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The mercury-mediated decarboxylation (Pesci reaction) of naphthoic anhydrides investigated by microwave synthesis

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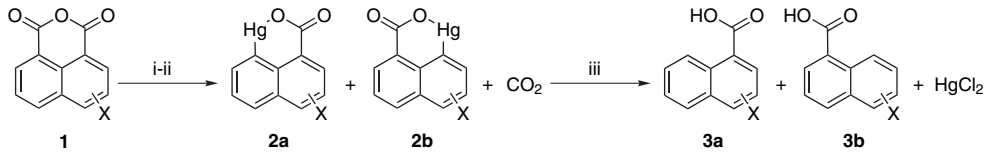
Abstract—The mercury-mediated decarboxylation (Pesci reaction) of several substituted naphthoic anhydrides has been investigated by microwave synthesis. A laboratory microwave reactor was found to be ideal for small-scale preparations of this slow reaction, reducing reaction times from typically four days to less than 1 h for the three-step process. The ionic reaction medium rapidly heated to high temperatures under microwave heating and could be efficiently maintained by low microwave power settings. Generation of stoichiometric CO_2 was safely contained within the reaction tubes. A simplified reaction procedure has been developed. For substituted naphthoic anhydrides, ^{1}H NMR analysis of the naphthoate ester derivatives indicated no change in the regioisomer ratio compared to previously reported thermal values.

1. Introduction

The selective mercury-mediated decarboxylation of an aromatic anhydride to give the mono-acid and carbon dioxide (after acidic hydrolysis) was first reported by Pesci.[1] Whitmore reported on the mechanism and effect of the substitution pattern on the mercury insertion of various phthalic, naphthoic and related anhydrides in a series of reports.[2–5] More recently, Newman has investigated the decarboxylation of phthalic, naphthoic and phenanthroic anhydrides in greater detail,[6] and confirmed many of Whitmore's findings. Mercury-mediated decarboxylations have been reviewed by Deacon et al. in their article on the synthesis of organometallics by decarboxylation reactions.[7]

In the early studies, the arene anhydride (**1**) (Scheme 1, naphthoate series shown for convenience) was hydrolysed to its dicarboxylate anion and treated in situ with HgO in acetic acid and water (effectively $Hg(OAc)_2$). The Hg species possibly adds initially between the carboxyl groups, and then into the arene ring displacing one or other of the carboxylate groups, which is then released as CO_2, giving the anhydro organo-mercury isomers (**2a**,**b**) in typically quantitative yield in all cases. These are very stable compounds that can be isolated and oven dried. They are thought to exist in polymeric chains,[7] which probably account for their low solubility in organic solvents.[8] Acidic hydrolysis (or hydride reduction)[6] releases Hg as its salt to yield the arene mono-acids (**3a**,**b**) (Scheme 1).

These reactions are thermally driven and can take up to 96 h at reflux in water. Newman[6] and others have shown that a radical pathway is unlikely, although it is common in much other organo-mercury synthesis. The exact mechanism is unclear, and this may be because alternative mechanisms are favoured in different cases. Whitmore used an unsymmetrically substituted phthalide to establish that Hg directly displaces one of the carboxylate groups, rather than at either *ortho* position.[2] Further evidence supports both cationic and anionic initiated S_E1 and S_Ei type mechanisms, as well as classical electrophilic aromatic *ipso* substitution pathways. However, the reaction rate appears to be



Scheme 1. (i) NaOH, H_2O; (ii) HgO, $AcOH/H_2O$ (3:1), or $Hg(OAc)_2$ neat; (iii) concentrated HCl.

Keywords: Decarboxylation; Mercury; Microwave; Naphthoic anhydride.
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relatively insensitive to the nature of the substituent, perhaps not surprising given the forcing conditions. The nature and position of any substituent does, however, affect the ratio of the resulting regioisomers, and appears to depend on both polar and steric components; however, release of ring strain may be dominant in sterically crowded cases.[6,7] A more detailed discussion of possible mechanisms can be found in Deacon's review.[7]

Newman has also shown that in higher boiling solvents with powdered glass the reaction can be accelerated to shorter periods, and that $NaBH_4$ can be used to quickly reduce the organo-mercury species (**2a**,**b**) to their respective mono-acids (**3a**,**b**). However, the work-up procedure using these solvents and reagents was both more complicated and more dilute than the original conditions. As we will show, the microwave procedure is very convenient for accelerating the reaction and simplifying the work-up without recourse to high-boiling solvents or reducing agents.

2. Results and discussion

Our interest in this reaction initially resulted from a requirement to synthesise 3-cyano-1-naphthoic acid,[9,10] which has a particularly awkward substitution pattern for electrophilic aromatic substitution chemistry (i.e., two deactivating substituents in the same ring). Application of the Pesci reaction to the decarboxylation of 3-bromonaphthoic anhydride (**4b**) and subsequent derivatisation via its acid (**5b**) and methyl ester (**7b**) actually provides a relatively short sequence to this naphthoic acid (Scheme 2). In our experience, the decarboxylation reaction required from two to four days at reflux in water to complete the decarboxylation step, before a 4 h hydrolysis in refluxing HCl completed the transformation. These conditions are typical of other reported examples.

