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Efficient Microwave-Assisted Synthesis of Methyl 4- or 5-Nitroanthranilate

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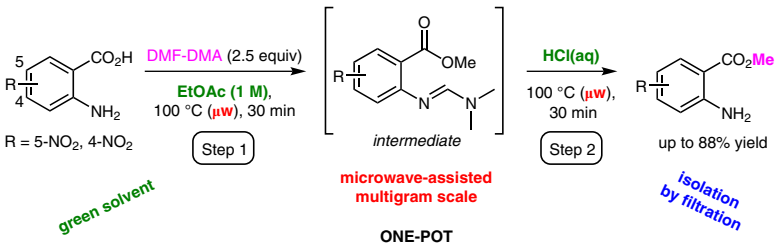

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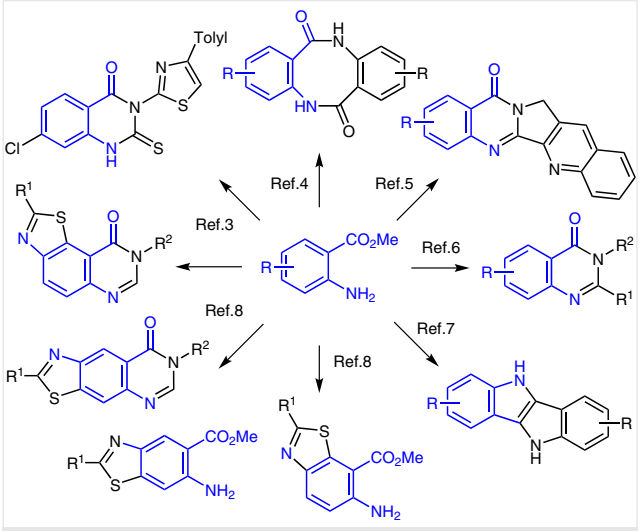
Abstract A novel method for the synthesis of anthranilate esters is described. The esterification reaction of nitro-substituted anthranilic acids was carried out under microwave irradiation. A range of solvents and other reaction parameters were investigated to provide the most environmentally friendly reaction conditions. The feasibility of scale-up was demonstrated, allowing a simple and inexpensive production of anthranilate esters.

Key words microwave chemistry, green solvent, sustainable chemistry, one-pot reactions, hydrolysis

Anthranilate esters are a major class of organic compounds in pharmaceutical and cosmetic fields.[1] Amongst them, methyl anthranilate is employed extensively in the perfume industry and is also a precursor of numerous Schiff bases used in fragrance formulation.[2] In the course of various works over the past few years, methyl anthranilates have been found to be key building blocks for the synthesis of relevant bioactive molecules (Scheme 1).[3–8] In this context, methyl 2-amino-5-nitrobenzoate (**3a**) and 2-amino-4-nitrobenzoate (**3b**) (see Scheme 3 below) were recently converted into tricyclic thiazolo[5,4-*f*]quinazolin-9(8*H*)-ones.[8] Indeed, these chemical platforms were found to be of particular interest in the design of multi-target-directed ligands (MTDLs) of kinases,[9] which is an innovative strategy for the development of new tools against neurodegenerative diseases.

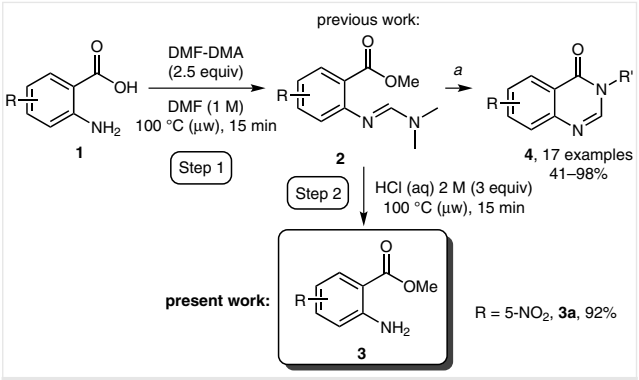
Unfortunately, both key precursors, methyl 4- and 5-nitroanthranilate isomers **3a** and **3b**, are commercially available in only small amounts and are quite expensive. Considering all these facts, syntheses of methyl anthranilates were planned from less expensive 5-nitro- and 4-nitroanthranilic acids, with the aim of producing the corresponding esters on a multi-gram scale while maintaining time-efficient, clean and ecological procedures. Thus, this chemistry was achieved under microwave irradiation as a continuation of our global strategy focused on the design of appropriate reagents and techniques offering operational, economic and environmental benefits over conventional methods.[10]



