives and conventional heating where this bond elongation is not promoted. Moreover, it should be noted that MW irradiation directly interacted with

the reactants, catalysts, and solvent molecules, ensuring efficient heating of the mixture and fast conversion into the product. Also, during MW irradiation, both energy input (Supplementary material, Figure S2) and reaction time were reduced, due to localized superheating effects providing a higher reaction temperature of the medium, which was a product of the interactions between mixture molecules and microwave energy. In the review paper by Javed et al. [28], all relevant publications about MW esterification approaches can be found.

Moreover, the synthetic potential of the presented methodology was confirmed by scale-up synthesis of methyl benzoate (**1a**) under optimal reaction conditions, but with the methanol quantity reduced four times. The quantitative conversion of benzoic acid (20 mmol) was observed; thus, from an industrial standpoint, additional savings in sources and energy can be achieved.

3. Materials and Methods

3.1. General Information

All reactions were performed in a MW reactor Anton Paar Monowave 300. The ^1H , ^{13}C , and ^{19}F nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Ascend 400 (400 MHz) spectrometer. CDCl_3 was used as a solvent, and chemical shifts were given in parts per million (δ) downfield from tetramethylsilane as the internal standard (SI, List S1). All chemicals used for synthesis were obtained from commercial sources and were of reagent grade purity or better (Merck, Sigma Aldrich, Carlo Erba, Fluka, Fisher Scientific, Apollo Scientific, etc.). Copies of ^1H NMR and ^{13}C NMR spectra of the isolated final products and ^{19}F NMR spectra of the NFSi and crude reaction mixture are available in the Supplementary material (SI, List S2 and S3, respectively).

3.2. Experimental Design

The determination of the influence of the independent process variables was found as follows: temperature (X_1), time (X_2), and amount of catalyst (X_3) on the reaction conversion (Y) were performed by RSM [47] applying statistical analysis software, Design-Expert software (Version 11, Stat-Ease, Inc., Minneapolis, MN, USA). The small five-level three-factor central composite design (CCD) was used, and the experiment consisted of 15 trials (SI, Table S1). The models' significances were evaluated by the analysis of variance (ANOVA, $p < 0.05$) and the regression analysis (R^2). The optimal parameters were chosen after the numerical optimization.

3.3. Experimental Procedures

General Procedure for the Esterification between Carboxylic Acids and Alcohols

The mixture of carboxylic acid (1 mmol), alcohol (2 mL), and NFSi (7 mol%) was stirred (600 rpm) in a 10 mL reactor tube and MW irradiated at 120 °C for 30 min. These optimal conditions were established after the RSM optimization process. When the reaction was completed, the solution mixture was cooled to room temperature, and the alcohol was evaporated under reduced pressure. The isolation procedure was as follows, except where noted differently. The residue was dissolved in ethyl acetate, washed with 5 mL of saturated NaHCO_3 (aq), and consecutively with 10 mL of distilled water. The water phase was extracted with ethyl acetate (3×5 mL). The organic layers were combined, dried over Na_2SO_4 , and the solvent was evaporated under reduced pressure.

The scale-up preparation of methyl benzoate (**1a**) was performed. The mixture of benzoic acid (20 mmol, 2.44 g), MeOH (10 mL), and NFSi (7 mol%, 0.44 g) was stirred (600 rpm) in a 30 mL reactor tube and MW irradiated at 120 °C for 30 min. After the completion of the reaction, the mixture was cooled to room temperature, and the alcohol was evaporated under reduced pressure. The previously described isolation procedure was performed.

4. Conclusions

In summary, a convenient method for direct dehydrative esterification of free aromatic/aliphatic acids with different alcohols was developed, using acid-/metal-free and easy-to-handle *N*-fluorobenzenesulfonimide—NFSi. NFSi can be classified as a moisture- and air-tolerant recyclable catalyst which manifests its catalytic activity through halogen bond activation of carbonyl moieties in the presence of MW irradiation. Importantly, in contrast to esterification under thermal conditions, where *N*-halo compounds behave as pre-catalysts, in the MW-supported protocol, a distinct reaction mechanism was proposed by assuming NFSi as a sustainable catalyst. Applying MWs, both the energy input and reaction time were reduced. Combining MWs and acid-/metal-free NFSi as a promising catalyst for direct esterification, the proposed protocol can be classified as a green one, without the need for simultaneous water removal and excessive reagents. Despite some scope limitations, the method provides excellent product yielding in the majority of examples, enabling simple isolation of products only by extraction. Moreover, in the case of poly-carboxy aromatic/aliphatic acids (di- and tri-), esterification was successfully performed without an additional amount of NFSi catalyst, compared with mono-carboxy alkyl acids. The large-scale synthesis of methyl benzoate, a commercially-interesting ester, was successfully accomplished with quantitative conversion of benzoic acid.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/catal12111413/s1>, Table S1. The central composite design and experimental results; Table S2: Coefficients for quadratic equation. Figure S1: 2D plot obtained after RSM analysis and numerical optimization; Figure S2. Energy input (gray line—power [W]) and temperature (blue line—in °C) for esterification under optimal reaction conditions and MW irradiation. List S1. NMR spectral data of synthesized esters. List S2. ¹H and ¹³C NMR spectra of synthesized esters. List S3. ¹⁹F NMR spectra of NFSi (A) and crude reaction mixture of cinnamic acid, MeOH and NFSi (B). [18,48–72].

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