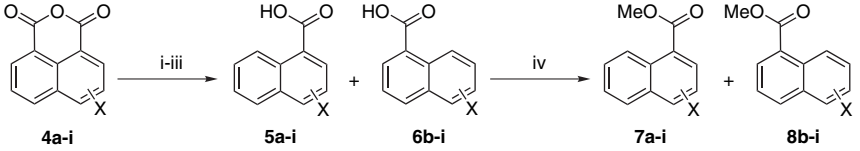
Such a reaction, with its long reaction time at elevated temperature, ionic reaction medium and metal-mediated transformation, seemed an ideal candidate with which to investigate the application of microwave chemistry. We were interested to determine whether microwave synthesis could be used to enhance the rate of reaction, and to see if there was any significant microwave effect. We were also interested to compare the ratio of regioisomeric naphthoic acids derived from various substituted naphthoic anhydrides under microwave conditions with the ratios determined under purely thermal conditions. Lastly, the stoichiometric generation of CO_2 was an additional challenge for use in the sealed microwave tubes typical of modern microwave reactors.[11]

Before commencing any studies in a microwave reactor, a Carius tube test was conducted on a sample of compound **4b** conveniently left over from previous work.[10] Assuming a 20% fill in a 10 mL microwave tube, which conveniently approximated to 1 mmol scale for the limiting naphthoic anhydride, a maximum pressure of ~200 psig was achieved at 180 °C. The tubes are rated for 250 psig in operational use[12] from which a maximum operating limit of 200 °C was extrapolated with an adequate safety margin, assuming no increase in either tube fill or molar equivalents. It must be acknowledged that these pressures, although transient in most cases, would present problems for scale up, although these could be off-set by lower reaction temperatures or slower heat up ramps. In the first instance, however, millimole scale quantities can be prepared to support a medicinal chemistry programme.

For the initial investigations, we started with the conversion of readily available unsubstituted naphthoic anhydride **4a** into naphthoic acid **5a** (Scheme 2). In a standard protocol, the anhydride was dissolved in excess 1 M NaOH at 50 °C for 15 min to achieve hydrolysis to the dicarboxylate salt. Meanwhile, red HgO was dissolved in a warm solution of 3:1 acetic acid/water to give a colourless solution. This was added to the dicarboxylate salt resulting in a dense white precipitate, which was then heated to 100 °C for several days. The intermediate organo-mercury species are highly insoluble and gave very poor chromatography on HPLC. Consequently, the reaction could only usefully be monitored after the acidic hydrolysis step, achieved by adding a large excess of concentrated HCl (~24 equiv) and heating to 100 °C for 4 h. The insoluble product could be filtered from the cooled reaction mixture, washed copiously with water to remove $HgCl_2$ and dried in a vacuum oven to give typically a quantitative yield of naphthoic acid as an off-white solid. LC analysis of the isolated solids was then satisfactory.

To achieve a representative thermal reaction rate profile, a series of tube scale reactions was performed in sealed tubes heated in an aluminium block at 100 °C. At various time points, a reaction was quenched by the addition of HCl and after a further 4 h heating at 100 °C, the resulting solid was isolated as described above. The results are shown in Figure 1, and confirm previous results; namely that whilst ~90% conversion can be achieved after 48 h, more than 96 h (four days) is required to achieve nearly 100% conversion.

We now conducted the reaction under microwave conditions, keeping all the parameters same except the temperature.[13] Rather than lengthening the reaction time excessively, we chose to fix the reaction time to a convenient 15 min, and increased the reaction temperature significantly. We then ran a series of microwave tube scale experiments on



Scheme 2. (i) NaOH, H_2O; (ii) $Hg(OAc)_2$; (iii) concentrated HCl and (iv) $SOCl_2$, MeOH. Substituent X is given in Table 2. NB. Regioisomer notation: **5/7** series, substituent in same ring as carboxylate; **6/8** series, substituent in opposite ring to carboxylate. For X=H, only **5a** and **7a** are used.

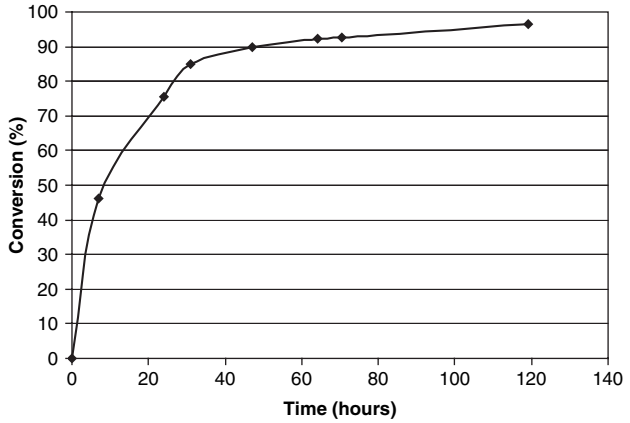


Figure 1. Thermal heating rate (% conversion at time indicated, with HgO).

identical conditions, with a fixed hold time of 15-min microwave irradiation once the set-point temperature had been reached. Temperatures from 100 to 200 °C were studied at 20 °C intervals. The acidic work-up was, however, conducted as before with a 4 h reflux in excess HCl at only 100 °C under conventional heating. The results are shown in Figure 2 and the comparison with Figure 1 shows that 15 min in the microwave at ~180–200 °C is approximately equivalent to the thermal heating rate at 100 °C after ~48 h.[14] This comparison of the thermal and microwave heating data strongly suggests that there is no inherent difference in reaction rate when allowing for the increased reaction temperature under microwave conditions, i.e., the thermal rate at these elevated temperatures would give comparable reaction rates.

