

Improved Fischer Esterification of Substituted Benzoic Acid under Sealed-Vessel Microwave Condition

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Abstract: *Ethyl-4-fluoro-3-nitro benzoate was synthesised in good yield under closed vessel conditions using a single-mode microwave. This simple method involved adding catalytic amounts of H₂SO₄ at specific intervals of time to overcome the problems associated with equilibrium. The method was first optimised in terms of temperature, and the effect of using various solvents on the ester product was also investigated. Primary alcohols produced the highest yield of the ester product compared to secondary alcohols, and tertiary alcohol resulted in the lowest.*

Keywords: Esterification, sealed-vessel microwave, benzoic acid

1. INTRODUCTION

Microwave-assisted organic synthesis (MAOS) is gaining popularity as an alternative source of heat in organic reactions. It is far superior to conventional heating methods such as heating mantels, Bunsen burners, hot plates, and oil baths due to its ability to reduce reaction time, produce few by-products, and increase product yield.¹ The first report of using a household microwave to carry out an organic reaction was published in 1986 by Gedye² and Giguera³. However, the application of household microwaves was limited due to the inability to control the microwave energy, poor reproducibility and safety concerns. In the mid-1990s, Strauss⁴ pioneered the usage of controlled MAOS in sealed vessels using standard solvents, and today, over 90% of reported microwave synthesis protocols rely on the use of single-mode microwaves in combination with closed vessel conditions.⁵

In closed vessels, solvents can be heated above their boiling points. As a result, the reaction rates can be accelerated compared to reactions that are performed under conventional reflux conditions or in open vessels.⁶ However, while this may be an advantage to many reactions, it is not favourable for reactions involving equilibrium processes such as esterification. Esterification can be successfully carried out using various types of catalysts such as mineral

acids,^{7,8} ionic liquids,^{9,10} or solid acid catalysts.^{11,12} Its applications include enzyme-catalysed reactions,¹³ biodiesel production¹⁴ and polymer synthesis.¹⁵ Traditionally, esterification of benzoic acid can be performed in excess amounts of ethanol in the presence of catalytic acid, typically H₂SO₄. A major disadvantage in Fischer esterification lies in the equilibrium nature of the reaction. It is even more difficult when the reaction is conducted in a closed vessel because either the product or the water generated needs to be removed to drive the reaction to completion. Hence, performing esterification in open vessels is rationally the best solution because water can be removed during the course of the reaction.

A number of researchers have devised and modified their apparatus to ensure the efficient removal of the undesired water during esterification. Amore and Leadbeater¹⁶ made extensive modifications to their microwave reactor for esterification, and several researchers have used a Dean-Stark apparatus,¹⁷ fractional distillation¹⁸ and solvent-free systems in open vessels.¹⁹ Attempts made by Baghbanzadeh and Kappe²⁰ to use molecular sieves as water scavengers in a sealed-vessel microwave gave negative results because the sieves only absorbed water at room temperature and were ineffective in the microwave reactions.

4-Fluoro-3-nitrobenzoic acid was used in this experiment as a precursor to synthesise benzimidazole derivatives. Esterification of the compound protected the carboxylic acid moiety for subsequent reactions. Initially, esterification consisting of refluxing benzoic acid with excess ethanol and H₂SO₄ resulted in a 78% yield. However, when the experiment was repeated under the same conditions in a sealed-vessel microwave (Figure 1), the yield was very low, which is in agreement with Amore and Leadbeater.¹⁶ In a kinetic study on the effect of water on the H₂SO₄ catalyst, Liu and co-workers²¹ proposed that the presence of water deactivates the autocatalysis of H₂SO₄ due to its preferential solvation by water over alcohol. Prompted by these results, we investigated whether the yield of the ester could be increased when the reaction is performed in sealed vessels without any modifications to the reactor. We also evaluated the effects of reaction temperature, catalyst amount and holding time on the yield of the ester. To determine the scope of the optimised conditions, we also reacted benzoic acid with other alcohols.

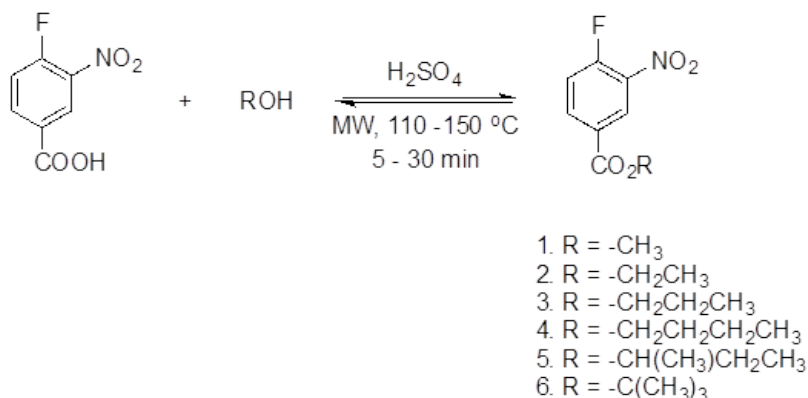


Figure 1: General synthesis of Alkyl 4-fluoro-3-nitro benzoate.