Scheme 1 Examples of heterocyclic natural and synthetic scaffolds derived from methyl anthranilate esters

Anthranilate esters are usually synthesised from the corresponding anthranilic acids, but they can also be obtained from benzylic alcohols or *ortho*-halogenated aromatic acids.[11] However, these processes suffer from major drawbacks including the use of concentrated strong acids, toxic and/or non-ecofriendly solvents, and toxic and/or expensive reagents, or metals.[12–20] They are often not suited to use on a large scale and are not environmentally compatible, according to green chemistry rules.[21]

In a previous study, a convenient sequential one-pot procedure to synthesize pyridopyrimidin-4-(3*H*)-ones and quinazolin-4(3*H*)-ones with good to excellent yields was described (Scheme 2).[8] Microwave-assisted heating of anthranilic acid (e.g., **1**) under atmospheric conditions in *N*,*N*-dimethylformamide (DMF), with dimethylformamide-dimethylacetal (DMF-DMA) yielded the corresponding formimidamide (e.g., **2**), which is a versatile intermediate that, after evaporation of DMF, rapidly cyclized under acidic conditions upon addition of an aliphatic primary amine to provide bicyclic compound **4** in good yield (Scheme 2). In the one-pot procedure, we observed that intermediate **2** was partially hydrolyzed into the corresponding aminoester (e.g., **3**), our key building block used in kinase MTDLs. The outcome and rate of the hydrolysis was highly dependent on the acidity of the final mixture. To find a scalable and reliable route to the key aminoesters (e.g., **3**), we decided to investigate and optimise the conditions of the hydrolysis.



Scheme 2 New access to methyl 5-nitroanthranilate (**3a**) inspired by a previous work, under microwave irradiation. *Reagents and conditions*: (a) R′NH_2 (1.1 equiv), AcOH (1 M), 100 °C (MW), 15 min.

In a first approach, 5-nitroanthranilic acid (**1a**) was treated with DMF-DMA (2.5 equiv) in DMF. After 15 minutes heating at 100 °C under microwave irradiation, the resulting mixture was concentrated to dryness. Addition of aq HCl (2 M; 3 equiv) to the solid residue and heating (15 min at 100 °C) provided the crude anthranilate ester **3a**. The reaction mixture was treated with sat. aq $NaHCO_3$ and extracted three times with ethyl acetate. The combined organic layers were then washed with water and brine, and dried over magnesium sulfate. Concentration in vacuo afforded methyl 5-nitroanthranilate (**3a**) in analytically pure form, as a yellow solid, with 92% yield (Scheme 2).

Despite this success, the procedure needed to be improved with respect to its environmental compatibility, taking into account aspects such as the type of radiation chosen (energy efficiency), the stoichiometry of reagents, the choice of safer solvent, the acidic conditions for the hydrolysis step and finally, our need to scale up the synthesis.

The small-scale experiments were conducted in a monomode cavity with a microwave power delivery system ranging from 0 to 850 W, which allows pressurised reactions (0 to 30 bar) to be performed in sealed glass vials (4 to 30 mL) equipped with snap caps and silicon septa.[22–24]

Studies for the preparation of anthranilate esters (**3** series) were carried out on substrate **1a**. The required amount of DMF-DMA was first examined. Unexpectedly, 2.5 equivalents of this reagent were necessary to reach complete conversion of substrate **1a** into intermediate **2a** and transformation into **3a**.

The nature of the solvent was then studied. In this case, two major technical constraints were identified: The solvent should be considered as environmentally compatible as possible[21] and also have appropriate dielectric properties (loss tangent[22]), allowing good interactions with microwaves for a convenient heating with this technology.

Methyltetrahydrofuran (Me-THF), cyclopentyl methyl ether (CPME), methyl ethyl ketone (MEK), dimethyl carbonate (DMC), ethanol (EtOH) and ethyl acetate (EtOAc) were tested as common green solvents to replace DMF. All these solvents furnished the desired anthranilate ester **3a** with satisfactory yields. EtOAc was chosen, in line with the guidelines for selection of classical- and less classical-solvents.[21] Indeed, ethereal solvents (e.g., Me-THF and CPME) are problematic and their use is often dismissed because they may generate explosive peroxides at high temperatures. In EtOH, the esterification reaction of **1a** did not allow complete conversion of the substrate (possibility because of transesterification). In DMC, which is particularly attractive because it is regarded as a nonvolatile organic compound (VOC) due to its low vapor pressure,[18] product **3a** was obtained in 79% yield. Nevertheless, under our reaction conditions, this solvent was ruled out because of an increase in the pressure in the sealed tube, even after cooling, due to degradation of DMC into 1,2-dimethoxyethane (DME), carbon dioxide (CO_2), and methanol (MeOH), which is known to occur at a temperature of 90 °C and above.[25] This degradation may be accelerated under acidic conditions and may also be favoured under microwave irradiation. Taking all these facts into account, DMC cannot be considered as a green solvent. In MEK, product **3a** was obtained in 79% yield, whereas the reaction in EtOAc showed a better result (81%). Although it is seldom used as a solvent in chemical reactions,[26] EtOAc was the best green solvent for the formation of anthranilate ester **3a**.