Making up a solution of HgO in a specific ratio of pre-heated acetic acid/water was rather tedious and we determined to simplify the procedure by swapping this with neat $Hg(OAc)_2$. Initially we added acetic acid and water to the NaOH solution to keep the overall solution volume constant, but found that both could be eliminated and the reaction and work-up still performed reliably. Adding $Hg(OAc)_2$ (initially 1.25 equiv) in place of HgO gave comparable results with >90% conversions in similar times, as long as the $Hg(OAc)_2$ was thoroughly mixed by shaking with the hydrolysed dicarboxylate before microwave irradiation began.

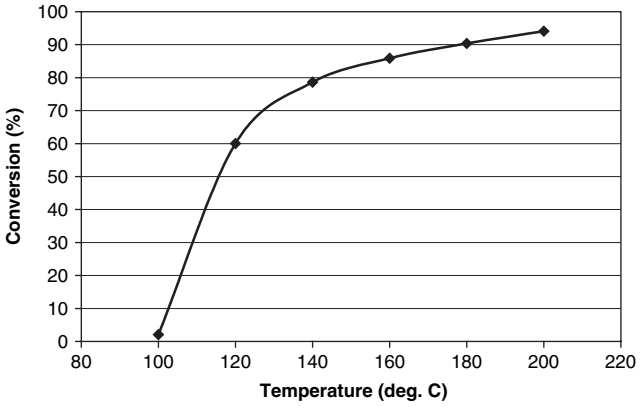


Figure 2. Microwave heating rate (% conversion after 15 min. MW heating at set temperature, with HgO).

We also tested microwave heating for the NaOH hydrolysis step and found that 1 min at 100 °C was adequate to form the dicarboxylate anion.

We had deliberately separated the acidic hydrolysis from the decarboxylation reaction so far, but clearly a 4 h hydrolysis for a 15-min microwave reaction was highly inefficient. Therefore, a series of tubes was run under what were now our standard microwave conditions (i.e., 180 °C for 15 min with $Hg(OAc)_2$), and then hydrolysed with concentrated HCl at several elevated temperatures from 120 to 150 °C. The results at 120 °C proved most reliable, with no significant difference being seen between heating for 15, 30, 60 or 120 min (conversions varied from 90–93%, i.e., within experimental error). Heating for 15 min at higher temperatures proved less robust; the product was often isolated in poor form under these conditions being typically a hard brown solid rather than the usual off-white powder, and LC analysis was variable. Therefore, hydrolysis at 120 °C for 15 min under microwave heating was chosen for future reactions, since this was both convenient and robust, and 15 min appeared to be adequate under most conditions.

Confident that we could now run the whole reaction sequence under microwave conditions in less than 1 h, we now decided to investigate other parameters systematically in the microwave. Initial studies had been conducted with a slight excess of HgO (or $Hg(OAc)_2$), from 1.05 to 1.15 equiv. Using the same conditions as before, but now with microwave assisted HCl hydrolysis at 120 °C for 15 min, we assessed the impact of Hg stoichiometry on the reaction conversion. The results are shown graphically in Figure 3 where it can be seen that no benefit is achieved by adding more than ~1.2 equiv of Hg (given its toxicity, clearly the less used the better). This graph also shows a duplicate point for a repeat reaction, which was performed to assess the overall reproducibility of the microwave procedure now that it was well-defined; as can be seen, the reproducibility was excellent.

The reaction did not quite reach completion even with a significant excess of Hg available, however. We speculated that if the release of CO_2 was a reversible process, then the increased partial pressure of CO_2 in a sealed tube might inhibit complete conversion (Le Chatelier's principle). Although

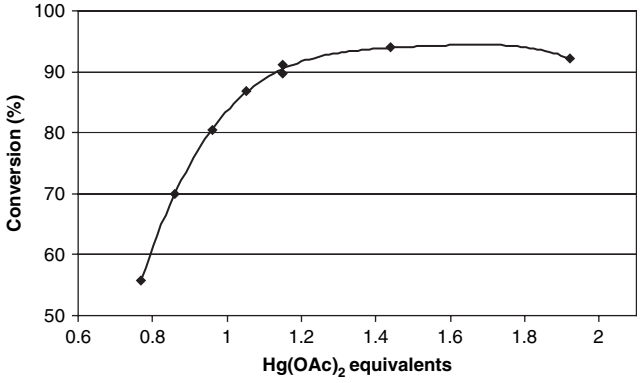


Figure 3. % Conversion with increasing $Hg(OAc)_2$ stoichiometry.