2. EXPERIMENTAL

2.1 Chemicals and Equipment

The microwave experiments were performed using a CEMTM Discover Labmate single-mode microwave reactor (CEM Corp.). The ¹H and ¹³C NMR spectra were recorded on a Bruker Avance III 500 MHz instrument in CDCl₃. Reaction progress was monitored using TLC and purified using PLC plates with ethyl acetate:hexane (4:1). All chemicals were purchased from Merck and Sigma Aldrich and used without further purification.

2.2 General Procedure for the Preparation of Ester Compounds (1–6)

A mixture of 4-fluoro-3-nitro benzoic acid (0.25 g, 1.35 mmol), 4% concentrated H₂SO₄ (2.88 μL) and 1 ml of alcohol were combined in a 3 ml microwave reaction vessel. The reaction mixture was irradiated in the CEMTM microwave at selected temperatures with total holding times of 5, 10, 15, 20, 25, and 30 minutes, during which the acid catalyst was loaded every 5 minutes. Once the reaction was complete, the solvent was evaporated under pressure, and the crude residue was dissolved in ethyl acetate. The organic layer was washed with NaHSO₃ and dried with anhydrous Na₂SO₄. The mixture was then purified using PLC plate and concentrated *in vacuo* to give the ester product.

2.2.1 Methyl 4-fluoro-3-nitro benzoate²² (1):

Yellow liquid obtained after concentration *in vacuo* gave **1** (0.22 g, 77%). ¹H NMR (500 MHz, CDCl₃): δ 3.98 (s, 3H, OCH₃), 7.39 (dd, *J* = 5.0, 10.0

Hz, 1H, benzene-H), 8.31-8.34 (m, 1H, benzene-H), 8.75 (dd, $J = 5.0, 10.0$ Hz, 1H, benzene-H); ^{13}C NMR (125 MHz, CDCl_3): δ 52.9 (OCH_3), 118.8, 127.2, 127.8, 136.5, 136.6, 158.1, 164.1 ($\text{C}=\text{O}$); ^{19}F NMR (500 MHz, CDCl_3): -110.5; ESI-MS: m/z calc. for $\text{C}_8\text{H}_6\text{O}_4\text{FN} + \text{Na}^+$ 222.1; found $\text{M} + \text{Na}^+$ 222.0.

2.2.2 Ethyl 4-fluoro-3-nitro benzoate²³ (2):

Yellow liquid obtained after concentration *in vacuo* gave **2** (0.21 g, 74%). ^1H NMR (500 MHz, CDCl_3): δ 1.43 (t, $J = 5.0$ Hz, 3H, OCH_2CH_3), 4.44 (q, $J = 5.0$ Hz, 2H, OCH_2CH_3), 7.39 (dd, $J = 5.0, 10.0$ Hz, 1H, benzene-H), 8.31-8.35 (m, 1H, benzene-H), 8.74 (dd, $J = 5.0, 10.0$ Hz, 1H, benzene-H); ^{13}C NMR (125 MHz, CDCl_3): δ 14.3 (OCH_2CH_3), 62.1 (OCH_2CH_3), 118.7, 127.6, 127.8, 136.5, 136.6, 158.0, 163.6 ($\text{C}=\text{O}$); ^{19}F NMR (500 MHz, CDCl_3): -110.75; ESI-MS: m/z calc. for $\text{C}_9\text{H}_8\text{O}_4\text{FN} + \text{Na}^+$ 236.2; found $\text{M} + \text{Na}^+$ 236.0.

2.2.3 Propyl 4-fluoro-3-nitro benzoate (3):

Yellow liquid product obtained after concentration *in vacuo* gave **3** (0.24g, 83%). ^1H NMR (500 MHz, CDCl_3): δ 1.05 (t, $J = 5.0$ Hz, 3H, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.83 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 4.34 (t, $J = 5.0$ Hz, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 7.40 (dd, $J = 5.0, 10.0$ Hz, 1H, benzene-H), 8.32-8.35 (m, 1H, benzene-H), 8.74 (dd, $J = 5.0, 10.0$ Hz, 1H, benzene-H); ^{13}C NMR (125 MHz, CDCl_3): δ 10.4 ($\text{OCH}_2\text{CH}_2\text{CH}_3$), 22.0 ($\text{OCH}_2\text{CH}_2\text{CH}_3$), 67.7 ($\text{OCH}_2\text{CH}_2\text{CH}_3$), 118.8, 127.7, 127.8, 136.5, 136.6, 158.0, 163.7 ($\text{C}=\text{O}$); ^{19}F NMR (500 MHz, CDCl_3): -110.8; ESI-MS: m/z calc. for $\text{C}_{10}\text{H}_{10}\text{O}_4\text{FN} + \text{Na}^+$ 250.2; found $\text{M} + \text{Na}^+$ 250.0.