Finally, weak acids such as acetic and citric acids were tested to replace hydrochloric acid. Under these conditions, methyl 2-formamido-5-nitrobenzoate was obtained instead of the desired ester **3a**,[8b] highlighting the necessity to use a strong acid to drive the hydrolysis of intermediate **2a** to completion.

With the operating conditions in hands, the synthesis of anthranilate ester was settled: in a sealed tube (30 mL), 5-nitroantranilic acid (**1a**) was dissolved in ethyl acetate (1

Scheme 3 Optimised reaction for the preparation of anthranilate esters **3a** and **3b** (sealed vials, monomode microwave system)

M). Then DMF-DMA (2.5 equiv) was added under stirring at room temperature. The mixture was heated under microwave irradiation at 100 °C for 15 minutes. After cooling to 60 °C, hydrochloric acid (aq 0.1 M, 4 mol%) was added and the solution was heated under microwave irradiation at 100 °C for 30 minutes. After cooling to 60 °C, the warm reaction mixture was poured into a beaker containing water (20 mL) at room temperature. After 10 minutes stirring, the formed precipitate was filtered and then rinsed with water. Finally, the solid product **3a** was dried under vacuum. To sum up, product **3a** could be obtained from acid **1a** by using ethyl acetate as a green solvent, under weakly acid conditions. It was isolated by simple filtration, without extraction/washing or purification steps. The residual by-products rinsed down (MeOH, NMe_2 and traces of DMF) result from the thermal decomposition of DMA-DMF and then DMF as described in various works.[27]

This convenient procedure was also tested with 4-nitroanthranilic acid (**1b**), the corresponding methyl ester of which is commonly used in our laboratory (Scheme 3). Methyl 4-nitroanthranilate (**3b**) was obtained from **1b** with 88% yield.

The large-scale experiments were carried out in a closed multimode cavity, which serves as a batch-type scale-up reaction in a 250–750 mL scale by following the one-vessel-at-a-time concept. Recently, this microwave system proved to be very efficient for the scale-up of several organic transformations, affording products with excellent yields and purities.[24] Moreover, although reaction times clearly increase on moving from small-scale to large-scale reactions, it was shown that very similar isolated yields and/or conversions were obtained without modification of the protocols. The scale-up of the esterification reaction was performed on 0.3 mol of substrates **1a** and **1b**. Methyl anthranilate **3a** and **3b** were obtained with similar yields (82 and 88%, respectively) to those obtained in the small-scale investigations. The procedure allowed a rapid and efficient synthesis of 48.54 grams of **3a** and 51.79 grams of **3b** (Scheme 4).

Some comments can be made concerning the technology employed. Under usual thermal conditions (heating bath or oil bath) the same reaction conditions (same parameters of compounds quantities, solvent volumes, heating temperature and reaction time) were not so efficient and lower yields were observed. It may be suggested that although EtOAc is a low microwave absorbing solvent (tan δ = 0.058),[23] its combination with the reagents allowed favourable dielectric properties of the mixture, leading to an effective synthesis of various precursors of bioactive molecules that generally requiring higher cost and less environmentally friendly synthetic processes.

In summary, we have developed a simple, scalable, and efficient procedure to access anthranilate esters, which are common intermediates in the syntheses of valuable heterocyclic scaffolds. This method offers easy and inexpensive access to key precursors of various biologically active molecules.