Table 1. % Conversion under microwave heating (isolated yields)

Temperature (°C)	Standard protocol (1×15 min)	With gas venting (2×7 min)	With pulsed heating (3×4 min)
160	85.9	84.9	88.2
180	90.4	93.4	94.0
200	94.1	96.4	95.4

we did not think this very likely, it was worth investigating briefly. Several reactions were conducted under the previously described conditions, but in two 7 min cycles of microwave heating, with the cool down in the middle used to vent CO_2 from the reaction tubes. Total heating for 14 min with two heat up cycles was taken to be approximately equal to one period of 15 min with a single heat up period. Reactions were performed at 160, 180 and 200 °C, with the cooled tubes vented to atmosphere at the halfway point. An analysis of the gas generation from the initial hazard study, and the gas pressure profile from the microwave reactions themselves, showed that most of the CO_2 release occurred in the first 7 min; the additional pressure generated in the second 7 min was relatively low. Therefore, although the conversions were already high after 7-min heating, this also maximised the removal of CO_2, which we felt would afford the best conditions for detecting any further progress in conversion. The results are presented in Table 1 along with the equivalent results from Figure 2 for comparison. This shows that there was in fact no benefit in releasing CO_2; higher conversions were achieved simply due to higher temperatures, which matched previous results.

Some anecdotal reports attribute microwave enhancements to rapid heating effects rather than the absolute temperature reached. We attempted to test this hypothesis by subjecting a number of standard reactions to pulsed heating protocols of three cycles of 4-min heating at 160, 180 and 200 °C and compared them to the control values for a single 15 min reaction. However, there was no discernable difference between these protocols within the experimental error of reproducibility for these reactions (~2–3%) (Table 1). As with the gas-venting experiments, the product was a pale cream solid of good form and yield.

Finally, to check for robustness in our procedure, we ran a further set of six reaction tubes, varying NaOH equivalents at two levels (2.0 and 2.5 mmol) and $Hg(OAc)_2$ equivalents at three levels (1.05, 1.15 and 1.25 equiv), but with all other parameters using the standard conditions (i.e., 180 °C for minutes). The form of the product was good in all cases, with conversions typically 93–96%, indicating that the process was robust for minor charging errors within the tested range. With these final results, an optimised tube reaction was performed as described in Section 4. This used a microwave NaOH hydrolysis step (1 min at 100 °C), 1.05 equiv of $Hg(OAc)_2$ with microwave heating (15 min at 200 °C), and completed with a microwave HCl hydrolysis step (15 min at 120 °C), to give an isolated yield of 99% of naphthoic acid with 98.9% quality by LC as a pale cream powder of good form. Significantly, all stages were performed in the same reaction tube in a 'one pot' process by sequential addition of the required reagents, thus simplifying the overall procedure. This process was then used as the basis for decarboxylation of the substituted naphthoic anhydrides.

Substituted naphthoic anhydrides **4b–i** were subjected to the Pesci reaction under microwave heating using the conditions optmised for the unsubstituted compound **4a** (Scheme 2). Further limited optimisation was required for each substituent, with temperature varying from 180 to 200 °C, time from 15 to 30 min and $Hg(OAc)_2$ charge from 1.05 to 1.15 equiv. The specific conditions and results are presented in Table 2. In nearly all cases a high conversion with a quantitative yield could be obtained. The electron-withdrawing substituents (Br, Cl and NO_2) tended to give better conversions with longer heating at 200 °C, compared to the electron-donating ones (**4a**,**e**–**f**). The exact equivalents of $Hg(OAc)_2$ appeared to be less critical. In as much as these conditions appear to favour electron-donating groups over electron-withdrawing ones, this suggests that a classical electrophilic aromatic substitution may be operating. But as Deacon warns in cases that are extremely forcing (such as these), one should be cautious in deducing too much about the preferred mechanism.[7]

Product quality was good in all cases, with the colour generally derived from the quality of the input anhydride **4a–i**. Only the 4-chloro acids (**5d/6d**) gave less than full recovery, which appeared to be due to higher water solubility. The 3-OH acids (**5e/6e**), available from commercially available **4e**, gave a product of moderate form and quality. The strong mustard yellow colour was certainly carried through from the starting material. Attempts to force consumption of **4e**

Table 2. Optimised conditions for conversion of substituted naphthoic anhydrides (**4**) to naphthoic acids (**5** and **6**) under microwave heating

Entry	Anhydride (**4**) X=	Temperature (°C)	Time (min)	Equivalents of $Hg(OAc)_2$	Conversion[a] (%)	Product quality	Product colour	Total yield (%)
a	H	200	15	1.05	98.9	Good	Cream	100
b	3-Br	200	30	1.05	94.6	Fair	White	100
c	4-Br	200	30	1.15	84.7	Good	White	100
d	4-Cl	200	30	1.05	82.2	Good	White	70[b]
e	3-OH	180	15	1.15	66.9[c]	Poor	Mustard	181[d]
f	3-OMe	180	15	1.15	98.4	Good	Yellow	100
g	2-NO_2	180	15	1.05	93.0	Good	Light brown	89
h	3-NO_2	200	30	1.15	94.1	Good	Cream	100
i	4-NO_2	200	30	1.05	89.1	Good	Brown	100

[a] Determined by LC on isolated dried product.
[b] This product retained high water solubility and much was lost on washing.
[c] The product was contaminated with 25% residual starting material.
[d] Visible mercury was present, which probably accounts for the high yields.

could be achieved, but gave a black product of poor form and significant impurities. The yield was also suspiciously high, which may be explained by naphthol salt formation, although metallic mercury was also visibly present. Unsurprisingly, derivatisation to the esters was unsuccessful. Given the relative ease of alternative synthesis of naphthoic acids with hydroxyl substituents, we did not pursue this example further. However, the 3-OMe series (**4/5/6f**), derived from methylation of **4e**[15] gave excellent results throughout.