2.2.4 Butyl 4-fluoro-3-nitro benzoate (4):

Yellow liquid product obtained after concentration *in vacuo* gave **4** (0.28g, 98%). ^1H NMR (500 MHz, CDCl_3): δ 1.00 (t, $J = 5.0$ Hz, 3H, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.48 (sextet, $J = 5.0$ Hz, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.78 (pentet, $J = 5.0$ Hz, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 4.38 (t, $J = 5.0$ Hz, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 7.40 (dd, $J = 5.0, 10.0$ Hz, 1H, benzene-H), 8.31-8.34 (m, 1H, benzene-H), 8.74 (dd, $J = 5.0, 7.5$ Hz, 1H, benzene-H); ^{13}C NMR (125 MHz, CDCl_3): δ 13.4 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 19.2 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 30.7 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 66.0 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 118.8, 127.7, 127.8, 136.5, 136.6, 158.0, 163.7 ($\text{C}=\text{O}$); ^{19}F NMR (500 MHz, CDCl_3): -110.9; ESI-MS: m/z calc. for $\text{C}_{11}\text{H}_{12}\text{O}_4\text{FN} + \text{Na}^+$ 264.2; found $\text{M} + \text{Na}^+$ 264.0.

2.2.5 *sec*-Butyl 4-fluoro-3-nitro benzoate (5):

Yellow liquid product obtained after concentration *in vacuo* gave **5** (0.11g, 38%). ^1H NMR (500 MHz, CDCl_3): δ 0.98 (t, $J = 5.0$ Hz, 3H, $\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 1.37 (d, $J = 5.0$ Hz, 3H, $\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 1.68 - 1.81 (m, 2H, $\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 5.14 (sextet, $J = 5.0$ Hz, 1H, $\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 7.39 (dd, $J = 5.0, 10.0$ Hz, 1H, benzene- H), 8.31- 8.34 (m, 1H, benzene- H), 8.72 (dd, $J = 5.0, 10.0$ Hz, 1H, benzene- H); ^{13}C NMR (125 MHz, CDCl_3): δ 9.7 ($\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 19.5 ($\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 28.8 ($\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 74.5 ($\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 118.7, 127.7, 128.0, 136.5, 136.5, 158.0, 163.3 (C=O); ^{19}F NMR (500 MHz, CDCl_3): -111.1; ESI-MS (EI- ve^+): m/z calc. for $\text{C}_{11}\text{H}_{12}\text{O}_4\text{FN} + \text{Na}^+$ 264.2; found $M + \text{Na}^+$ 264.0.

2.2.6 *tert*-Butyl 4-fluoro-3-nitro benzoate (6):

Yellow liquid product obtained after concentration *in vacuo* gave **6** (2.80mg, 1%). ^1H NMR (500 MHz, $\text{CDCl}_3\text{-}d_6$): δ 1.62 (s, 9H, $\text{OC}(\text{CH}_3)_3$), 7.35 (dd, $J = 5.0, 10.0$ Hz, 1H, benzene- H), 8.25-8.28 (m, 1H, benzene- H), 8.66 (dd, $J = 5.0, 10.0$ Hz, 1H, benzene- H); ^{13}C NMR (125 MHz, CDCl_3): δ 28.1 ($\text{OC}(\text{CH}_3)_3$), 82.9 ($\text{OC}(\text{CH}_3)_3$), 118.5, 127.6, 129.1, 136.3, 136.4, 156.8, 162.7 (C=O); ^{19}F NMR (500 MHz, CDCl_3): -111.7; ESI-MS: m/z calc. for $\text{C}_{11}\text{H}_{12}\text{O}_4\text{FN} + \text{Na}^+$ 264.2; found $M + \text{Na}^+$ 264.0.

3. RESULTS AND DISCUSSION

All of the experiments were performed in a single-mode microwave equipped with sealed vessels. We added 4% H_2SO_4 to the mixture containing benzoic acid and ethanol following the method of Amore and Leadbeater.¹⁶ The mixture was irradiated at 90°C in a single-mode microwave, which was held for two, five and 13 minutes consecutively (Table 1). TLC indicated that the reactions did not achieve completion throughout the experiment and only produced 6% of the ester product (Table 1, entry 1). Increasing the temperature to 100°C only increased the per cent yield to 16%. When the experiment was repeated with the addition of the same amount of catalyst after every five minutes of irradiation for 25 minutes (5×5 minutes), a 28% yield was obtained (Table 1, entry 3). Prompted by these results, we repeated the experiment with irradiation of the reaction up to 130°C (Table 1, entries 4–5). Addition of the catalyst at specific time intervals gave significantly higher yields compared to adding acid only at the beginning of the reaction. Because water deactivates, or "poisons", the catalyst, the addition of the catalyst at intervals can revive its effectiveness in reacting with the alcohols and hence move the reaction forward.