All reagents and solvents were obtained from Fisher Scientific, Alfa Aesar, Sigma–Aldrich, or VWR and were used without further purification. Melting points of solid compounds were measured with a STUART Melting Point SMP3 instrument with a precision of ±1.5 °C. IR spectra were recorded with a PerkinElmer Spectrum 100 Series FTIR spectrophotometer. Solids were investigated with a single-reflection attenuated total reflectance (ATR) accessory; the absorption bands are given in cm^{-1}. NMR spectra (^1H and ^{13}C) were acquired at 295 K with a Bruker AVANCE 300 MHz spectrometer operating at 300 and

Scheme 4 Scale-up of the reaction for the preparation of anthranilate esters **3a** and **3b** (closed tube, multimode microwave system)

75.4 MHz. Chemical shifts (δ) are reported in parts per million (ppm) relative to trace amounts of DMSO in the corresponding deuterated solvent. Coupling constants *J* are in Hz.

General Information for Microwave Irradiation Experiments

Small-scale microwave irradiation experiments were performed with a Monowave 300 single-mode microwave reactor (Anton Paar GmbH) using a standard 30 mL Pyrex vessel (G30). The reaction temperature was controlled by an FO probe (IR as slave), and stirring speed was set to 600 rpm. The 'heat to temperature as fast as possible' mode was chosen. For the large-scale experiments, a Masterwave BTR with 1 L PTFE reaction vessel were employed. The same setup parameters were used. Starting materials were weighed directly into the reaction vessel and dissolved with the appropriate solvent. An agitator was inserted and the vessel was closed. For optimum results, the stirring speed was set in accordance to the filling volume (rpm equals mL). For safety, when large chemical quantities were heated, the instrument was installed inside a fume hood, and a connection to an appropriate expansion system was assured. With the provided standard stainless steel tubing with standard Swagelok bulkhead fitting (L10 mm), even a simple stainless steel barrel (ca. 50 L) can be connected as the minimum required expansion tank. In case of an overpressure venting action, the vessel's metal safety disk ruptures and empties the vessel content safely into the expansion tank.[24]

Synthesis of Anthranilate Ester 3

In a standard 30 mL Pyrex® vessel (G30 tube, Monowave 300) or in a 1 L PTFE reaction vessel, antranilic acid **1a** or **1b** (Monowave 300: 5 mmol; Masterwave 0.3 mol) was dissolved in EtOAc (1 M, Monowave 300: 5 mL; Masterwave BTR: 300 mL). Then DMF-DMA (2.5 equiv, Monowave 300: 12.5 mmol, 1.7 mL; Masterwave BTR: 750 mmol, 100 mL) was added under stirring. The mixture was heated under microwave irradiation at 100 °C for 15 min with the Monowave 300 or for 20 min with the Masterwave BTR. After cooling to 60 °C, an aqueous solution of hydrochloric acid (4 mol% or 2 equiv) was added to the mixture. The solution was heated under microwave irradiation at 100 °C for 30 min. After cooling to 60 °C, the warm reaction mixture was poured into a beaker containing water [20 mL (small scale) or 800 mL (large scale)] at r.t. After 10 min stirring, the precipitate was filtered off and rinsed with water. Solid products **3a** and **3b** were dried under vacuum.

Methyl 2-Amino-5-nitrobenzoate (3a; CAS: 3816-62-4)

Yield: 0.794 g (81%; Monowave 300); 48.54 g (82%; Masterwave); yellow solid; mp 165–167 °C (Lit.[27] 169 °C).

IR: 3469, 3358, 3038, 2964, 1703, 1627, 1313, 1249, 1125, 1068, 827 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.56 (d, *J* = 2.8 Hz, 1 H, H-6), 8.07 (dd, *J* = 9.3, 2.8 Hz, 1 H, H-4), 7.83 (br. s, 2 H, NH_2), 6.88 (d, *J* = 9.3 Hz, 1 H, H-3), 3.85 (s, 3 H, OMe).

^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 166.4, 155.8, 135.1, 128.9, 128.3, 116.8, 107.5, 52.1, 39.5.

Methyl 2-Amino-4-nitrobenzoate (3b; CAS: 3558-19-8)

Yield: 0.863 g (88%; Monowave 300); 51.79 g (88%; Masterwave); orange solid; mp 156–158 °C (Lit.[28] 156–157 °C).

IR: 3490, 3375, 3107, 3080, 2955, 1698, 1583, 1345, 1246, 1082, 729 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.88 (d, *J* = 8.8 Hz, 1 H, H-6), 7.65 (d, *J* = 2.4 Hz, 1 H, H-3), 7.23 (dd, *J* = 8.8, 2.4 Hz, 1 H, H-5), 7.13 (br. s, 2 H, NH_2), 3.83 (s, 3 H, OMe).

^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 166.6, 151.6, 150.9, 132.6, 113.1, 110.9, 108.1, 52.1, 39.5.

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