The regioisomer ratio of the naphthoic acids could not be easily determined by HPLC, as there were known to be significant differences in the UV responses at a given wavelength for each pair of alternately substituted naphthoic acids.[16] Furthermore, although direct analysis of the acids (**5/6**) by ^{1}H NMR is in principle possible, their solubility even in d_6-DMSO was too low to give reliable results. We therefore decided to derivatise samples of the mixed acids to their respective methyl esters (**7/8**), which could then be analysed by ^{1}H NMR in $CDCl_3$. The methyl ester signal also provided a further peak to check the integration against, although in most cases, at least one distinctive aromatic signal could be found to determine the regioisomer ratio. Assignments of the major and minor regioisomers were also made on esters **7/8**.

The methyl esters were prepared by treatment with excess thionyl chloride in methanol (or concentrated H_2SO_4 in methanol for **4a**),[10] concentrated to dryness and purified by flash silica gel chromatography. No attempt was made to separate the methyl ester isomers, and ^{1}H NMR analysis was conducted on the clean product mixtures as planned. The results are shown in Table 3, alongside the reported ratios where available for the naphthoic acids (**5/6**). These figures are mainly derived from Whitmore's work,[2,4] and Newman is wise to point out that the number of fractional crystallisations involved in some cases makes the comparison uncertain. However, using the most reliable figures from Whitmore, with which Newman also agrees, our microwave mediated regioisomer ratios are in good-to-excellent agreement with all previously reported values. Furthermore, for those compounds with no previous data, the regioisomer ratios matched the observed trend, i.e., generally ~3:1 for 3-/6-substituents, and ~6:4 for 4-/5-substituents. Only the 4-chloro (**4/7/8d**) and 2-nitro series (**4/7/8g**) gave an alternative ratio in favour of substitution in the opposite ring to that of the remaining carboxyl functionality. The effect was slight for the 4-chloro series (35:65 **7d**:**8d**); consequently the ^{1}H and ^{13}C NMR assignments were re-examined at some length and the original assignments confirmed. The effect on the ratio was complete and unambiguous in the case of the 2-nitro series (0:100 **7g**:**8g**), thus showing that steric constraints are dominant for 2-substituted naphthalenes, as is generally the case. In summary, microwave heating has not altered the regioisomer ratio resulting from mercury-mediated decarboxylation. Our results are in full agreement with those of Whitmore[4] and Dewar[9] and refute again the disputed results discussed by Deacon.[7,17]

3. Conclusions

We have investigated the mercury-mediated decarboxylation (Pesci reaction) of eight substituted naphthoic anhydrides and shown that microwave heating is especially convenient for this type of slow, metal-mediated reaction. Reaction times have been reduced from four days to less than 1 h for the three-step sequence with a simplified reaction procedure, which can be conducted as a 'one pot' process. Stoichiometric generation of CO_2 was safely contained within the microwave reaction tubes. For substituted naphthoic anhydrides, the regioisomer ratio of the resulting acids was identical to those previously reported by thermal methods. Accounting for the temperature increase under microwave conditions, no significant increase in the reaction rate was detected beyond what would be expected under identical thermal conditions. In this case, microwave chemistry has therefore been proven to be a reliable and predictable substitute for thermal reaction conditions, with the additional benefit of convenient access to very high reaction temperatures.

4. Experimental

4.1. General

All microwave reactions were performed exclusively in a regularly calibrated CEM *Discover* 300 W focused microwave reactor with IR temperature monitor and non-invasive pressure transducer in 10 mL sealed tubes. The heating time

Table 3. Regioisomer ratios and data on substituted methyl naphthoate esters **7b–i** and **8b–i**

Entry	Anhydride (**4**) X=	Ratio **7**:**8** (MW)[a]	Ratio **5**:**6** (lit.)[b]	Lit. ref.		Total yield[c]
				7	**8**	**7**+**8** (%)
b	3-Br	72:28	75:25 (9, 10)	18, 19	9, 10	65
c	4-Br	60:40	n/d	20	20	50
d	4-Cl	35:65	n/d	19, 20	19, 20	76
e	3-OH	n/d	n/d	n/a	n/a	n/a
f	3-OMe	72:28	n/d	21	20	78
g	2-NO_2	0:100	n/d	22	9, 23	47
h	3-NO_2	76:24	65:35 (4); 83:17 (6)[d]	19, 20	20	100
i	4-NO_2	96:4	96:4 (4)	20	20	73

n/a=Not applicable.
n/d=Not determined.
[a] Determined from ^{1}H NMR integration of esters **7** and **8**.
[b] Literature values reported for acids **5** and **6** (references given in parentheses).
[c] Total yield of combined esters from **4**; low yields may reflect incomplete decarboxylation reactions to acids **5** and **6**.
[d] The data are difficult to interpret; the minor isomer is almost certainly over-estimated in Ref. 4 and a ratio of ~3:1 would be more likely.

to reach the set temperature was typically 45–90 s, depending on the maximum wattage supplied (30–90 W) and the temperature required (100–200 °C) (typically 90 W to heat a 2 mL sample to 200 °C in ~90 s). The heating time is not included in the specified hold time for any given procedure; control studies show that the heating time has negligible effect on a 15 min reaction. The maximum wattage supplied was capped well below the maximum 300 W available to avoid the reaction mixture significantly over-shooting the set-point temperature; the ionic reaction medium absorbs microwaves very readily in this case. Reaction tubes were rapidly cooled once irradiation was complete by a stream of compressed air, and generally removed from the instrument when at 70 °C.