We then determined the optimal method conditions. Repeating the same experiment, we increased the irradiation time from five to 30 minutes, and the yield was determined every five minutes. The temperature was varied from 110–150°C (Figure 2). As time increased, the yield of the ester also increased until it reached a plateau after 15 minutes (3×5 minutes). The highest ester yields were obtained at 130–150°C. Based on these results, the optimised condition involved a lower temperature (130°C) with a total irradiation time of 15 minutes (3×5 minutes).

Table 1: Esterification reaction of 4-fluoro-3-nitro benzoic acid under microwave using catalytic amount of H_2SO_4 (cat.) and ethanol as a solvent.

Entry	Temperature, °C	Hold time ^d	Yield (%) ^a
1 ^b	90	(2 + 5 + 13 min)	6
2 ^b	100	(2 + 5 + 13 min)	16
3 ^c	100	(5 × 5 min)	28
4 ^b	130	(5 × 5 min)	52
5 ^c	130	(5 × 5 min)	78

Notes: ^aRefer to isolated products, ^bCatalyst was added at the beginning of reaction. ^cCatalyst was added at the interval time, ^dIrradiation time at the reaction temperature exclude the ramping time.

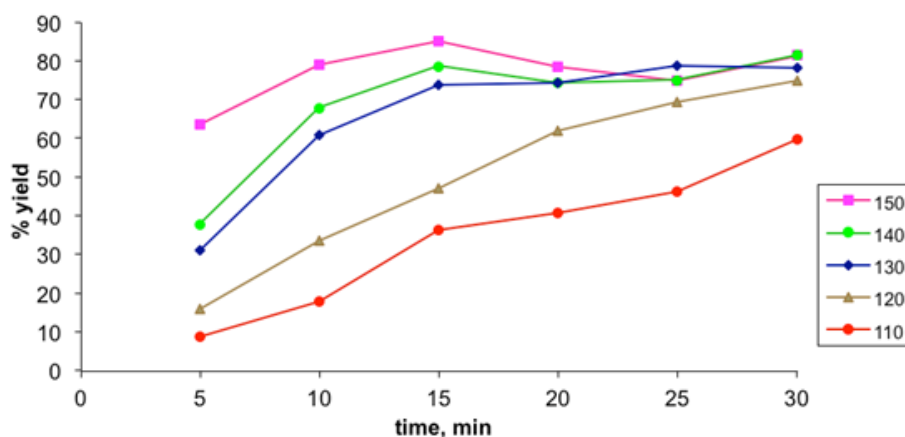


Figure 2: Effect of temperatures on esterification reaction.

Under the optimised microwave conditions, we evaluated other alcohols in the esterification reaction. In general, primary alcohols gave higher product yields compared to branched alcohols (Table 2), with butanol giving the highest yield (98%). Our results agree well with the findings of Rad et al.,²⁴ who also found that the ester yield in esterification with aliphatic alcohols increased in the following order: primary > secondary > tertiary. The enhanced reactivity of primary alcohols is ascribed to the lower steric hindrance experienced by these

alcohols and the thermal stability of straight alkyl chains compared to branched chains.

Table 2: Esterification reaction with different alcohols.

Compound ^a	Solvent	Yield (%)
1	Methanol	77
2	Ethanol	74
3	Propanol	83
4	Butanol	98
5	Sec-butanol	38
6	<i>t</i> -butyl-alcohol/ <i>tert</i> -butanol	1

Notes: ^aIrradiation performed in sealed-vessels at 130 °C, 4% H₂SO₄ was added at interval (5 × 5 minutes).

4. CONCLUSION

In summary, we have demonstrated an improved method of esterification that is efficient and simple using a single-mode microwave under sealed-vessel conditions. Adding catalyst at intervals can overcome its deactivation during the course of the reaction. The temperature, amount of catalyst, holding time and type of alcohol can affect the product yield. The reaction conditions were optimised at 130°C and a total irradiation time of 15 minutes (3 × 5 minutes). Among the alcohols tested, the optimal solvent with the highest product yield was butanol. This simple and practical experimental setup is an improved microwave method for Fischer esterification, particularly for reactions conducted in closed vessels. As this was a preliminary study, we only focused on simple substituted benzoic acid derivatives, but this work could also be extended to other ester derivatives to further expand its application.

5. ACKNOWLEDGEMENTS

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