Isolated products were fully characterised by LC/TLC, ^{1}H and ^{13}C NMR spectroscopy, MS and mp where applicable. Except where relevant to the discussion in the main text, the data are not reproduced since all compounds are known in the literature (see Table 3 for references). The regioisomer ratios of the methyl naphthoate esters (**7** and **8**) were determined by ^{1}H NMR spectroscopy ($CDCl_3$) on any cleanly resolved and identifiable peaks between any pair of regioisomers, ideally using the methyl ester signal and a resolved aromatic signal. The ^{13}C NMR integration was usually in very good agreement with the ^{1}H NMR integration results. The regioisomers were also determined where possible by LC but the NMR results have been used in preference, since the LC results are subject to variations in the UV chromophores between the regioisomers, which are known to be significant in many cases.[16]

Reverse phase HPLC was performed on an Agilent 1100 series instrument as follows: column, Zorbax SB-C8, 750 mm×4.6 mm i.d., 3.5 μm packing; flow rate 1.00 mL/min; temperature 45 °C; injection volume 5 μL; wavelength 240 nm; eluent A, 100% purified water with 0.02% v/v formic acid; eluent B, 100% methanol; timetable; 0 min, 60% eluent A; 6 min, 30% eluent A; 7.5 min, 5% eluent A; 10 min, 5% eluent A; post-time, 2.5 min. HPLC purities are area % normalised, unless noted otherwise. Melting points were determined using a Griffin melting point apparatus (aluminium heating block) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 400 spectrometer at 400 and 100.6 MHz, respectively, with chemical shifts given in parts per million relative to TMS at δ=0. Electrospray (ES^+) mass spectra were performed on a Micromass ZQ LCMS using ESCi mode with both positive and negative ionisation; a water/acetonitrile gradient with either formic acid or ammonium carbonate was used for the LC component. Analytical TLC was carried out on commercially prepared plates coated with 0.25 mm of self-indicating Merck Kieselgel 60 F_{254} and visualised by UV light at 254 nm. Preparative scale silica gel flash chromatography (for lab work) was carried out by standard procedures using Merck Kieselgel 60 (230–400 mesh). Where not stated otherwise, assume that standard practices have been applied.

4.2. Specific thermal and microwave procedures

4.2.1. Thermal rate reactions (with HgO). Ten reactions were conducted in sealed boiling tubes in an aluminium heating block as follows. In each tube naphthoic anhydride (205 mg, 1.00 mmol) was added to 2.5 mL 1.0 M NaOH (2.50 mmol) and heated in an aluminium hot block with magnetic stirring at 50–60 °C for 15–20 min. In a separate flask, a stock solution was prepared of HgO dissolved in water and glacial acetic acid (1:3 ratio) with magnetic stirring at 50–60 °C for 15–20 min to give a clear, colourless solution of $Hg(OAc)_2$. A 1.0 mL aliquot of this Hg salt solution (~1.20–1.25 mol equiv) was added to each tube of hydrolysed naphthoic anhydride to give a dense white precipitate, which was shaken up thoroughly to achieve intimate mixing of the Hg salts. Each tube was simultaneously heated to 100 °C in the heating block with magnetic stirring. At convenient intervals, concentrated HCl (2.0 mL) was added to a given tube, shaken up and re-heated in the hot block at 100 °C with stirring for a further 4 h. Some foaming was observed at this point. Once complete, the tube was allowed to cool to rt, the solid filtered off and the product slurry washed twice on a small sinter with water (5 mL each; later increased to 10 mL). The crude product cake was pulled dry on the sinter and dried in a vacuum oven at 45 °C to yield naphthoic acid as a pale cream solid in typically quantitative yield (0.16–0.18 g). Each sample was analysed in duplicate by LC and the mean result is used in Figure 1. Tubes allowed to run for long time points (>48 h) tended to lose solvent and had to be topped up with purified water to keep the volume constant.

4.2.2. Microwave rate reactions (with HgO). Six reactions were conducted in microwave tubes at temperatures from 100 to 200 °C at 20 °C intervals. In each tube naphthoic anhydride (205 mg, 1.00 mmol) was added to 2.5 mL 1.0 M (2.50 mmol) NaOH in a microwave tube and heated in aluminium hot block with magnetic stirring at 50–60 °C for 15–20 min. In six separate vials, HgO (241 mg, 1.10 mmol) was dissolved in water (241 μL) and glacial acetic acid (721 μL) with magnetic stirring at 50–60 °C for 15–20 min to give a clear, colourless solution of $Hg(OAc)_2$. This was added in one portion to the hydrolysed naphthoic anhydride to give a dense white precipitate, which was shaken up thoroughly to achieve intimate mixing of the Hg salts. Each tube was then heated in the microwave with stirring at 30–90 W maximum power, depending on the final temperature required. After 15 min of heating at the desired temperature, compressed air cooled the tube and concentrated HCl was added (2.0 mL). This was shaken up and re-heated in the hot block at 100 °C with stirring for 4 h. The crude product was isolated, washed and dried as above, to yield naphthoic acid in typically quantitative yield (0.16–0.18 g). Each sample was analysed in duplicate by LC and the mean result is used in Figure 2.

4.2.3. Microwave rate reactions with $Hg(OAc)_2$. The same procedure was used throughout as reported in Section 4.2.2 above, with the exception that instead of HgO in an acetic acid/water mixture, solid $Hg(OAc)_2$ (411 mg, 1.25 mmol) was added to the NaOH solution after the hydrolysis period, and shaken well before commencing microwave heating. An additional charge of water (0.96 mL) had been added to the NaOH solution to maintain the overall solvent volume in these cases (not used in later experiments). The rest of the procedure and work-up was identical to that reported above and the naphthoic acid products were isolated as pale cream solids in typically 95–105% yield (0.16–0.18 g). Each

sample was analysed in duplicate by LC and gave results comparable to those in Figure 2.

4.2.4. Microwave HCl hydrolysis reactions. Seven reactions were conducted in microwave tubes varying the HCl hydrolysis time and temperature under microwave heating as follows: 15, 30, 60 and 120 min at 120 °C, and 15 min at 130, 140 and 150 °C. In each tube naphthoic anhydride (205 mg, 1.00 mmol) was added to 2.5 mL 1.0 M NaOH (2.50 mmol) in a microwave tube and heated in aluminium hot block with magnetic stirring at 50–60 °C for 15–20 min. After this time $Hg(OAc)_2$ (374 mg, 1.15 mmol) was added in one portion to the hydrolysed naphthoic anhydride to give a dense white precipitate, which was shaken up thoroughly to achieve intimate mixing of the Hg salts. Each tube was then heated in the microwave with stirring at 80 W maximum power, to achieve after ~90 s a set-point temperature of 180 °C, which was maintained for 15 min. After compressed air cooling, concentrated HCl (2.0 mL) was added to each tube and shaken up, and further microwave heating was applied at the set-point temperature for 15 min or longer as appropriate with stirring. The crude product was isolated, washed and dried as in previous examples, except for using 10 mL wash volumes, to yield the naphthoic acid in typically quantitative yield (0.17–0.18 g). Each sample was analysed in duplicate by LC and the mean result was used. Samples hydrolysed at 120 °C gave a typically good form of pale cream naphthoic acid, whilst those hydrolysed at higher temperatures gave darker coloured solids with fair to poor form, including hard brown lumps. Yields remained consistently high for all.

4.2.5. Microwave Hg stoichiometry reactions. Eight reactions were conducted in microwave tubes varying the $Hg(OAc)_2$ equivalents as follows: 0.77 equiv (250 mg); 0.86 (281 mg); 0.96 (312 mg); 1.05 (343 mg); 1.15 (375 mg); 1.44 (468 mg); 1.92 (624 mg). In each tube naphthoic anhydride (205 mg, 1.00 mmol) was added to 2.5 mL 1.0 M NaOH (2.50 mmol) in a microwave tube and heated in aluminium hot block with magnetic stirring at 50–60 °C for 15–20 min. After this time $Hg(OAc)_2$ was added in one portion to the hydrolysed naphthoic anhydride to give a dense white precipitate, which was shaken up thoroughly to achieve intimate mixing of the Hg salts. Each tube was then heated in the microwave with stirring at 80 W maximum power, to achieve after ~90 s a set-point temperature of 180 °C, which was maintained for 15 min. After compressed air cooling, concentrated HCl (2.0 mL) was added to each tube and shaken up, and further microwave heating was applied at 120 °C for 15 min with stirring. The crude product was isolated, washed and dried as in previous examples, except for using 10 mL wash volumes, to yield the naphthoic acid in typically quantitative yield (0.17–0.18 g). Each sample was analysed in duplicate by LC and the mean result is used in Figure 3. The 1.15 equiv reaction was repeated as above but with a 16 h NaOH hydrolysis time at rt.

4.2.6. Microwave reactions with gas venting. The standard procedure described in Section 4.2.5 above was used, but with 1.15 equiv of $Hg(OAc)_2$ (374 mg, 1.15 mmol) in every case. Tubes were heated at 160, 180 and 200 °C under microwave heating at 70–90 W for 7 min before cooling to 70 °C. The residual gas pressure was released by opening the caps (care). The tubes were then re-sealed and re-heated to the set temperature for a further 7 min, then hydrolysed and isolated as described above. All samples gave a pale cream solid of good form. Each sample was analysed in duplicate by LC and the mean result is used in Table 1. Typical maximum pressures recorded were initially ~200–240 psig, reducing to ~50–60 psig residual pressure after the first 7-min heating. Residual pressure after the second period of heating was typically only 6–18 psig.

4.2.7. Optimised microwave process for naphthoic anhydride. (This optimised procedure is conducted in a single tube as a 'one pot' process by sequential additions of reagents.) Naphthoic anhydride (205 mg, 1.00 mmol) was added to 2.5 mL 1.0 M NaOH (2.50 mmol) in a microwave tube and heated in a microwave with magnetic stirring at 100 °C for 1 min. After cooling to 70 °C, $Hg(OAc)_2$ (341 mg, 1.05 mmol) was added in one portion, mixed thoroughly and heated in a microwave with stirring at 200 °C (with 90 W maximum power) for 15 min. After cooling to 70 °C, concentrated HCl (2.0 mL) was added, mixed thoroughly and heated in a microwave with stirring at 120 °C for 15 min. After cooling to rt, the crude product was isolated on a sinter, slurry was washed twice with water (10 mL each) and dried in a vacuum oven at 45 °C to yield the naphthoic acid product as a pale cream solid (0.17 g, 99%). LC quality 98.9%.

4.2.8. Microwave reactions with substituted naphthoic anhydrides. (This procedure is conducted in a single tube as a 'one pot' process by sequential additions of reagents.) The appropriate naphthoic anhydride **4** (1.00 mmol) was added to 2.5 mL 1.0 M NaOH (2.50 mmol) in a microwave tube and heated in a microwave with magnetic stirring at 100 °C for 1 min. After cooling to 70 °C, $Hg(OAc)_2$ (341 mg, 1.05 mmol or 374 mg, 1.15 mmol) was added in one portion, mixed thoroughly and heated in a microwave with stirring at 180 or 200 °C (80–90 W maximum power) for 15 or 30 min. After cooling to 70 °C, concentrated HCl (2.0 mL) was added, mixed thoroughly and heated in a microwave with stirring at 120 °C for 15 min. After cooling to rt, the crude product was isolated on a sinter, slurry washed twice with water (10 mL each) and dried in a vacuum oven at 45 °C to yield the substituted naphthoic acids (**5** and **6**) as an unresolved mixture. Exact conditions, yield and quality for each anhydride are shown in Table 2.

4.3. Preparation of methyl naphthoate esters (7/8)

4.3.1. Methyl naphthoate (7a). Six combined naphthoic acid samples (0.95 g in total with a mean quality of 90% w/w, 4.97 mmol) were slurried in methanol (9.5 mL) and concentrated H_2SO_4 was added (150 μL, 2.48 mmol). The resulting mixture was heated to reflux (65 °C) for 20 h, after which time LC analysis showed that the reaction was 90% complete. A further three drops of H_2SO_4 were added and heating continued for a further 10 h, after which a slight improvement was detected. The reaction mixture was cooled to rt and water (20 mL) was added, which gave a milky white suspension. This was extracted with MTBE (4×15 mL), the combined organic extracts washed with saturated brine (1×15 mL), dried over $MgSO_4$ and

concentrated to dryness to give a brown oil (921 mg). The crude oil was purified by flash silica chromatography in 7:1 to 1:1 *iso*-hexane/ethyl acetate to yield the title compound as a light oil (819 mg, 88%), comparable to a commercially available sample (Aldrich) (LC R_t=7.29 min; TLC R_f=0.60 in 4:1); and recovered naphthoic anhydride as a light brown solid (37 mg, 4%), comparable to a commercially available sample (Aldrich) (LC R_t=4.48 min; TLC R_f=0.16 in 4:1).

4.3.2. Preparation of methyl naphthoate esters (7/8). The following is a typical procedure for the formation, isolation and characterisation of methyl naphthoate esters **7/8**. An unresolved mixture of the 3- and 6-methoxynaphthoic acids (**5f/6f**) (150 mg, 0.74 mmol) was slurried in methanol (2.0 mL) and thionyl chloride was (108 μL, 1.48 mmol) added dropwise over 1 min. The resulting yellow solution was heated thermally in a sealed tube to 75 °C for 3 h, and then cooled to rt and the methanol allowed to evaporate. The crude oil was purified by flash silica chromatography in 9:1 *iso*-hexane/MTBE to yield an unresolved mixture of the methyl 3- and 6-methoxynaphthoate esters (**7f/8f**) as a light brown gum (115 mg, 79% from starting naphthoic anhydride **4f**). TLC R_f=0.42, strong blue spot; MS (ES^+) 217 (M+1, 100%), 185 (M–OMe, 19%). The regioisomer ratio was determined by ^1H NMR spectroscopy ($CDCl_3$) integration of the aromatic H-7 signal to be 74:26 in favour of the 3-methoxy-substituted naphthoate ester (**7f**) over the 6-methoxy-substituted naphthoate ester (**8f**) (the OMe and Me-ester signals were not resolved in this case).

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11. (a) www.cem.com; (b) www.biotage.com; (c) www.milestonesrl.com.
12. A CEM *Discover* was used throughout this work. Due to the high pressures these reactions can generate in a sealed tube, the maximum safe pressure limits for both tubes and instruments should be checked if using alternative microwave reactors.
13. The Hg stoichiometry was also reduced from 1.2 to 1.1 equiv in the later microwave case, but as subsequent studies showed (Fig. 3), this was inconsequential.
14. We also repeated the identical procedure using 1.25 equiv of $Hg(OAc)_2$. This gave very similar results but with the experimental advantage of being operationally much simpler, as discussed in the main text.
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